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**To screen or not to screen? Celiac antibodies in liver diseases**

Narciso-Schiavon JL *et al.* Celiac antibodies in liver diseases

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**Abstract**

Celiac disease (CD) is a systemic immune-mediated disorder triggered by dietary gluten in genetically predisposed individuals. The typical symptoms are anemia, diarrhea, fatigue, weight loss, and abdominal pain. Celiac disease has been reported in patients with primary sclerosing cholangitis, primary biliary cholangitis, autoimmune hepatitis, aminotransferase elevations, nonalcoholic fatty liver disease, hepatitis B, hepatitis C, portal hypertension and liver cirrhosis. We evaluate recommendations for active screening for celiac disease in patients with liver diseases, and the effect of a gluten-free diet in these different settings. Active screening for CD is recommended in patients with liver diseases, particularly in those with autoimmune disorders, steatosis in the absence of metabolic syndrome, noncirrhotic intrahepatic portal hypertension, cryptogenic cirrhosis, and in the context of liver transplantation. In hepatitis C, diagnosis of CD can be important as a relative contraindication to interferon use. Gluten-free diet ameliorates the symptoms associated with CD; however, the associated liver disease may improve, remain the same, or progress.

**Key words:** Celiac disease; Cholangitis; Sclerosing; Liver cirrhosis; Biliary; Hypertension; Portal; Hepatitis; Autoimmune

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**Core tip:** Liver involvement in celiac disease (CD) has been reported for more than four decades. However, CD antibodies are seldom investigated by clinicians in routine hepatology consultations. In this article, we perform extensive literature review on liver and CD and evaluate if one should screen for celiac antibodies in various liver diseases and clinical settings.

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**INTRODUCTION**

Celiac disease (CD) is a systemic immune-mediated disorder triggered by dietary gluten in genetically predisposed individuals. Its typical symptoms are anemia, diarrhea, fatigue, weight loss, and abdominal pain[[1](#_ENREF_1)]. Therefore CD is always considered as a differential diagnosis for malabsorption syndrome and iron-deficiency anemia, but it is often overlooked as a differential diagnosis for liver diseases[[2](#_ENREF_2)]. Its clinical presentation can comprise varied symptoms, including musculoskeletal, neurological, endocrine, kidney, heart, lung, and liver manifestations, concomitant with other autoimmune diseases and malignancies[[1](#_ENREF_1),[3-5](#_ENREF_3)].

The serological diagnosis of CD is based on the presence of the following antibodies: antigliadin (AGA) immunoglobulin A (IgA) and immunoglobulin G (IgG), antiendomisyal antibody (anti-EmA), antitissue transglutaminase (anti-tTG), and antideamidated gliadin peptide (anti-DGP). AGA has become obsolete and is no longer recommended for diagnosis in the adult population owing to its low levels of sensitivity and specificity[[6](#_ENREF_6),[7](#_ENREF_7)]. Anti-EmA testing is performed using an indirect immunofluorescence assay and detects CD with lower levels of sensitivity than other modern serological assays, particularly in the presence of IgA deficiency[[8](#_ENREF_8)]. However, EmA antibody is an extremely specific marker of mucosal damage in untreated patients and has been indicated as a useful diagnostic tool[[7](#_ENREF_7),[9](#_ENREF_9)]. Anti-tTG enzyme-linked immunosorbent assay (ELISA) exhibits optimum sensitivity and lack of specificity with positive predictive values that are significantly lower than those obtained for the EmA assay[[10](#_ENREF_10)]. Therefore, tTG IgA has been recommended as the most efficient single serological test for the detection of CD, whereas EmA IgA can be used as a confirmatory test in case of borderline-positive (low titers) or possibly false-positive results of tests for anti-tTG IgA that may occur in other autoimmune diseases[[7](#_ENREF_7),[9](#_ENREF_9),[11](#_ENREF_11)]. Selective IgA deficiency affects approximately 2%–5% of patients diagnosed with CD[[12](#_ENREF_12)]. Majority of serological tests for CD are IgA based; consequently, these tests do not identify individuals who have both CD and selective IgA deficiency. Therefore, IgA levels must be tested along with other autoantibodies, and individuals with IgA deficiency should go through an IgG-based antibody test[[13](#_ENREF_13)]. A decade ago, anti-DGP had been introduced as a diagnostic tool for CD[[14](#_ENREF_14)]. tTG mediates its effects through an ordered and specific deamidation of certain glutamines to glutamates, increasing the antigenicity of peptides; this deamidation creates an epitope that efficiently binds to DQ2 and is recognized by gut-derived T cells[[15](#_ENREF_15)]. Nowadays, both DGP and tTG antibodies are considered as serological hallmarks of CD[[16](#_ENREF_16)]. There is new serological biomarker for CD available: the tTg neo-epitope (tTg-neo), with high sensitivity and specificity[[17](#_ENREF_17)]. tTg-neo IgG has demonstrated better performance when compared to the tTg-IgA, and has been recommended as a novel diagnostic technique for CD[[17](#_ENREF_17),[18](#_ENREF_18)]. Because no diagnostic test is 100% effective in diagnosing CD, a combined search for celiac antibodies is recommended for optimal diagnostic accuracy[[19](#_ENREF_19),[20](#_ENREF_20)]. Hence, combined antibodiy kits have been made commercialy available and have demonstrated excellent diagnostic performance; they may soon be added to the procedures in diagnostic flow charts[[21](#_ENREF_21)].

Small intestinal biopsy has been central to the confirmation of diagnosis of CD since the late 1950s. Nowadays, distal duodenal biopsies (4–8 fragments) reveal typical histological findings: villous atrophy, crypt hyperplasia, and lymphocytic inflammatory infiltrate[[9](#_ENREF_9)]. It is important to point out that positive serology with normal histology, formerly termed latent CD[[22](#_ENREF_22)], are now defined as potential CD[[23](#_ENREF_23)]. The American College of Gastroenterology recommends human leukocyte antigen (HLA) testing for DQ2 and DQ8 when there is disagreement between serological and histological results[[24](#_ENREF_24)];however, certain authors perform HLA determination in patients with positive anti-tTG and negative EmA to identify false-positive tTG results[[25](#_ENREF_25)].

Liver involvement in CD has been widely described in case reports and case series in the past four decades[[26](#_ENREF_26)]. In London in 1973, Tatcher *et al*[[27](#_ENREF_27)] reported a case of Turner's syndrome with CD, thin bones, and abnormal liver function tests. Nowadays, it is well known that hepatic steatosis is the most frequent finding in Turner’s syndrome[[28](#_ENREF_28)], but architectural changes in the liver, including cirrhosis and biliary lesions such as primary biliary cholangitis (PBC), have also been described[[29](#_ENREF_29)].

