

## To screen or not to screen? 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. CD 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 CD 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<sup>[1]</sup>. 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<sup>[2]</sup>. Its clinical presentation can comprise varied symptoms, including musculoskeletal, neurological, endocrine, kidney, heart, lung, and liver manifestations, concomitant with other autoimmune diseases and malignancies<sup>[1,3-5]</sup>.

The serological diagnosis of CD is based on the presence of the following antibodies: antigliadin (AGA) immunoglobulin A (IgA) and immunoglobulin G (IgG), antiendomysial 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<sup>[6,7]</sup>. 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<sup>[8]</sup>. However, EmA antibody is an extremely specific marker of mucosal damage in untreated patients and has been indicated as a useful diagnostic tool<sup>[7,9]</sup>. 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<sup>[10]</sup>. 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<sup>[7,9,11]</sup>. Selective IgA deficiency affects approximately 2%-5% of patients diagnosed with CD<sup>[12]</sup>. 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<sup>[13]</sup>. A decade ago, anti-DGP had been introduced as a diagnostic tool for CD<sup>[14]</sup>. 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<sup>[15]</sup>. Nowadays, both DGP and tTG antibodies are considered as serological hallmarks of CD<sup>[16]</sup>. There is new serological biomarker for CD available: the tTg neo-epitope (tTg-neo), with high sensitivity and specificity<sup>[17]</sup>. tTg-neo IgG has demonstrated better performance when compared to the tTg-

IgA, and has been recommended as a novel diagnostic technique for CD<sup>[17,18]</sup>. Because no diagnostic test is 100% effective in diagnosing CD, a combined search for celiac antibodies is recommended for optimal diagnostic accuracy<sup>[19,20]</sup>. Hence, combined antibody kits have been made commercially available and have demonstrated excellent diagnostic performance; they may soon be added to the procedures in diagnostic flow charts<sup>[21]</sup>.

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<sup>[9]</sup>. It is important to point out that positive serology with normal histology, formerly termed latent CD<sup>[22]</sup>, are now defined as potential CD<sup>[23]</sup>. The American College of Gastroenterology recommends human leukocyte antigen (HLA) testing for DQ2 and DQ8 when there is disagreement between serological and histological results<sup>[24]</sup>; however, certain authors perform HLA determination in patients with positive anti-tTG and negative EmA to identify false-positive tTG results<sup>[25]</sup>.

Liver involvement in CD has been widely described in case reports and case series in the past four decades<sup>[26]</sup>. In London in 1973, Thatcher *et al.*<sup>[27]</sup> 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<sup>[28]</sup>, but architectural changes in the liver, including cirrhosis and biliary lesions such as primary biliary cholangitis (PBC), have also been described<sup>[29]</sup>.

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<sup>[30]</sup>. 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<sup>[31,32]</sup>. The development of autoimmune disorders in CD has been related to the age at diagnosis<sup>[33]</sup>. 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<sup>[33]</sup>. Nonetheless, AIH has been reported in patients with treated CD<sup>[34]</sup>.

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.

## LITERATURE SEARCH

We performed a review for liver involvement in CD by conducting a broad search for MeSH terms "celiac

