

Hepatic manifestations of celiac disease

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Abstract: Different hepatic and biliary tract disorders may occur with celiac disease. Some have been hypothesized to share genetic or immunopathogenetic factors, such as primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis. Other hepatic changes in celiac disease may occur with malnutrition resulting from impaired nutrient absorption, including hepatic steatosis. In addition, celiac disease may be associated with rare hepatic complications, such as hepatic T-cell lymphoma.

Keywords: celiac disease, autoimmune liver disease, primary biliary cirrhosis, fatty liver, gluten-free diet

Introduction

Several hepatobiliary disorders occur in celiac disease, a genetically-based small bowel disorder that resolves with the complete restriction of dietary gluten.¹ Almost three decades ago, changes in the liver were first recognized in celiac disease.² Later, these observations were prospectively confirmed and findings were extended to effects induced by treatment with a gluten-free diet.³ In some, hepatic changes entirely reversed after a gluten-free diet, while in others, clinically significant liver disease was not corrected by diet alone.³ Overall recognition of celiac disease has been improved in recent years, in large part related to development and application of modern serological assays for celiac screening.⁴⁻⁶ Likely, as a result, more precise estimates of overall liver disease burden in celiac disease will emerge. Indeed, in a recent extensive population-based study from Sweden, individuals with celiac disease were found to be at increased risk for both prior and subsequent liver disease, however, the risk of liver transplantation was not increased.⁷

If unexplained elevations of liver enzymes occur, almost 10% will prove to have celiac disease.^{8,9} In 55 patients with increased liver chemistry tests, in the absence of other known cause, endomysial and gliadin antibodies were examined.⁸ Five patients were sero-positive and small bowel biopsies showed changes of celiac disease that responded to a gluten-free diet. In a further investigation, liver biopsies revealed a non-specific inflammatory process and liver chemistry tests normalized with a gluten-free diet. In 140 patients with chronic elevation of transaminase values, gliadin and endomysial antibodies were positive in 13 cases.⁹ After one year on a gluten-free diet, 12 had normalization of liver enzyme tests.⁹

In already documented celiac disease, abnormal liver enzyme tests may also be present.^{2,10-12} Elevated liver enzymes were recorded in 30 of 75 patients, or almost 40%.²

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Others showed increased levels in 39 of 65 children, or about 60%.¹⁰ Later, about 50% of celiacs had increased liver enzyme values.¹¹ In some, a liver biopsy revealed an entirely non-specific inflammatory process although a more specific label of “chronic active hepatitis” was provided in five of 37 patients, or 13.5%. Finally, 158 consecutive adults with celiac disease were reported with 42% having abnormal liver enzyme levels. A gluten-free diet ranging from 1–10 years resulted in complete normalization of liver chemistry tests in 95%.¹²

Not all studies have demonstrated completely normal liver chemistry results after institution of a gluten-free diet in all patients. This may reflect, in part, the heterogeneous nature of celiac disease. For instance, in some, involvement along the length of the small bowel may be extensive, while in others, changes may be limited to the proximal small bowel alone. In some studies, different durations of exposure to a gluten-free diet may have been critical before liver chemistry tests were observed to normalize. Other factors may play a role. For example, Selcuk et al noted a case with apparent progression of liver disease from steatosis to steatohepatitis associated with weight gain on gluten-free diet, possibly related to development of a metabolic syndrome.¹³ A concomitant infection, such as hepatitis C¹⁴ could play a role, possibly through a molecular-mimicry-like pathogenetic mechanism suggested for adenovirus 12 in celiac disease,¹⁵ but others have concluded that no clear correlation is evident.^{16–18} Alternatively, treatment of hepatitis C with interferon/ribavirin has been hypothesized to activate celiac disease,¹⁹ prompting some to raise the issue of routine screening for celiac disease prior to anti-viral treatment.²⁰ Finally, celiac disease has also been detected after orthotopic liver transplantation in a case of hepatitis C associated cirrhosis.²¹

Persistent abnormalities in liver chemistry tests may also be due to a clinically occult, but specific hepatobiliary tract disorder sharing common immunopathogenetic features with celiac disease. Examples of immune-mediated disorders include primary biliary cirrhosis, autoimmune (lymphocytic) sclerosing cholangitis, or autoimmune hepatitis. Moreover, in hemochromatosis, a genetically-based disorder with altered control of small intestinal iron absorption with concomitant iron overload, celiac disease has been recorded. In addition, chronic changes in liver chemistry tests may reflect a direct effect of celiac disease on the liver *per se*. For example, impaired absorption and resultant malnutrition may lead to abnormal hepatic fat deposition, related, in part, to impaired fat mobilization from hepatocytes. In fact, even

massive hepatic steatosis has been reported in celiac disease. Finally, but very rarely, patients may develop a specific complication of celiac disease that involves the liver, such as malignant lymphoma, including a specific, but rare T-cell type, hepatosplenic lymphoma.