CD has been associated not only with autoimmune liver diseases such as primary sclerosing cholangitis (PSC), PBC, and autoimmune hepatitis (AIH) but also with viral hepatitis B and C, and nonalcoholic steatohepatitis, as well as with Wilson’s disease, cirrhosis, and portal hypertension[[30](#_ENREF_30)]. Swedish epidemiological studies have revealed that patients with CD have a 2–6-fold increased risk of future liver disease and an 8-fold increased risk of mortality from liver cirrhosis[[31](#_ENREF_31),[32](#_ENREF_32)]. The development of autoimmune disorders in CD has been related to the age at diagnosis[[33](#_ENREF_33)]. Early diagnosis and treatment of CD is not associated with an increased prevalence of autoimmune disorders, and autoimmune disorders develop in individuals with unrecognized and untreated CD[[33](#_ENREF_33)]. Nonetheless, AIH has been reported in patients with treated CD[[34](#_ENREF_34)].

The aim of the present study was to perform extensive literature review to organize published data on liver and CD and evaluate if one should screen for celiac antibodies in various liver diseases and clinical settings.

**METHODS**

We performed a review for liver involvement in CD by conducting a broad search for MeSH terms “celiac disease” AND “primary sclerosing cholangitis,” “primary biliary cirrhosis,” “autoimmune hepatitis,” “alanine transaminase,” “nonalcoholic fatty liver disease,” “hepatitis B,” “hepatitis C,” “portal hypertension,” “liver cirrhosis,” and “liver transplantation,” in PubMed, with no data limit. In addition, references of the selected articles were consulted for relevant articles on the subject.

**PRIMARY SCLEROSING CHOLANGITIS**

In 1988, Hay *et al*[[35](#_ENREF_35)] described the first three cases of a possible association between PSC and CD observed at Mayo Clinic. Patients presented steatorrhea, and CD was assumed based on typical histological findings of small bowel biopsy and clinical or clinical response to a gluten-free diet. Thereafter, a few case reports have been published (Table 1), some of which do not include serological diagnosis of CD. CD was diagnosed “in the old way”: on the basis of histological findings and clinical response to a gluten-free diet. In several patients, liver disorder had developed when CD was still undiagnosed. Most cases exhibited clinical improvement in intestinal symptoms and anemia with dietary gluten exclusion, whereas more severe liver lesions showed no response to dietary changes[[35-37](#_ENREF_35)].

The association between ulcerative colitis and PSC has been well established[[38](#_ENREF_38)]. CD combined with ulcerative colitis has also been reported[[39](#_ENREF_39),[40](#_ENREF_40)]. Certain cases described associations among ulcerative colitis, CD, and PSC, which is very rare[[35](#_ENREF_35),[37](#_ENREF_37),[41-43](#_ENREF_41)]. Brazier *et al*[[44](#_ENREF_44)] reported an association between ulcerative colitis, PSC, CD, and Hashimoto’s thyroiditis wherein improvements were observed in liver biochemistry and histology.

PSC and CD share some of these predisposing HLA haplotypes. Although it is expected that PSC patients with HLA DR3, DQ2 haplotype would be at risk of CD, such patients have previously been noted to exhibit a more rapid progression of liver disease. Therefore one could imagine whether or not patients with CD who develop PSC suffer from more aggressive liver disease than those without CD[[45](#_ENREF_45)]. Although this has not been specifically studied, in a previous study, patients with high AGA titers demonstrated advanced portal fibrosis[[46](#_ENREF_46)].

Based on global reports of less than 20 cases of PSC and CD, it is not wise to establish a true association between both the disorders. This can only be determined if cholangiography is performed in a consecutive series of patients with CD and if celiac antibodies and small bowel biopsies are recorded in all patients with PSC[[47](#_ENREF_47)]. MacMathuna *et al*[[46](file:///C:\Users\baishideng-2014\Desktop\revised-jyu\30332\30332-Review.docx#_ENREF_46)] studied 69 patients with PSC and observed that 55% of patients presented AGA-positive results, and none of the biopsied patients (0/26) revealed typical findings in duodenal biopsies. Rubio-Tapia *et al*[[48](#_ENREF_48)] evaluated 155 PSC patients with end-stage autoimmune liver disease; those who expressed HLA-DQ2 or HLA-DQ8 molecules have a high prevalence of CD-associated antibodies: 9% of these were tTG positive and 3% were EmA positive.

Taking into account the aforementioned studies, a diagnosis of CD in patients with PSC requires medical awareness of possible coexistence of the two lesions[[47](#_ENREF_47)]. In clinical settings, active screening for celiac antibodies in PSC patients cannot be routinely recommended (Table 1[35-37,41-55]).

**PRIMARY BILIARY CHOLANGITIS**

Recently, the governing boards of both the European Association of the Study for the Liver (EASL) and American Association of the Study for the Liver (AASLD) have approved the change of nomenclature for PBC from “primary biliary cirrhosis” to “primary biliary cholangitis”[[56](#_ENREF_56),[57](#_ENREF_57)].

The first report of CD in patients with PBC was published in 1978[[58](#_ENREF_58)]. Four patients presented characteristic symptoms of CD, typical findings on jejunal biopsy, and clinical improvement with a gluten-free diet. Since then, concomitancy of the two diseases has been extensively reported in several cases[[59-71](#_ENREF_59)] (some of these are enlisted in Table 2), and other disorders have been reported in association with both diseases, including serum IgA deficiency, dermatitis herpetiformis, renal tubular acidosis, Sjögren syndrome, bacterial overgrowth, osteomalacic myopathy, fanconi syndrome, and *Helicobacter pylori* (*H. pylori*) infection.

In 1998, Kingham and Parker studied the relative prevalence of CD and PBC in the UK[[72](#_ENREF_72)]. A 12-year study of a stable population of 250000 individuals revealed a relative prevalence of PBC in 3% of 143 patients with CD and a relative prevalence of CD in 6% of 67 patients with PBC[[72](#_ENREF_72)]. Accordingly, in Ireland, Dickey *et al*[[73](#_ENREF_73)] reported that the prevalence of celiac sprue in patients with PBC is at least 10 times that in the general population. Sørensen *et al*[[74](#_ENREF_74)] reported a high risk of PBC in patients with CD. The risk was similar when independently assessed in two separate national hospital databases during two different study periods: an incidence ratio of 27.6 in Denmark and 25.1 in Sweden. Conflicting results were published in Sweden[[75](#_ENREF_75)], Italy[[76](#_ENREF_76),[77](#_ENREF_77)], and Greece[[78](#_ENREF_78)], where researchers have failed to demonstrate an increased risk of coeliac disease in patients with PBC. Dickey *et al*[[79](#_ENREF_79)] searched for liver abnormalities in 129 patients with CD and none of the patients were positive for AMA.