**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, steatorrhea	No	Typical <sup>1</sup>	Yes	Yes	Yes	2 Chronic ulcerative colitis	United States, 1988	Hay <i>et al</i> <sup>[35]</sup>
Abstract	69	Screening	55% AGA (+)	0/26 altered	-	-	-	-	Ireland, 1992	MacMathuna <i>et al</i> <sup>[46]</sup>
Case report	1	Diarrhea, weight loss, growth retardation	No	Typical <sup>1</sup>	Yes	Yes	Yes	Chronic colitis Turner's syndrome	France, 1995	Lacaille <i>et al</i> <sup>[37]</sup>
Case report	2	Anemia	AGA IgA (+)	Villous atrophy	Yes	Yes	Yes	-	Italy, 1996	Fracassetti <i>et al</i> <sup>[36]</sup>
Case report	1	Diarrhea	No	Villous atrophy	Yes	Yes	Yes	Ulcerative colitis	Sweden, 1994	Tysk <sup>[41]</sup>
Case report	1	Folic acid deficiency	AGA (-) EmA (+)	Typical <sup>1</sup>	-	Yes	Yes	Ulcerative colitis Hashimoto's thyroiditis	France, 1994	Brazier <i>et al</i> <sup>[44]</sup>
Case report	2	Weight loss	EmA (+)	Typical <sup>1</sup>	Yes	Yes	Yes	-	Italy, 1998	Venturini <i>et al</i> <sup>[39]</sup>
Case report	1	Anemia	No	Not mentioned	Not mentioned	Yes	Yes	Rheumatoid arthritis	United Kingdom, 2001	Gow <i>et al</i> <sup>[50]</sup>
Case series	1	Diarrhea Protruding abdomen Failure to thrive	tTG (+) EmA (-)	Villous atrophy	No adherence	Yes	Not mentioned	Not mentioned	Finland, 2002	Kaukinen <i>et al</i> <sup>[51]</sup>
Case report	2	Active screening for CD	EmA (+) tTG (+)	Typical <sup>1</sup>	Yes	Yes	Yes	Ulcerative colitis	Poland, 2002	Habior <i>et al</i> <sup>[43]</sup>
Prospective cohort	61	Active screening for CD	1.6% EmA (+) 3.3% tTG (+)	100% (1/1) Typical <sup>1</sup>	Yes	Yes	Yes	-	Italy/Spain 2002	Volta <i>et al</i> <sup>[52]</sup>
Case report	2	Weight loss, steatorrhea	EmA (+)	Villous atrophy	Yes	No	Yes	Ulcerative colitis	United Kingdom, 2003	Wurm <i>et al</i> <sup>[42]</sup>
Case report	1	Routine UDE	AGA (+) EmA (+)	Typical <sup>1</sup>	Yes	Yes	Yes	-	United States, 2004	Al-Osaimi <i>et al</i> <sup>[53]</sup>
Case report	1	Diarrhea	EmA (+)	Typical <sup>1</sup>	Yes	Yes	Yes	-	Spain, 2005	Cadahia <i>et al</i> <sup>[54]</sup>
Prospective cohort	155	Screening	3% EmA (+) 9% tTG (+)	-	-	-	-	-	United States, 2008	Rubio-Tapia <i>et al</i> <sup>[48]</sup>
Case report	1	Short stature and anemia	tTG (+)	Typical <sup>1</sup>	Yes	Yes	No, MRC	-	Saudi Arabia, 2013	Al-Hussaini <i>et al</i> <sup>[55]</sup>

<sup>1</sup>Vilous 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.

disease" and "PSC", "primary biliary cirrhosis", "AIH", "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.

## PSC

In 1988, Hay *et al*<sup>[35]</sup> 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<sup>[35-37]</sup>.

The association between ulcerative colitis and PSC has been well established<sup>[38]</sup>. CD combined with ulcerative colitis has also been reported<sup>[39,40]</sup>. Certain cases described associations among ulcerative colitis,

CD, and PSC, which is very rare<sup>[35,37,41-43]</sup>. Brazier *et al.*<sup>[44]</sup> reported an association between ulcerative colitis, PSC, CD, and Hashimoto's thyroiditis wherein improvements were observed in liver biochemistry and histology with a gluten-free diet.

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<sup>[45]</sup>. Although this has not been specifically studied, in a previous study, patients with high AGA titers demonstrated advanced portal fibrosis<sup>[46]</sup>.

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<sup>[47]</sup>. MacMathuna *et al.*<sup>[46]</sup> 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.*<sup>[48]</sup> 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<sup>[47]</sup>. In clinical settings, active screening for celiac antibodies in PSC patients cannot be routinely recommended (Table 1<sup>[35-37,41-44,46-55]</sup>).

## PBC

Recently, the governing boards of both the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases have approved the change of nomenclature for PBC from "primary biliary cirrhosis" to "PBC"<sup>[56,57]</sup>.

The first report of CD in patients with PBC was published in 1978<sup>[58]</sup>. 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<sup>[59-71]</sup> (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 United Kingdom<sup>[72]</sup>. 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<sup>[72]</sup>. Accordingly, in Ireland, Dickey *et al.*<sup>[73]</sup> reported that the prevalence of CD in patients with PBC is at least 10 times that in the general population. Sorensen *et al.*<sup>[74]</sup> 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<sup>[75]</sup>, Italy<sup>[76,77]</sup>, and Greece<sup>[78]</sup>, where researchers have failed to demonstrate an increased risk of CD in patients with PBC. Dickey *et al.*<sup>[79]</sup> searched for liver abnormalities in 129 patients with CD and none of the patients were positive for AMA.