Primary biliary cirrhosis

In 1978, primary biliary cirrhosis was described with celiac disease.²² Later, additional cases were described.^{23–25} For both primary biliary cirrhosis and celiac disease, other concomitant immune-mediated conditions were noted, including diabetes and thyroiditis.^{25–28} In addition to reports from Europe and the Americas, concurrent primary biliary cirrhosis and celiac disease was also noted in South Asians²⁹ and the Coast Salish, an aboriginal population in Canada, believed to be of Asian descent.²⁶ Weight loss, malabsorption, osteopenic bone disease, steatorrhea, and elevated alkaline phosphatase levels are common in both disorders. As a result, celiac disease and primary biliary cirrhosis may be difficult to recognize as two distinct disorders, especially early in their clinical onset. Restriction of dietary gluten may improve the celiac disease, but usually, abnormal liver chemistry tests persist suggesting that the liver disease is not affected.

More recent studies have explored serological screening in both diseases. Using a patient registry in the United Kingdom,³⁰ the prevalence of primary biliary cirrhosis was defined in 143 celiac patients as 3%, while the prevalence of celiac disease in 67 primary biliary cirrhosis patients was 6%. As a result, screening with antimitochondrial antibodies in celiac disease was recommended, while in primary biliary cirrhosis, serological screening with gliadin antibodies or small intestinal biopsy was suggested.³¹ Similar findings of 7% of 57 primary biliary cirrhosis patients were noted based on initial evaluation using endomysial antibodies (11% positive) followed by later duodenal biopsy confirmation. Despite 12 to 24 months on gluten-free diets, however, improvement in liver chemistry tests was not detected even though endomysial antibodies disappeared. Using Danish and Swedish registry data based on over 8000 patients with celiac disease, an increased risk of primary biliary cirrhosis was also suggested.³² Later, stored sera from 378 Canadian patients with primary biliary cirrhosis were employed to screen for celiac disease in our laboratory.³³ Both IgA antibodies to endomysium and tissue transglutaminase were positive in 10 patients (2.6%). Of these, five patients had small bowel biopsies confirming celiac disease. An additional 44 primary biliary cirrhosis patients had raised IgA tissue transglutaminase antibodies, but the same sera were

negative for IgA endomysium antibodies. In 255 patients with autoimmune cholestatic liver disorders (including 173 with primary biliary cirrhosis), a different investigative group³⁴ found nine with celiac disease (including seven in those with primary biliary cirrhosis, or 4%). Finally, the importance of biopsy confirmation in primary biliary cirrhosis was noted as false-positive IgA or IgG-tTG antibodies may occur in primary biliary cirrhosis.^{35,36}

In a later study using a general practice longitudinal database from the United Kingdom,³⁷ an overall three-fold risk of primary biliary cirrhosis was demonstrated in 4,732 patients diagnosed with celiac disease compared to 23,620 age- and sex-matched controls.

Primary sclerosing cholangitis

In 1988, primary sclerosing cholangitis was linked to celiac disease in three patients with diarrhea and steatorrhea.³⁸ Two also had concomitant “ulcerative colitis” known to be associated with primary sclerosing cholangitis. In these, hepatic and biliary tract changes were defined by liver biopsy and cholangiograms, but these did not respond to a gluten-free diet. Subsequent reports have described other cases.^{11,34,39–42} In one, the predominant lymphocytic nature of the portal tract inflammatory process was noted with increased intra-epithelial lymphocytes in biliary ductal epithelium,⁴² also noted in gastric and colonic epithelium of celiac patients.^{43,44} Another patient with sclerosing cholangitis in celiac disease developed a cholangiocarcinoma.⁴⁵ To date, however, it has been difficult to confirm any definitive hepatobiliary tract response to a gluten-free diet. In part, this may reflect sampling error associated with liver biopsy as well as the limited specificity of liver chemistry test markers for cholestasis (eg, serum alkaline phosphatase). Indeed, the origin of serum alkaline phosphatase in this setting may include the hepatobiliary tract as well as other sources (eg, bone, intestine). Each of these sources might be substantially altered in celiac disease, and potentially improved with a gluten-free diet.