According to Bizzaro *et al*[[25](#_ENREF_25)], 26.7% of PBC patients exhibited tTG positivity on performing at least one of six different ELISA tests (human recombinant, Eurospital; human recombinant, Pharmacia; human placenta, Euroimmun; human red blood cells, Inova; guinea pig liver, Eurospital; and guinea pig liver, Inova); however, a true association between PBC and CD was present in only 2% of patients who exhibited EmA positivity and showed histological patterns indicative of CD. Moreover, Floreani *et al* reported a high prevalence of false-positive results: 27.5% of PBC patients showed serum IgA-tTG above normal limits, only two patients had IgA-tTG > 30 IU, and EmA positivity was detected in only 3.4% of patients[[80](#_ENREF_80)]. Hence both authors suggest that, in most cases, the false positive results were attributable to the type of substrate used in the tTG assay, suggesting that in PBC patients positive findings in the anti-tTG antibody assay should be confirmed using the EmA test[[25](#_ENREF_25),[80](#_ENREF_80)]. IgA-tTG is characterized by wide heterogeneity in the kit’s performance, depending on both the commercial assay variant used and the cut-offs provided by the supplier. The significant range of test accuracies are haphazard[[11](#_ENREF_11)]. In fact, high-titer IgA-tTG antibodies are specific for detecting CD, whereas in the lower range of titers, there is a broad overlap with other gastrointestinal and liver diseases[[81](#_ENREF_81)]. Studies on screening CD in patients with PBC are listed in Table 3.

In regions with a low prevalence of CD, in the absence of clinical suspicion, the cost benefit of routinely screening all patients with PBC for CD remains debatable. In addition, gluten-free diets have failed to improve liver biochemistry in patients with coexistent PBC[[58](#_ENREF_58),[61](#_ENREF_61),[72](#_ENREF_72)]. The Neuberger report of two patients with PBC who had been referred to their liver unit in the UK for transplantation because of deteriorating liver tests, lethargy, and diarrhea is noteworthy; however, these patients were diagnosed and treated for CD, with consequent improvements so that transplantation was no longer needed[[82](#_ENREF_82)]. Abenavoly *et al*[[83](#_ENREF_83)] reported a case of association among CD, PBC, and *H. pylori* infection, wherein a short period of GFD associated with eradication therapy of *H. pylori* and ursodeoxycholic acid (UDCA) administration led to marked histological and serological improvements in PBC. In addition, Sedlack *et al*[[84](#_ENREF_84)] demonstrated clinical and biochemical improvements with a gluten-free diet and UDCA. However, it is important to point out that the patient received the recommended treatment for CBP, which was most likely responsible for the hepatic improvements.

Therefore, it is important to recognize that patients with these two conditions may share several common clinical features. Weight loss, malabsorption, steatorrhea, bone disease, and elevated alkaline phosphatase are frequently observed in both diseases[[58](#_ENREF_58),[71](#_ENREF_71),[85](#_ENREF_85)]. Hence, they may not be readily recognized during the early stages.

Numerous theories have been considered to explain the concomitant presence of CD and PBC. A genetic connection has not been determined as CD is strongly linked to HLA-DQ2; HLA associations are less clearer and vary among report centers and different ethnic populations[[86](#_ENREF_86)]. Intestinal permeability is increased and disrupted intestinal barrier function has been reported[[87](#_ENREF_87),[88](#_ENREF_88)]. Such changes can lead to an augmented absorption of toxins or antigens into portal blood, which can lead to the hepatic injury observed in such patients[[89](#_ENREF_89)]. It is suggested that immune complexes are formed with molecular mimicry, and this mechanism mediates tissue damage; however, no specific antigen has been identified[[90](#_ENREF_90)]. It has been proposed that chronic bacterial exposure may initiate the development of antibodies, which then cross react with human antigens in PBC patients[[91](#_ENREF_91),[92](#_ENREF_92)]. Alternatively, diminished function of suppressor T cells in patients with both diseases might allow effector cytotoxic lymphocytes to attack a modifying antigen such as gluten[[90](#_ENREF_90)]. These effector cells might then recognize an attack on a patient’s histocompatibility antigens, which are present in high concentrations in biliary as well as intestinal epithelial cells[[90](#_ENREF_90)]. Moreover, tTG is present in the liver and in other tissues besides the intestinal basal membrane, which suggests a pathological role of humoral immunity (anti-tTG) in the hepatic injury observed in patients with CD[[93](#_ENREF_93),[94](#_ENREF_94)].

Screening for CD in patients with PBC is recommended because a gluten-free diet may remit CD symptoms and prevent the development of other autoimmune diseases and intestinal malignancies[[95](#_ENREF_95),[96](#_ENREF_96)] (Table 3[25,65,72,73,78,80,97-105]).

**AUTOIMMUNE HEPATITIS**

AIH has been classified into two or three different subtypes according to the distribution of autoantibodies and clinical presentation[[106](#_ENREF_106)]. Although not all authors adopt this classification[[107](#_ENREF_107)], type 1 AIH (the most frequent form) is characterized by the presence of SMA and/or ANA[[106](#_ENREF_106),[108](#_ENREF_108)]. SMA antibodies are directed against microfilaments by the presence of actin, against intermediate filaments by the presence of vimentin, and against microtubules by the presence of tubulin, with a clear predominance of antiactin antibody in type 1 AIH[[109](#_ENREF_109),[110](#_ENREF_110)]. Type 2 AIH is characterized by the detection of specific antiliver/kidney microsomal antibody type 1 (anti-LKM1) or infrequently by that of anti-LKM type 3 (anti-LKM3) and/or antibodies against liver cytosol type 1 antigen (anti-LC1)[[106](#_ENREF_106)]. The third type was previously known to be seronegative and posteriorly characterized by the presence of antibodies against soluble liver antigen (anti-SLA), which were later found to be identical with previously described antibodies against liver pancreas (anti-LP) and consequently termed as anti-SLA/LP antibodies[[111](#_ENREF_111)]. Thus, initial studies regarding the seroprevalence of CD in AIHconsidered the presence of such autoantibodies, typical histological lesions, hypergammaglobulinemia, and the absence of viral markers. Since the 1990s, a diagnostic scoring system has been used for this[[112](#_ENREF_112)].