According to Bizzaro *et al.*<sup>[25]</sup>, 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.*<sup>[80]</sup> 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. 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<sup>[25,80]</sup>. 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<sup>[11]</sup>. 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<sup>[81]</sup>. 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<sup>[58,61,72]</sup>. The Neuberger report of two patients with PBC who had been referred to their liver unit in the United Kingdom 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<sup>[82]</sup>. Abenavoli *et al.*<sup>[83]</sup> reported a case of association among CD, PBC, and *H. pylori* infection, wherein a short period of gluten-

**Table 2** Case reports<sup>2</sup> 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	Typical <sup>1</sup>	Yes	Yes	(+)	serum-IgA deficiency	Scotland, 1978	Logan <i>et al</i> <sup>[58]</sup>
1	Weight loss, diarrhea, anorexia	No	Typical <sup>1</sup>	Yes	Yes	No	-	United Kingdom, 1978	Lee <i>et al</i> <sup>[59]</sup>
1	Malabsorption	No	Typical <sup>1</sup>	Poor adherence	Yes	(+)	-	Canada, 1979	Iliffe <i>et al</i> <sup>[60]</sup>
1	Diarrhea, anemia, short stature	No	Subtotal villous atrophy	Yes, but PBC was diagnosed afterwards	Yes	(+)	-	Ireland, 1983	Shanahan <i>et al</i> <sup>[62]</sup>
1	Dermatitis herpetiformis	No	Typical <sup>1</sup>	Yes	Yes	(+)	Dermatitis herpetiformis	Norway, 1985	Gabrielsen <i>et al</i> <sup>[64]</sup>
1	Anemia	AGA (-)	Typical <sup>1</sup>	Yes	Yes	(+)	Renal tubular acidosis, Sjögren Syndrome	Ireland, 1987	Whitehead <i>et al</i> <sup>[68]</sup>
1	Weight loss, diarrhea	No	Typical <sup>1</sup>	Yes	Yes	(+)	-	United States, 1992	Ginn <i>et al</i> <sup>[69]</sup>
1	Weight loss, anemia	No	Typical <sup>1</sup>	Yes	Yes	(+)	-	Canada, 1994	Freeman <sup>[70]</sup>
1	Diarrhea	No	Typical <sup>1</sup>	Yes, but PBC was diagnosed afterwards	Yes	(+)	-	Germany, 1994	Löhr <i>et al</i> <sup>[196]</sup>
1	Diarrhea, weight loss	AGA (+)	Typical <sup>1</sup>	No	Yes	(+)	-	Spain, 1994	Gálvez <i>et al</i> <sup>[97]</sup>
1	Weight loss, steatorrhea	AGA (+) EmA (+)	Typical <sup>1</sup>	Yes	Yes	(+)	Bacterial overgrowth	United States, 1998	DiBaise <i>et al</i> <sup>[71]</sup>
1	Anemia	EmA (+)	Typical	Yes	Yes	No	-	United States, 2002	Sedlack <i>et al</i> <sup>[84]</sup>
1	Diarrhea, weight loss	EmA (+)	Typical <sup>1</sup>	Yes	Yes	(+)	Renal tubular acidosis, Sjögren Syndrome, Graves' disease	Italy, 2004	Fracchia <i>et al</i> <sup>[98]</sup>
1	Inability to walk, anemia	AGA (-) EmA (-)	Typical <sup>1</sup>	Yes	Yes	(+)	Osteomalacic Myopathy	Turkey, 2008	Demirag <i>et al</i> <sup>[99]</sup>
1	Bone pain	AGA (+) EmA (+) tTG (+)	Typical <sup>1</sup>	Yes	Yes	(+)	Fanconi syndrome	Paris, 2008	Terrier <i>et al</i> <sup>[100]</sup>
1	Dispepsia	tTG (+)	Typical <sup>1</sup>	Yes	Yes	(+)	<i>Helicobacter pylori</i>	Italy, 2010	Abenavoli <i>et al</i> <sup>[83]</sup>
1	Diarrhea, bloating	EmA (+) tTG (+)	Typical <sup>1</sup>	Yes	Yes	(+)	-	India, 2013	Lodh <i>et al</i> <sup>[101]</sup>