Autoimmune hepatitis and cholangitis

This has been noted in limited case reports and survey studies.^{46–49} Unfortunately, many appeared before hepatitis C testing.^{46,47} In one, liver biopsies were done in 37 of 171 celiac patients and changes of “chronic active hepatitis” were detected in five, or 2.3%. In another survey study of 157 patients with “type 1” autoimmune hepatitis and 24 with “type 2” autoimmune hepatitis for celiac disease, eight

of these 181 patients (4%) were positive for endomysial antibodies, including six with “type 1” disease (4%) and two with “type 2” disease (8%). Five of the eight patients, most being asymptomatic, had a duodenal biopsy and all showed typical changes of untreated celiac disease. Effects on symptoms and small bowel biopsy changes caused by drugs (steroids, azathioprine, or both) may have been important, but were not detailed. In a recent study, 47 consecutive patients with autoimmune hepatitis, including 39 with “type 1” disease and eight with “type 2” disease were evaluated. Anti-IgA tissue transglutaminase and endomysial antibodies were positive in three patients (6.4%) and small bowel biopsies confirmed the presence of the celiac disease histological changes. Finally, a recent report showed that celiac disease associated antibodies fell in autoimmune liver disease after hepatic transplantation.⁵⁰

Celiac disease and other types of autoimmune liver and biliary tract disease may coexist. A case report of autoimmune cholangitis,⁵¹ a cholestatic liver disorder with biochemical evidence of cholestasis, histological evidence of inflammatory bile duct damage and an absence of antimitochondrial antibodies, was previously described in a patient with celiac disease. Interestingly, this patient’s small intestinal biopsies were reported to be normal without a gluten-free diet while being treated with steroids and azathioprine. In another case, hepatic blood tests were improved without necessitating use of immunosuppressive drugs.⁵²

Hemochromatosis or iron overload liver disease

Celiac disease has been associated with hemochromatosis.^{53–56} Since both are relatively common, however, any association could be coincidental.⁵⁷ Iron absorption largely occurs in the proximal duodenum, the site most often histologically altered in celiac disease. Indeed, “isolated” iron deficiency with anemia may be the initial clinical manifestation of celiac disease. In contrast, in iron overload liver disease, inappropriate iron absorption from the proximal small intestine occurs as body iron stores are markedly increased. In an early study, treatment of celiac disease and improved small intestinal histology led to worsening liver chemistry test values and recognition of occult iron overload liver disease (C282Y-negative), thought to be related to increased intestinal uptake of iron. Another similar case of C282Y-positive hemochromatosis presented with diarrhea, positive anti-gliadin, and endomysial antibodies. Subsequent small bowel biopsies showed villous atrophy. In this case, phlebotomy treatment was terminated early due to an unanticipated

rapid fall in serum ferritin. As both disorders are associated with the HLA-region on chromosome 6, there could be a genetically-based linkage. Later investigations have sought to resolve the possible relationship. In one report,⁵⁸ HFE (hemochromatosis susceptibility gene) locus mutations were noted to be common in celiac disease, possibly for protection of the celiac from iron deficiency.⁵⁹ A later study in an Italian population with untreated celiac disease found that HFE mutations failed to protect against the development of iron deficiency.⁶⁰ In a case study of a patient with homozygous C282Y and celiac disease,⁶¹ reduced expression of the divalent metal transporter 1 (DMT1) was observed, but not ferroportin 1 (FP1) or the transferrin receptor 1 (TfR1).

Other liver disorders in celiac disease

Fatty liver

Common causes of hepatic steatosis in celiac disease could include alcohol-induced steatosis, diabetes mellitus, non-alcoholic fatty liver disease, and some forms of drug therapy including corticosteroids. In developing countries, dietary protein deficiency and kwashiorkor may be important causes. Intestinal malabsorption per se has been associated with hepatic steatosis after jejunoileal bypass for morbid obesity^{62,63} and sometimes in those with inflammatory bowel disease, particularly following extensive intestinal resections.⁶⁴ Because celiac disease is now frequently recognized in a clinically occult form before manifestations of marked nutrient depletion are detected, hepatic steatosis is probably less common than in other intestinal diseases.