An interesting peculiarity is that antifilamentous actin antibodies have been described in 90% of pediatric and 60% of adult CD patients and has thus been proposed as a diagnostic tool[[110](#_ENREF_110),[113](#_ENREF_113)]. In the presence of CD and altered liver enzymes, antiactin positivity may reflect villous atrophy and may not be diagnostic of AIH[[114](#_ENREF_114)].

A genetic link between CD and AIH has been suggested because both disorders express selected combinations of genes coding for class II HLA molecules on chromosome 6[[115](#_ENREF_115)]. Coexistence of the two diseases has been stated in EASL practice guidelines[[106](#_ENREF_106)]. The prevalence of AIH in adults with CD is 1.6 and in children is 2%[[116](#_ENREF_116),[117](#_ENREF_117)] whereas CD in patients with AIH is ten times more seroprevalent than that in the general population[[118](#_ENREF_118)]. A similar tendency has been observed in children[[117](#_ENREF_117),[119](#_ENREF_119),[120](#_ENREF_120)]. The clinical impact of a gluten-free diet on the outcomes of liver disorders in patients with AIH is still uncertain[[114](#_ENREF_114),[119](#_ENREF_119),[121](#_ENREF_121)]. However, probable long-term beneficial effects of a gluten-free diet were suggested because patients with AIH and CD seem less prone to relapse after immunosuppressive withdrawal compared with patients with AIH unrelated to CD[[122](#_ENREF_122),[123](#_ENREF_123)].

Tables 4 and 5[34,76,118,122,128-143] exhibit different studies on the association between the two diseases. Active screening for CD in patients with AIH is strongly recommended[[115](#_ENREF_115),[124](#_ENREF_124),[125](#_ENREF_125)].

**Asymptomatic persistent elevation of aminotransferases**

Asymptomatic persistent elevation of aminotransferases unrelated to the usual causes of liver disease, such as nonalcoholic fat liver disease (NAFLD), alcohol abuse, viral infection, AIH, or rare genetic and metabolic disorders, is relatively common among patients undergoing outpatient hepatology[[144](#_ENREF_144)]. Studies suggest that celiac is the cause of liver disease in up to 10% of patients with cryptogenic hepatitis[[145](#_ENREF_145),[146](#_ENREF_146)]. On the other hand, hypertransaminasemia has been reported to be the cause in 9%–40% of individuals with CD[[116](#_ENREF_116),[147-151](#_ENREF_147)]. Abnormal aminotransferases in CD patients habitually normalize with a gluten-free diet. In patients with normal pretreatment liver enzyme levels, a significantly decreased serum levels with a gluten-free diet has been observed[[146](#_ENREF_146),[148](#_ENREF_148),[151](#_ENREF_151),[152](#_ENREF_152)].

**NON-ALCOHOLIC FATTY LIVER DISEASE**

Non-Alcoholic Fatty Liver Disease (NAFLD) is a major cause of chronic liver disease, with an estimated global prevalence of approximately 24%[[153](#_ENREF_153)]. High prevalence rates of obesity worldwide have influenced the economic and clinical burden of NAFLD[[154](#_ENREF_154)]. When metabolic syndrome is absent, NAFLD may be related to the concomitant presence of CD. Individuals with CD are at an increased risk of NAFLD compared with the general population[[155](#_ENREF_155)]. Among patients with hypertransaminasemia and biopsy-proven NAFLD, approximately 3%, in whom liver enzymes normalize after 6 mo of a gluten-free diet, present with CD[[156-159](#_ENREF_156)]. The association between NASH cirrhosis and refractory CD has been reported[[160](#_ENREF_160)]. In addition, a pathogenetic link has been proposed between NAFLD and CD involving gut permeability, microbiota, and diet, but the pathogenesis of liver steatosis in CD remains unclear[[161](#_ENREF_161),[162](#_ENREF_162)]. Considering the frequency of subclinical or silent presentations of CD, patients with NAFLD should be screened for celiac antibodies when steatohepatitis is present in the absence of metabolic risk factors and once other causes of liver disease are excluded[[161](#_ENREF_161), [162](#_ENREF_162)].

**HEPATITIS C**

HCV might be involved in the breaking of tolerance to self-antigens and thus in triggering autoreactivity. HCV has been implicated both in the triggering of autoimmune diseases and in the development of autoantibodies[[163](#_ENREF_163)].

The association between CD and hepatitis C is controversial and is yet to be elucidated. Although certain authors have reported a higher prevalence of CD among patients with hepatitis C[[164](#_ENREF_164),[165](#_ENREF_165)], this association could not be confirmed in low-prevalence regions[[166](#_ENREF_166)]. Nonetheless, the primary concern is for hepatitis C patients who will receive interferon-alpha (IFN)-based treatment because studies have reported severe cases of overt CD wherein receiving HCV treatment has led to the discontinuation of IFN[[163](#_ENREF_163)].

Like CD patients, individuals undergoing IFN-based treatment may present severe diarrhea, refractory anemia, and hypoferritinemia that may persist after treatment discontinuation[[167-169](#_ENREF_167)]. An early differential diagnosis facilitates the appropriate management of the underlying disease.

The heterogeneity of per capita incomes and health insurance systems across the world has determined the necessity to continue the use of IFN-based regimens in certain nations; however, newer drugs have become the first choice in most developed countries[[170](#_ENREF_170)]. Considering the aforementioned exposed possibilities, patients should be screened for CD antibodies before treatment, and those with positive serology should be selected for IFN-free treatment regimens. If newer drugs are unavailable, a gluten-free diet must be preemptively initiated, and patients should be carefully monitored during the IFN treatment period[[163](#_ENREF_163),[164](#_ENREF_164),[171](#_ENREF_171)]. It is important to emphasize that CD behavior with newer treatments is unknown, but it seems to be a safer alternative considering its mechanism of action.

**HEPATITIS B**

Studies that evaluated the coexistence of hepatitis B and CD have provided no evidence of an association between the two diseases. When serological screening for CD is performed in patients with chronic hepatitis B, EmA and tTG positivity vary in the ranges of 0%–8% and 0%–10%, respectively, and only 6% exhibit compatible histological changes[[172-175](#_ENREF_172)].

Several studies have reported lower efficacy of anti-HBV vaccines in individuals with CD[[176](#_ENREF_176),[177](#_ENREF_177)] , which has been confirmed by a recent meta-analysis[[178](#_ENREF_178)]. Therefore, novel immunization strategies have been proposed to ensure complete protection in such cases; these strategies include higher doses of vaccine and/or additional injection and intramuscular or preferably intradermal administration of booster doses of HBV vaccine because direct administration into the skin can activate an immune response mediated by dendritic cells through lower doses of antigen as opposed to intramuscular route of administration, which acts on cellular immune response. Moreover, administration of an additional booster dose of vaccine every 10 years is recommended for all patients with CD, including those who had developed anti-HBs with vaccine, because it has been shown that CD patients are predisposed to losing their memory antibodies[[179](#_ENREF_179), [180](#_ENREF_180)].