<sup>1</sup>Vilous atrophy, crypt hyperplasia, lymphoplasmocytic infiltrate; <sup>2</sup>Case 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; tTG: Tissue transglutaminase.

free diet 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*<sup>[84]</sup> 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<sup>[58,71,85]</sup>. 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<sup>[86]</sup>. Intestinal permeability is increased and disrupted intestinal barrier function has been reported<sup>[87,88]</sup>. 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<sup>[89]</sup>. It is suggested that immune complexes are formed with molecular mimicry, and this mechanism mediates tissue damage; however, no specific antigen has been identified<sup>[90]</sup>. It has been proposed that chronic bacterial exposure may initiate the development of antibodies, which then cross react with human antigens in PBC patients<sup>[91,92]</sup>. 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<sup>[90]</sup>. These effector cells might then recognize an attack on a patient's histocompatibility antigens, which

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

Study	Screening method	Number of positive patients	Typical duodenal biopsy <sup>1,2</sup>	Response to gluten-free diet	Country, year	Ref.
Prospective	Duodenal biopsy	5/26 (19.2%)	19, 2%	No improvement in liver biochemistry	Sweden, 1982	Olsson <i>et al</i> <sup>[61]</sup>
Retrospective	Previous diagnose	2/18 (11.1%)	Not mentioned	No improvement in liver biochemistry or liver histology	Sweden, 1985	Löfgren <i>et al</i> <sup>[65]</sup>
Prospective	EmA IFI > 1:5	6/57 (11%) EmA (+)	7%	No improvement in liver biochemistry	Ireland, 1997	Dickey <i>et al</i> <sup>[73]</sup>
Prospective cohort	AGA IgG IgA > 1 AU IgA EmA IFI	0/62 (0%) EmA (+) 11/62 (16%) AGA (+)	0/0	-	United States/ Italy	Volta <i>et al</i> <sup>[76]</sup>
Prospective	malabsorption, haematinic deficiency, positive antigliadin antibody, or CD family history	4/67 (6%)	4/67 (6%)	No improvement in liver biochemistry	United Kingdom, 1998	Kingham <i>et al</i> <sup>[72]</sup>
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 <i>et al</i> <sup>[102]</sup>
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 (+)	1.30%	-	United Kingdom, 2000	Gillett <i>et al</i> <sup>[103]</sup>
Prospective	EmA IFI tTG IgA > 10 IU	3/87 (3.4%) EmA (+) 24/87 (27.5%) tTG (+)	0/17	-	Italy, 2002	Floreni <i>et al</i> <sup>[80]</sup>
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	Chatzicostas <i>et al</i> <sup>[78]</sup>
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 biochemistry	Italy/Spain 2002.	Volta <i>et al</i> <sup>[52]</sup>
Prospective cohort	IgA tTG > 7 AU IgG anti-Ttg > 30 AU EmA IFI tTG < 1:100 EmA IFI AGA Elisa	5/48 (10.4%) tTG (+) 7/115 (6.1%) tTG (+) 1/115 (0.9%) EmA (+) 8/115 (7.0%) AGA (+)	- 1/8	- Duodenal histological improvement	Italy, 2003 Poland, 2003	Bizzaro <i>et al</i> <sup>[104]</sup> Habior <i>et al</i> <sup>[105]</sup>
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 <i>et al</i> <sup>[25]</sup>

<sup>1</sup>Vilous atrophy, crypt hyperplasia, lymphoplasmocytic infiltrate; <sup>2</sup>Only 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; CD: Celiac disease; AGA: Anti-gliadin antibody.

are present in high concentrations in biliary as well as intestinal epithelial cells<sup>[90]</sup>. 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<sup>[93,94]</sup>.

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<sup>[95,96]</sup> (Table 3<sup>[25,52,61,65,72-73,76,78,80,102-105]</sup>).

## AIH

AIH has been classified into two or three different subtypes according to the distribution of autoantibodies and clinical presentation<sup>[106]</sup>. Although not all authors adopt this classification<sup>[107]</sup>, type 1 AIH (the most frequent form) is characterized by the presence of SMA and/or ANA<sup>[106,108]</sup>. 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<sup>[109,110]</sup>. 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)<sup>[106]</sup>. 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 and consequently termed as anti-SLA/LP antibodies<sup>[111]</sup>. Thus, initial studies regarding the seroprevalence of CD in AIH considered 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<sup>[112]</sup>.