Several cases of massive fatty infiltration of the liver have been described in adults with celiac disease.^{65–68} Clearly, lesser degrees of hepatic fat deposition may also occur. Most often if massive steatosis is evident, elevated transaminase and alkaline phosphatase activities occur along with alterations in coagulation. However, in most, clinical and biochemical changes attributed to the hepatic steatosis were improved with a gluten-free diet. In a patient with massive hepatic steatosis,⁶⁷ a gluten-free diet for about one year also resulted in normalization of the histologically-defined fatty changes in the liver.

Precise mechanisms involved in fat deposition in the liver are poorly defined. Following jejunoileal bypass, reduced serum levels of some essential and nonessential amino acids may be observed.^{62,63} In addition, changes in serum amino acids have been recorded in patients with starvation-associated kwashiorkor.^{69,70} Based on these other largely nutrition-based disorders, it has been hypothesized

that malabsorption in celiac disease might lead to chronic deficiency of a lipotropic factor (eg, choline). With an associated pyridoxine deficiency, hepatic steatosis might occur.⁷¹ In a recent study, increased intestinal permeability and altered tight junctions were documented in nonalcohol fatty liver disease as well as in primary biliary cirrhosis.^{72,73} The changes appeared to be related, in part, to the presence of small intestinal bacterial overgrowth. Similar permeability changes occur in celiac disease,^{74–76} and may be a factor in development of liver alterations in celiac disease. Further studies are needed to define the pathogenesis for these liver changes in celiac disease.

Hepatic vein obstruction

Although mesenteric vascular ischemia⁷⁷ and vasculitis^{78–81} have been described in celiac disease, there are also reports of a unusual Budd–Chiari-like syndrome among celiac children from North Africa, particularly Tunisian and Algeria.^{82,83} Hepatic vein obstruction was also documented in three adults.⁸⁴ Deficiencies in protein C and antithrombin III were detected, and malabsorption of vitamin K in celiac disease was proposed to cause transient protein C or protein S deficiencies. Further studies are needed to identify possible factors, either dietary or other environmental agents that may be critical. More recently, a celiac patient with a Budd–Chiari syndrome associated with membranous obstruction of the inferior vena cava treated successfully with percutaneous balloon angioplasty was reported.⁸⁵

Hepatic malignancies

While hepatocellular cancer has been reported in one patient, cirrhosis was also present.⁸⁶ Occasionally, the liver may be involved with lymphoma, the most frequently detected malignant disorder in celiac disease.⁸⁷ In some, lymphomatous deposits have been detected in the liver, presumably as metastatic lesions. For example, lymphoma in the liver was apparently secondary to jejunal lymphoma, complicating celiac disease. In general, involvement of the liver in celiac disease patients with lymphoma is limited and overshadowed by the clinical course of the intestinal disease. However, in a recent case report, an immune reaction in the splenoportal axis was postulated as a cause for severe portal hypertension.⁸⁸ Primary involvement with hepatic lymphoma may also occur. Indeed, a fulminant cholestatic syndrome has been described in celiac disease, resulting in hepatic failure.⁸⁹ Later investigations showed widespread hepatic involvement with an unusual lymphoid neoplasm classified as hepatosplenic lymphoma, a rare peripheral T-cell lymphoma with rearrangement of the

gamma-delta T-cell receptor.^{90,91} Similar necrotizing foci in the liver have recently been described in celiac disease with lymph node cavitation.⁹²

Liver failure

In patients from Finland with severe liver failure from a variety of causes in celiac disease, dietary treatment reversed hepatic dysfunction, even in cases where liver transplantation was being considered.⁹³ In these liver disease patients, congenital hepatic fibrosis, massive hepatic steatosis and progressive hepatitis were noted. In a post-transplant group, 4.3% had celiac disease discovered before or after transplant. In this group, liver diseases recorded were primary biliary cirrhosis, autoimmune hepatitis, primary sclerosing cholangitis, and congenital hepatic fibrosis. In a recent report, 13 patients are noted with liver failure and celiac disease that had an improvement in liver function with a gluten-free diet.⁹⁴ Causes in this report included primary biliary cirrhosis, primary sclerosing cholangitis, and chronic autoimmune hepatitis. Severe liver disease has also recently been described to complicate childhood celiac disease up to age three years.⁹⁵ Among six cases, four presented with acute liver failure with two requiring hepatic transplantation, prompting the suggestion that new onset celiac disease in children should be evaluated for evidence of liver dysfunction. Finally, children with severe liver disease should also be investigated for untreated celiac disease.

Disclosure

The author reports no conflicts of interest in this work.

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