**NONCIRRHOTIC PORTAL HYPERTENSION**

CD has been repetitively reported in association with idiopathic noncirrhotic intrahepatic portal hypertension (NCIHPH)[[181-184](#_ENREF_181)], including a case of variceal hemorrage[[185](#_ENREF_185)]. It has been suggested that in CD, repetitive stimulation by antigens along the portal vein - as well as immune responses to these result in the development of idiopathic portal hypertension[[183](#_ENREF_183)]. In India, 10% of NCIHPH patients present with biopsy-proven CD[[186](#_ENREF_186)]. Moreover, the presence of CD predicts reduced transplant-free survival in such patients[[187](#_ENREF_187)]. Current data advises that all patients with unexplained portal hypertension should be screened for CD[[186](#_ENREF_186),[188](#_ENREF_188)], although there is no evidence that a gluten-free diet can change the evolution of the disease or improve survival.

**LIVER FAILURE AND CIRRHOSIS**

CD is at least twice more common in cirrhotic patients than in the general population[[189](#_ENREF_189)]. An association between cryptogenic cirrhosis and CD has been suggested[[190](#_ENREF_190),[191](#_ENREF_191)]. The absence of a common histological pattern of liver injury in patients with CD does not favor the assumption that this disease directly damages the liver[[192](#_ENREF_192)]. There have been case reports of patients with decompensated cirrhosis that reversed after the introduction of a gluten-free diet[[55](#_ENREF_55),[192](#_ENREF_192),[193](#_ENREF_193)]. These data suggest that all cirrhotic patients, particularly those with hypoalbuminemia and ascites[[189](#_ENREF_189),[192](#_ENREF_192)], shuld be screened for CD, because independent of the etiology of liver cirrhosis, patients with advanced liver disease and CD may benefit from a gluten-free diet.

**LIVER TRANSPLANTATION**

Prevalence of celiac antibodies was evaluated before and after transplantation; it was observed that patients with end-stage autoimmune liver disease, particularly those who are HLA-DQ2 or -DQ8 positive, had a high prevalence of celiac antibodies. Liver transplantation and/or immunosuppressive drugs used to prevent allograft rejection produced a significant decrease in serum levels of tTG and EmA antibody titers, but the clinical impact on CD outcomes, particularly on the risk of malignancy, remains unclear[[48](#_ENREF_48)]. The reason(s) behind the significant and sustained decrease/normalization of CD related antibody serology after liver transplantation, particularly in the presence of gluten challenge, is obscure[[194](#_ENREF_194)]. Regardless, pretransplant monitoring of CD-related autoantibodies could be helpful, particularly in HLA-DQ2- or HLA-DQ8-positive patients with end-stage autoimmune liver disease; moreover, the diagnosis of CD in this patient group, either before or after transplant, must be based on duodenal biopsies and response to gluten-free diet[[194](#_ENREF_194)].

Diarrhea following orthotropic liver transplantation in patients receiving mycophenolic acid therapy is a noteworthy entity because it causes significant morbidity and mortality. The significance of duodenal histopathological findings and prevalence of tTG has been evaluated in this setting. Celiac-like changes and an increase in apoptotic counts are common in duodenal biopsies. Increased awareness of the clinical difference between CD and mycophenolate mofetil (MMF)-induced villous atrophy is imperative because in the latter case, patients do not require a gluten-free diet and may instead need discontinuation of mycophenolic acid therapy[[195](#_ENREF_195)].

Active screening for CD is recommended in patients with liver diseases, particularly in those with autoimmune disorders, steatosis in the absence of metabolic syndrome, NCIHPH, cryptogenic cirrhosis, and in the context of liver transplantation. In HCV, diagnosis of CD can be important as a relative contraindication to interferon use. Gluten-free diet ameliorates the symptoms associated with CD and may prevent the emergence of other autoimmune diseases and bowel cancer; however, the associated liver disease may improve, remain the same, or progress.

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191 **Demir H**, Yüce A, Caglar M, Kale G, Kocak N, Ozen H, Gürakan F, Saltik-Temizel IN. Cirrhosis in children with celiac disease. *J Clin Gastroenterol* 2005; **39**: 630-633 [PMID: 16000933]

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193 **Roumeliotis N**, Hosking M, Guttman O. Celiac disease and cardiomyopathy in an adolescent with occult cirrhosis. *Paediatr Child Health* 2012; **17**: 437-439 [PMID: 24082804]

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**Table 1 Studies regarding the association of primary sclerosing cholangitis and celiac disease**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of article** | **No. of patients** | **Symptoms** | **Celiac antibodies** | **Duodenal biopsy** | **Response to gluten-free diet** | **Liver Biopsy** | **ERCP** | **Comorbidities** | **Country/Year** | **Ref.** |
| Case report | 3 | Weight loss, steatorrhoea | No | Typical1 | Yes | Yes | Yes | 2 Chronic ulcerative colitis | USA, 1988 | Hay *et al*[[35](#_ENREF_35)] |
| Abstract | 69 | Screening | 55% AGA (+) | 0/26 altered | - | - | - | - | Ireland, 1992 | MacMathuna *et al*[[46](#_ENREF_46)] |
| Case report | 1 | Diarrhea, weight loss, growth retardation | No | Typical1 | Yes | Yes | Yes | Chronic colitis  Turner’s syndrome | France, 1995 | Lacaille *et al*[[37](#_ENREF_37)] |
| Case report | 2 | Anemia | AGA IgA (+) | Villous atrophy | Yes | Yes | Yes | - | Italy, 1996 | Fracassetti *et al*[[36](#_ENREF_36)] |
| Case report | 1 | Diarrhea | No | Villous atrophy | Yes | Yes | Yes | Ulcerative colitis | Sweden, 1994 | Tysk[[41](#_ENREF_41)] |
| Case report | 1 | Folic acid deficiency | AGA (-)  EmA (+) | Typical1 |  | Yes | Yes | Ulcerative colitis  Hashimoto’s thyroiditis | France, 1994 | Brazier *et al*[[44](#_ENREF_44)] |
| Case report | 2 | Weight loss | EmA (+) | Typical1 | Yes | Yes | Yes | - | Italy, 1998 | Venturini *et al*[[49](#_ENREF_49)] |
| Case report | 1 | Anemia | No | Not mentioned | Not mentioned | Yes | Yes | Rheumatoid arthritis | UK, 2001 | Gow *et al*[[50](#_ENREF_50)] |
| Case series | 1 | Diarrhea  Protruding  abdomen  Failure to thrive | tTG (+)  EmA (-) | Villous atrophy | No adherence | Yes | Not mentioned | Not mentioned | Finland, 2002 | Kaukinen *et al*[[51](#_ENREF_51)] |
| Case report | 2 | Active screening for CD | EmA (+)  tTG (+) | Typical1 | Yes | Yes | Yes | Ulcerative colitis | Poland, 2002 | Habior *et al*[[43](#_ENREF_43)] |
| Prospective cohort | 61 | Active screening for CD | 1.6% EmA (+)  3.3% tTG (+) | 100% (1/1) Typical1 | Yes | Yes | Yes | - | Italy/Spain 2002 | Volta *et al*[[52](#_ENREF_52)] |
| Case report | 2 | Weight loss, steatorrhoea | EmA (+) | Villous atrophy | Yes | No | Yes | Ulcerative colitis | UK, 2003 | Wurm *et al*[[42](#_ENREF_42)] |
| Case report | 1 | Routine UDE | AGA (+)  EmA (+) | Typical1 | Yes | Yes | Yes | - | USA, 2004 | Al-Osaimi *et al*[[53](#_ENREF_53)] |
| Case report | 1 | Diarrhea | EmA (+) | Typical1 | Yes | Yes | Yes | - | Spain, 2005 | Cadahía *et al*[[54](#_ENREF_54)] |
| Prospective cohort | 155 | Screening | 3% EmA (+)  9% tTG (+) | - | - | - | - | - | USA, 2008 | Rubio-Tapia *et al*[[48](#_ENREF_48)] |
| Case report | 1 | Short stature and anemia | tTG (+) | Typical1 | Yes | Yes | No, MRC | - | Saudi Arabia, 2013 | Al-Hussaini *et al*[[55](#_ENREF_55)] |