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<sup>[110,113]</sup>. In the presence of CD and altered liver enzymes, antiactin positivity may reflect villous atrophy and may not be diagnostic of AIH<sup>[114]</sup>.

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<sup>[115]</sup>. Coexistence of the two diseases has been stated in EASL practice guidelines<sup>[106]</sup>. The prevalence of AIH in adults with CD is 1.6 and in children is 2%<sup>[116,117]</sup> whereas CD in patients with AIH is ten times more seroprevalent than that in the general population<sup>[118]</sup>. A similar tendency has been observed in children<sup>[117,119,120]</sup>. The clinical impact of a gluten-free diet on the outcomes of liver disorders in patients with AIH is still uncertain<sup>[114,119,121]</sup>. 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<sup>[122,123]</sup>.

Tables 4 and 5<sup>[34,76,118,122,124-141]</sup> exhibit different studies on the association between the two diseases. Active screening for CD in patients with AIH is strongly recommended<sup>[115,142,143]</sup>.

#### **Asymptomatic persistent elevation of aminotransferases**

Asymptomatic persistent elevation of aminotransferases unrelated to the usual causes of liver disease, such as nonalcoholic fatty liver disease (NAFLD), alcohol abuse, viral infection, AIH, or rare genetic and metabolic disorders, is relatively common among patients undergoing outpatient hepatology<sup>[144]</sup>. Studies suggest that celiac is the cause of liver disease in up to 10% of patients with cryptogenic hepatitis<sup>[145,146]</sup>. On the other hand, hypertransaminasemia has been reported to be the cause in 9%-40% of individuals with CD<sup>[116,147-151]</sup>. 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<sup>[146,148,151,152]</sup>.

## **NAFLD**

NAFLD is a major cause of chronic liver disease, with an estimated global prevalence of approximately 24%<sup>[153]</sup>. High prevalence rates of obesity worldwide have influenced the economic and clinical burden of NAFLD<sup>[154]</sup>. 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<sup>[155]</sup>. 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<sup>[156-159]</sup>. The association between NASH

and refractory CD has been reported<sup>[160]</sup>. 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<sup>[161,162]</sup>. 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<sup>[161,162]</sup>.

## **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<sup>[163]</sup>.

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<sup>[164,165]</sup>, this association could not be confirmed in low-prevalence regions<sup>[166]</sup>. 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<sup>[163]</sup>.

Like CD patients, individuals undergoing IFN-based treatment may present severe diarrhea, refractory anemia, and hypoferritinemia that may persist after treatment discontinuation<sup>[167-169]</sup>. 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<sup>[170]</sup>. 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<sup>[163,164,171]</sup>. 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

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 ANA 1:1280 p-ANCA 1:2560, SMA 1:1200, LKM1 1:50	AGA IgA and IgG (+) EmA (+)	Typical <sup>1</sup>	Yes <sup>2</sup>	Active chronic hepatitis	Erythroblastopenia	France, 2001	Bridoux-Henno <i>et al</i> <sup>[124]</sup>
1	Weight loss, fatigue, abdominal pain, and diarrhea	ANA 1:1280, SMA 1:1200, LKM1 1:50	Reticulin antibodies to 1:2000 AGA IgA (+)	Typical <sup>1</sup>	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.	Thyrototoxicosis	Finland, 2002	Arvola <i>et al</i> <sup>[34]</sup>
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	With portal bridging necrosis and fibrosis and a Peri-portal inflammatory infiltrate of lymphocytes, Plasma cells and neutrophils	-	Italy, 2003	Leonardi <i>et al</i> <sup>[125]</sup>
1	Elevated liver enzymes detected, hypesthesia of the left foot, purpura and skin ulcers of both legs.	ANA (+)	AGA (+)	Typical <sup>1</sup>	Poor adherence to diet	Moderately active, chronic hepatitis with	Cryoglobulinaemia	Switzerland, 2003	Biecker <i>et al</i> <sup>[126]</sup>
1	Jaundice and pale stools.	All negative. Score probable	AGA IgA (+) AGA IgG (+) EmA (+) tIG IgA (+)	Typical <sup>1</sup>	Liver disease progressed despite the diet	Interface lesions and fibrosis of the portal tract, Bile duct lesions and ductular Proliferations. 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 <i>et al</i> <sup>[127]</sup>
1	Ferropenia and elevation of aminotransferases.	-	tIG (+)	Villous atrophy	Elevation of aminotransferases despite the diet.	severe lymphocytic inflammatory infiltrate with slight increase of collagen in portal tracts, foci of lobular necrosis and presence acdophilus bodies	-	Peru, 2006	Tagle <i>et al</i> <sup>[128]</sup>
1	Anorexia, severe diarrhea, rapid loss of weight, amenorrhea and anemia.	ANA (+) SMA (+) SMA (+)	EmA (+) tIG (+) AGA (+) EmA (+)	Villous atrophy	Developed cirrhosis despite the diet	Cirrhosis	Holmes-Adie syndrome	Hungary, 2006	Csak <i>et al</i> <sup>[129]</sup>
1	Jaundice	SMA (+) SMA (+)	tIG IgA (+) IgG (+)	Typical <sup>1</sup>	Poor adherence to diet	Confirmed the diagnosis of acute AIH	Multiple sclerosis	Italy, 2008	Ferrò <i>et al</i> <sup>[130]</sup>