1Vilous atrophy, crypt hyperplasia, lymphoplasmocytic infiltrate. ERCP: Endoscopic retrograde cholangio pancreatography; MRCP: Magnetic resonance cholangiopancreatography; AGA: Anti-gliadin antibody; EmA: Endomysial antibody; tTG: Tissue transglutaminase; CD: Celiac disease; UDE: Upper digestive endoscopy.

**Table 2 Case reports2 regarding the association of primary biliar cholangitis and celiac disease**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Number of patients** | **Symptoms** | **Celiac antibodies** | **Duodenal biopsy** | **Response to gluten-free diet** | **Liver Biopsy** | **AMA** | **Comorbidities** | **Country/Year** | **Ref.** |
| 4 | Weight loss, steatorrhea, anemia | No | Typical1 | Yes | Yes | (+) | serum-IgA deficiency | Scotland, 1978 | Logan *et al*[[58](#_ENREF_58)] |
| 1 | Weight loss, diarrhea, anorexia | No | Typical1 | Yes | Yes | No | - | UK, 1978 | Lee *et al*[[59](#_ENREF_59)] |
| 1 | Malabsorption | No | Typical1 | Poor adherence | Yes | (+) | - | Canada, 1979 | Iliffe *et al*[[60](#_ENREF_60)] |
| 1 | Diarrhea, anemia, short stature |  | Subtotal villous atrophy | Yes, but PBC was diagnosed afterwards | Yes | (+) | - | Ireland, 1983 | Shanahan *et al*[[62](#_ENREF_62)] |
| 1 | Dermatitis herpetiformis | No | Typical1 | Yes | Yes | (+) | Dermatitis herpetiformis | Norway, 1985 | Gabrielsen *et al*[[64](#_ENREF_64)] |
| 1 | Anemia | AGA (-) | Typical1 | Yes | Yes | (+) | Renal tubular acidosis, Sjögren Syndrome | Ireland, 1987 | Whitehead *et al*[[68](#_ENREF_68)] |
| 1 | Weight loss, diarrhea | No | Typical1 | Yes | Yes | (+) | - | USA, 1992 | Ginn and Workman[[69](#_ENREF_69)] |
| 1 | Weight loss, anemia | No | Typical1 | Yes | Yes | (+) | - | Canada, 1994 | Freeman[[70](#_ENREF_70)] |
| 1 | Diarrhea | No | Typical1 | Yes, but PBC was diagnosed afterwards | Yes | (+) | - | Germany, 1994 | Löhr *et al* |
| 1 | Diarrhea, weight loss | AGA (+) | Typical1 | No | Yes | (+) | - | Spain, 1994 | Gálvez *et al*[[97](#_ENREF_97)] |
| 1 | Weight loss, steatorrhea | AGA (+)  EmA (+) | Typical1 | Yes | Yes | (+) | Bacterial overgrowth | USA, 1998 | DiBaise *et al*[[71](#_ENREF_71)] |
| 1 | Anemia | EmA (+) | Typical | Yes | Yes | No | - | USA, 2002 | Sedlack *et al*[[84](#_ENREF_84)] |
| 1 | Diarrhea, weight loss | EmA (+) | Typical1 | Yes | Yes | (+) | Renal tubular acidosis, Sjögren Syndrome,  Graves’ disease | Italy, 2004 | Frachia *et al*[[98](#_ENREF_98)] |
| 1 | Inability to walk, anemia | AGA (-)  EmA (-) | Typical1 | Yes | Yes | (+) | Osteomalacic Myopathy | Turkey, 2008 | Demirag *et al*[[99](#_ENREF_99)] |
| 1 | Bone pain | AGA (+)  EmA (+)  tTG (+) | Typical1 | Yes | Yes | (+) | Fanconi syndrome | Paris, 2008 | Terrier *et al*[[100](#_ENREF_100)] |
| 1 | Dispepsia | tTG (+) | Typical1 | Yes | Yes | (+) | *Helicobacter pylori* | Italy, 2010 | Abevanoli *et al*[[83](#_ENREF_83)] |
| 1 | Diarrhea, bloating | EmA (+)  tTG (+) | Typical1 | Yes | Yes | (+) |  | India, 2013 | Lodh *et al*[[101](#_ENREF_101)] |

1Vilous atrophy, crypt hyperplasia, lymphoplasmocytic infiltrate; 2Case reports for which we had access to the full text. ERCP: Endoscopic Retrograde Cholangio Pancreatography; MRCP: Magnetic resonance cholangiopancreatography; AGA: Anti-gliadin antibody; EmA: Anti-endomysial antibody.