1	Weight loss, anorexia, fatigue, and diarrhea.	ANA+++	AGA IgA (+) AGA IgG (+)	Typical <sup>1</sup>	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 <i>et al</i> <sup>[131]</sup>
1	Malaise, intermittent pyrexia and vomiting, an urticarial-vasculitic rash and joint pains. Two miscarriages, iron deficiency anemia, osteopenia and alternating bowel habit, elevated aminotransferases	ANA, SMA, LKM-1, mitochondrial, anti-LCI, anti-SLA/LP, parietal cell	EmA (+) tTG (+) EmA (+)	Typical <sup>1</sup>	No, developed AIH despite of a gluten-free diet	Lymphoplasmacytic hepatitis (portal interface and lobular)	-	United Kingdom, 2009	Quail <i>et al</i> <sup>[133]</sup>
1	anemia, weakness and high aminotransferase levels	antibodies, all negative ANA +++, homogeneous; SMA ++, anti-4sDNA 0.1527778	EmA 1:160	Severe villous atrophy	Yes <sup>2</sup>	Chronic (fibrosis stage 1/6).	Lupus	Italy, 2010	Tovoli <i>et al</i> <sup>[133]</sup>
1	Miscontrol of diabetes Altered liver enzymes	ANA 1:640, SMA 1:320, pANCA 1:160 ANA 1:160	EmA (+) tTG (+) IgA tTG (+) EmA (-)	Flat mucosa Typical <sup>1</sup>	No, developed acute liver failure	Active hepatitis with piecemeal necrosis and lympho-plasmacellular periportal infiltrate Severe fibrosis	None	Italy, 2013	Volta <i>et al</i> <sup>[134]</sup>
1					Yes <sup>2</sup>	Moderate interface hepatitis and chronic inflammatory infiltrate, and foci of necrosis	Autoimmune thyroiditis and type 1 diabetes	Spain, 2016	Dieli-crimi <i>et al</i> <sup>[135]</sup>

<sup>1</sup>Vilous atrophy, crypt hyperplasia, lymphoplasmacytic infiltrate; <sup>2</sup>Patient under corticosteroids and azathioprine. AGA: Anti-gliadin antibody; EmA: Anti-endomysial antibody; tTG: Anti-tissue transglutaminase antibody; ANA: Anti-nuclear antibody; ASM: Anti-smooth muscle antibodies; anti-LP: Antibodies against liver pancreas; anti-SLA: Antibodies against soluble liver antigen.

compatible histological changes<sup>[172-175]</sup>.

Several studies have reported lower efficacy of anti-HBV vaccines in individuals with CD<sup>[176,177]</sup>, which has been confirmed by a recent meta-analysis<sup>[178]</sup>. 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<sup>[179,180]</sup>.