**Table 3 Research on screening celiac disease in patients with primary biliar cholangitis**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Screening method** | **Number of positive patients** | **Typical duodenal biopsy1,2** | **Response to gluten-free diet** | **Country/Year** | **Ref.** |
| Prospective | Duodenal biopsy | 5/26 (19.2%) | 19,2% | No improvement in liver biochemestry | Sweden, 1982 | Olsson *et al*[[61](#_ENREF_61)] |
| Retrospective | Previous diagnose | 2/18 (11.1%) | Not mentioned | No improvement in liver biochemestry or liver histology | Sweden, 1985 | Löfgren *et al*[[65](#_ENREF_65)] |
| Prospective | EmA IFI > 1:5 | 6/57 (11%) EmA (+) | 7% | No improvement in liver biochemestry | Ireland, 1997 | Dickey *et al*[[73](#_ENREF_73)] |
| Prospective cohort | AGA IgG IgA > 1 AU  IgA EmA IFI | 0/62 (0%) EmA (+)  11/62 (16%) AGA (+) | 0/0 | - | USA/Italy | Volta *et al*[[76](#_ENREF_76)] |
| Prospective | malabsorption, haematinic  deficiency, positive antigliadin antibody,  or CD family history | 4/67 (6%) | 4/67 (6%) | No improvement in liver biochemestry | UK, 1998 | Kingham and Parker[[72](#_ENREF_72)] |
| Prospective | AGA IgA > 25 AU/mL  IgG > 28 AU/mL  EmA IFI > 1:5 | 4/11 (36,4%) AGA IgA (+)  1/11 (9%) AGA IgG (+)  1/11 (9%) EmA (+) | 18% | - | Argentina, 1998 | Niveloni *et al*[[102](#_ENREF_102)] |
| Retrospective (stored sera) | EmA IFI > 1:5  tTG IgA ELISA > 140 AU/mL | * 10/378 (2.6%) EmA (+) + tTG (+) * 44/378 (11.6%) EmA (-) + tTG (+) | 1.3% | - | UK, 2000 | Gillett *et al*[[103](#_ENREF_103)] |
| Prospective | EmA IFI  tTG IgA > 10 IU | * 3/87 (3.4%) EmA (+) * 24/87 (27.5%) tTG (+) | 0/17 | - | Italy, 2002 | Floreani *et al*[[80](#_ENREF_80)] |
| Prospective | AGA IgA > 50 U/mL  AGA IgG > 50 U/mL  EmA IgA IFI ≥ 1:5  IgA tTG > 30 U/mL | * 13/62 (21%) AGA (+) * 0/62 EmA (+) * 6/62 (10%) tTG (+) | 0/10 | - | Greece, 2002 | Chatizicostas *et al*[[78](#_ENREF_78)] |
| Prospective cohort | EmA IFI > 1:5  tTG IgA > 7 AU  AGA IFI | * 7/173 (4%) EmA (+) * 5/173 (2.9%) tTG (+) | 7/7 | No improvement in liver biochemestry | Italy/Spain 2002. | Volta *et al*[[52](#_ENREF_52)] |
| Prospective cohort | IgA tTG > 7 AU  IgG anti-Ttg > 30 AU  EmA IFI | * 5/48 (10.4%) tTG (+) | - | - | Italy, 2003 | Bizzaro *et al*[[104](#_ENREF_104)] |
|  | tTG < 1:100  EmA IFI  AGA Elisa | * 7/115 (6.1%) tTG (+) * 1/115 (0.9%) EmA (+) * 8/115 (7.0%) AGA (+) | 1/8 | Duodenal histological improvement | Poland, 2003 | Habior *et al*[[105](#_ENREF_105)] |
| Prospective cohort | Six different ELISA tTG | * 28/105 (26.7%) tTG IgA (+) * 6/105 (5.7%) tTG IgG (+) | 100% EmA (+)  0% tTG (+) | - | Italy, 2006 | Bizzaro *et al*[[25](#_ENREF_25)] |

1Vilous atrophy, crypt hyperplasia, lymphoplasmocytic infiltrate; 2Only a small number of patients usually undergo intestinal biopsy. EmA: Anti-endomysial antibody; IIF: Indirect immunofluorescence; tTG: Anti-tissue transglutaminase; ELISA: Enzyme-linked immunosorbent assay.

**Table 4 Case reports regarding the association of autoimmune hepatitis and celiac disease**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Number of patients** | **Symptoms** | **AIH antibodies** | **Celiac antibodies** | **Duodenal biopsy** | **Response to gluten-free diet** | **Liver Biopsy** | **Comorbidities** | **Country/Year** | **Authors** |
| 1 | Anemia, infection | ASM 1:500  anti-vimentin 1:500 | * AGA IgA and IgG (+) * EmA (+) | Typical1 | Yes2 | Active chronic hepatitis | Erythroblastopenia | France, 2001 | Bridoux-Henno *et al*[[126](#_ENREF_126)] |
| 1 | Weight loss,  fatigue, abdominal pain, and diarrhea | ANA 1:1280, p-ANCA 1:2560, SMA 1:1200, LKM1 1:50 | Reticulin antibodies   * to 1:2000 * AGA IgA (+) | Typical1 | No, developed AIH despite of a gluten-free diet | Chronic inflammation  In the portal area and proliferation of the small hepatic  Ductules. Patchy degeneration of the liver cells. | Thyrotoxicosis | Finland, 2002 | Arvola *et al*[[34](#_ENREF_34)] |
| 2 | Diarrhea, abdominal enlargement and  failure to thrive. | ANA (+)  SMA (+)  antiactine (+) | ? | ? | case 1: poor response to a  gluten-free diet for the treatment of hepatitis; case  2: developed AIH despite the diet | Acute hepatitis  With portal bridging necrosis and fibrosis and a  Peri-portal inflammatory infiltrate of lymphocytes,  Plasma cells and neutrophils | - | Italy, 2003 | Leonardi *et al*[[127](#_ENREF_127)] |
| 1 | Elevated liver enzymes detected, hypesthesia of the left  foot, purpura and skin ulcers of both legs. | ANA (+) | AGA (+)  EmA (+) | Typical1 | Poor adherence to diet | Moderately active, chronic hepatitis with  Interface lesions and fibrosis of the portal tract,  Bile duct lesions and ductular  Proliferations. | cryoglobulinaemia | Switzerland, 2003 | Biecker *et al*[[128](#_ENREF_128)] |
| 1 | Jaundice and pale stools. | All negative. Score probable | AGA IgA (+)  AGA IgG (+)  Ema (+)  tTG IgA (+) | Typical1 | Liver disease progressed despite the diet | Moderate to severe  lobular inflammatory activity, mononuclear portal  inflammation, interface hepatitis, and portal and periportal  fibrosis with septae; rosetting of liver cells  and some giant cells. | .- | Italy, 2004 | Iorio *et al*[[129](#_ENREF_129)] |
| 1 | Ferropenia  and elevation of aminotransferases. | - | tTG (+) | Villous atrophy | Elevation of aminotranferases despite the diet. | severe ymphocytic inflammatory infiltrate  with slight increase of collagen in  portal tracts, foci of lobular necrosis and presence  acidophilus bodies |  | Peru, 2006 | Tagle *et al*[[130](#_ENREF_130)] |
| 1 | Anorexia, severe diarrhea, rapid loss of weight,  amenorrhea and anemia. | ANA (+)  SMA (+) | EmA (+)  tTG (+) | Villous atrophy | Developed cirrhosis despite the diet | Cirrhosis | Holmes-Adie syndrome | Hungary, 2006 | Csak *et al*[[131](#_ENREF_131)] |
| 1 | Jaundice | SMA (+) | AGA (+)  EmA (+)  tTG IgA (+)IgG (+) | Typical1 | Poor adherence to diet | Confirmed the diagnosis of acute AIH | Multiple sclerosis | Italy, 2008 | Ferro *et al*[[132](#_ENREF_132)] |
| 1 | Weight loss, anorexia, fatigue, and diarrhea. | ANA+++ | AGA IgA (+)  AGA IgG (+)  EmA (+)  tTG (+) | Typical1 | Liver disease was diagnosed on a gluten-free diet | Moderately active, chronic hepatitis with interface lesions  And fibrosis of the portal tracts, ductular injury and ductopenia. | Autoimmune cholangitis overlap, Autoimmune thyroiditis | Turkey, 2009 | Ozaslan *et al*[[133](#_ENREF_133)] |
| 1 | Malaise,  intermittent pyrexia and vomiting, an urticarial-vasculitic  rash and joint pains. | ANA, SMA, LKM-1, mitochondrial, anti-LC1,  anti-SLA/LP, parietal cell  antibodies, all negative | EmA (+)  tTG (+) | Typical1 | No, developed AIH despite of a gluten-free diet | Lymphoplasmacytic hepatitis (portal interface and lobular)  With moderate to marked activity and minimal  Chronicity (fibrosis stage 1/6). | - | UK, 2009 | Quail *et al*[[134](#_ENREF_134)] |
| 1 | Two miscarriages, iron deficiency anemia, osteopenia and alternating bowel habit, elevated aminotransferases | ANA +++, homogenou; SMA ++, anti-dsDNA  1:160 | * EmA 1:160 | Severe villous atrophy | Yes2 | Chronic  Active hepatitis with piecemeal necrosis and lympho-plasmacellular periportal infiltrate | Lupus | Italy, 2010 | Tovoli *et al*[[135](#_ENREF_135)] |
| 1 | anemia, weakness and high  aminotransferase levels | ANA 1:640,  SMA 1:320,  pANCA 1:160 | * EmA (+) * tTG (+) | Flat mucosa | No, developed acute liver failure | Severe fibrosis | None | Italy, 2013 | Volta *et al*[[136](#_ENREF_136)] |
| 1 | Miscontrol of diabetes  Altered liver enzymes | ANA 1:160 | * IgA tTG (+) * EmA (-) | Typical1 | Yes2 | Moderate interface hepatitis and chronic inflammatory infiltrate, and foci of necrosis | Autoimmune thyroiditis and type 1 diabetes | Spain, 2016 | Dieli-crimi *et al*[[137](#_ENREF_137)] |

1Vilous atrophy, crypt hyperplasia, lymphoplasmocytic infiltrate; 2Patient under corticosteroids and Azatioprine. AGA: Anti-gliadin antibody; EmA: Anti-endomysial antibody; tTG: Anti-tissue transglutaminase antibody; ANA: Anti-nuclear antibody; ASM: Anti-smooth muscle antibodies.

**Table 5 Research screening celiac disease in patients with autoimmune hepatitis**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Screening method** | **Number of positive patients** | **Typical duodenal biopsy1,2** | **Response to gluten-free diet** | **Country/Year** | **Authors** |
| Prospective cohort | AGA IgG IgA > 1 AU  IgA EmA IFI | 8/181 (4.4%) EmA (+)  7/181 (3.9%) AGA (+) | 5/5 | - | USA/Italy, 1998 | Volta *et al*[[76](#_ENREF_76)] |
| Retrospective | EmA  tTG IgA IgG | 3/47 (6.4%) | 3/3 | - | Italy, 2005 | Villalta *et al*[[138](#_ENREF_138)] |
| Retrospective | EmA  tTG IgA IgG | 19/140 (14%) | ? | No | Italy, 2008 | Caprai *et al*[[120](#_ENREF_120)] |
| Retrospective | AGA IgA, IgG  EmA IgA  tTG IgA | 5/40 (13%) | 5/5 | Mild decrease of transaminases, but never a complete normalization | Italy, 2008 | Diamanti *et al*[[139](#_ENREF_139)] |
| Retrospective | AGA IgA, IgG  EmA IgA  tTG IgA | 7/15 (47%) | 7/7 | - | Turkey, 2009 | Tosun *et al*[[140](#_ENREF_140)] |
| Retrospective | ? | 3/278 (1.1%) | ? | - | Germany, 2010 | Teufel *et al*[[141](#_ENREF_141)] |
| Prospective | IgA EmA IFI  tTG ELISA | 4/26 (15%) | 3/4 | - | Egypt, 2011 | El-Shabrawi *et al*[[142](#_ENREF_142)] |
| Retrospective | EmA IgA, IgG  tTG IgA, IgG | 15/79 (19%) | ? | All of the 15 patients achieved sustained  remission when treated with prednisone and azathioprine or cyclosporine | Italy, 2013 | Nastasio *et al*[[122](#_ENREF_122)] |
| Prospective | tTG IgA ELISA | 3/64 (4.7%) tTG (+) | 3/3 | - | Iran, 2014 | Najafi *et al*[[143](#_ENREF_143)] |
| Prospective | IgA EmA IIF  tTG ELISA  HLA DQ2 DQ8 | 6 previous diagnoses  10/460 tTG + EmA + HLA  (3.5%) | - | - | Netherlands, 2014 | vanGerven *et al*[[118](#_ENREF_118)] |

1Vilous atrophy, crypt hyperplasia, lymphoplasmocytic infiltrate; 2Only a small number of patients usually undergo intestinal biopsy. EmA: Anti-endomysial antibody; IIF: Indirect immunofluorescence; tTG: Anti-tissue transglutaminase; ELISA: Enzyme-linked immunosorbent assay.