## NONCIRRHOTIC PORTAL HYPERTENSION

CD has been repetitively reported in association with idiopathic noncirrhotic intrahepatic portal hypertension (NCIHPH)<sup>[181-184]</sup>, including a case of variceal hemorrhage<sup>[185]</sup>. 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<sup>[183]</sup>. In India, 10% of NCIHPH patients present with biopsy-proven CD<sup>[186]</sup>. Moreover, the presence of CD predicts reduced transplant-free survival in such patients<sup>[187]</sup>. Current data advises that all patients with unexplained portal hypertension should be screened for CD<sup>[186,188]</sup>, although there is no evidence that

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

Study	Screening method	Number of positive patients	Typical duodenal biopsy <sup>1,2</sup>	Response to gluten-free diet	Country, year	Authors
Prospective cohort	AGA IgG IgA > 1 AU	8/181 (4.4%) EmA (+)	5/5	-	United States/ Italy, 1998	Volta <i>et al</i> <sup>[76]</sup>
Retrospective	IgA EmA IFI	7/181 (3.9%) AGA (+)	3/3	-	Italy, 2005	Villalta <i>et al</i> <sup>[136]</sup>
Retrospective	tTG IgA IgG	3/47 (6.4%)	?	No	Italy, 2008	Caprai <i>et al</i> <sup>[120]</sup>
Retrospective	EmA	19/140 (14%)	?	Mild decrease of transaminases, but never a complete normalization	Italy, 2008	Diamanti <i>et al</i> <sup>[137]</sup>
Retrospective	tTG IgA IgG	5/40 (13%)	5/5	-	Turkey, 2009	Tosun <i>et al</i> <sup>[138]</sup>
Retrospective	AGA IgA, IgG	7/15 (47%)	7/7	-	Turkey, 2009	Tosun <i>et al</i> <sup>[138]</sup>
Retrospective	EmA IgA	7/15 (47%)	7/7	-	Turkey, 2009	Tosun <i>et al</i> <sup>[138]</sup>
Retrospective	tTG IgA	7/15 (47%)	7/7	-	Turkey, 2009	Tosun <i>et al</i> <sup>[138]</sup>
Retrospective	?	3/278 (1.1%)	?	-	Germany, 2010	Teufel <i>et al</i> <sup>[139]</sup>
Prospective	IgA EmA IFI	4/26 (15%)	3/4	-	Egypt, 2011	El-Shabrawi <i>et al</i> <sup>[140]</sup>
Retrospective	tTG ELISA	15/79 (19%)	?	All of the 15 patients achieved sustained remission when treated with prednisone and azathioprine or cyclosporine	Italy, 2013	Nastasio <i>et al</i> <sup>[122]</sup>
Retrospective	EmA IgA, IgG	15/79 (19%)	?	All of the 15 patients achieved sustained remission when treated with prednisone and azathioprine or cyclosporine	Italy, 2013	Nastasio <i>et al</i> <sup>[122]</sup>
Retrospective	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 <i>et al</i> <sup>[122]</sup>
Prospective	tTG IgA ELISA	3/64 (4.7%) tTG (+)	3/3	-	Iran, 2014	Najafi <i>et al</i> <sup>[141]</sup>
Prospective	IgA EmA IIF	6 previous diagnoses	-	-	Netherlands, 2014	van Gerven <i>et al</i> <sup>[118]</sup>
Prospective	tTG ELISA	10/460 tTG + EmA + HLA	-	-	Netherlands, 2014	van Gerven <i>et al</i> <sup>[118]</sup>
Prospective	HLA DQ2 DQ8	-3.50%	-	-	Netherlands, 2014	van Gerven <i>et al</i> <sup>[118]</sup>

<sup>1</sup>Vilous atrophy, crypt hyperplasia, lymphoplasmocytic infiltrate; <sup>2</sup>Only 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; HLA: Human leukocyte antigen; AGA: Anti-gliadin antibody.

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<sup>[189]</sup>. An association between cryptogenic cirrhosis and CD has been suggested<sup>[190,191]</sup>. 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<sup>[192]</sup>. There have been case reports of patients with decompensated cirrhosis that reversed after the introduction of a gluten-free diet<sup>[55,192,193]</sup>. These data suggest that all cirrhotic patients, particularly those with hypoalbuminemia and ascites<sup>[189,192]</sup>, should 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<sup>[48]</sup>. 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<sup>[194]</sup>. 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<sup>[194]</sup>.

Diarrhea following orthotopic 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-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<sup>[195]</sup>.

Active screening for CD is recommended in pa-

tients 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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