Hepatobiliary and pancreatic disorders in celiac disease

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Abstract

A variety of hepatic and biliary tract disorders may complicate the clinical course of celiac disease. Some of these have been hypothesized to share common genetic factors or have a common immunopathogenesis, such as primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune forms of hepatitis or cholangitis. Other hepatic changes in celiac disease may be associated 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. Finally, pancreatic exocrine function may be impaired in celiac disease and represent a cause of treatment failure.

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INTRODUCTION

A number of hepatobiliary and pancreatic disorders occur in celiac disease, a genetically-based small intestinal disorder that resolves with the complete restriction of dietary gluten[1]. Almost 3 decades ago, liver changes in celiac disease were first recognized by Hagander et al[2]. Later, Dickey et al[3] have confirmed these findings in a prospective evaluation of celiac disease patients and extended observations to results of gluten-free diet therapy. In some, these liver test changes are entirely reversible following administration of a gluten-free diet, while in others, clinically significant liver disease is not amenable to diet treatment alone[3]. Now, almost a decade after this report, recognition of celiac disease has been substantively improved, in part, a result of more modern serological assays for screening[4], the detection of tissue transglutaminase (tTG) as an autoantigen in celiac disease[5] and the increasingly widespread serological use of tTG ELISA to screen for celiac disease[6]. As a result of improved recognition of celiac disease, even more precise estimates of the overall disease burden related to hepatobiliary tract and pancreatic disorders will emerge.

In patients with unexplained elevations of liver enzymes, several studies using serological screening methods have estimated that almost 10% will prove to have celiac disease[7,8]. For example, Volta et al[7] examined endomysial and gliadin antibodies in 55 patients with elevations of liver chemistry tests in the absence of a known cause. Five patients had positive serological studies and small intestinal biopsies showed changes of celiac disease that responded to a gluten-free diet. Liver biopsies done in some patients showed a nonspecific inflammatory process and liver chemistry tests normalized with a gluten-free diet. Bardella et al[8] screened 140 patients with chronically elevated transaminase values for gliadin and endomysial antibodies; of these, 13 were sero-positive. After 1 year on a gluten-free diet, 12 patients had normalization of liver enzyme tests.

In patients with known celiac disease, abnormal liver enzyme tests also occur[2,9-11]. Hagander et al[2] described elevated liver enzymes in 30 of 75 (40%) patients, while Bonamico et al[9] showed increased levels in 39 of 65 (60%) children, and Jacobsen et al[10] documented almost 50% with increased liver enzymes. In some, liver biopsy showed a nonspecific inflammatory process, although a more specific "chronic active hepatitis" was detected in 5 of 37 (13.5%) patients. Bardella et al[11] evaluated 158 consecutive adults with celiac disease and showed that 42% had abnormal liver enzyme levels. A gluten-free diet for 1 to 10 years resulted in complete normalization of liver chemistry tests in 95% patients.

In celiac disease, persistently abnormal liver chemistry tests may reflect the presence of a clinically occult hepatobiliary tract disorder with a possibly common immunopathogenesis. Specific examples of immune-mediated disorders include primary biliary cirrhosis, primary (lymphocytic, autoimmune) sclerosing cholangitis or autoimmune hepatitis. Alternatively, in some, a common genetically-based disorder, including altered control of small intestinal iron absorption resulting in a concomitant iron overload disorder, may be present, such as hemochromatosis. In addition, chronic changes

in liver chemistry tests may reflect a direct effect of the celiac disease. For example, impaired absorption and resultant malnutrition may lead to deposition of fat in the liver, related, in part, to reduced fat mobilization from hepatocytes. Indeed, massive hepatic steatosis has occasionally been reported in celiac disease. Finally, but very rarely, patients may develop a specific complication of celiac disease that involves the liver, such as a T-cell form of lymphoma.

HEPATOBILIARY TRACT DISEASES

Primary biliary cirrhosis

In 1978, Logan et al[12] described the first cases of primary biliary cirrhosis with celiac disease. Later, numerous additional cases have been reported[13-16]. In both disorders, other conditions having an immunological basis have been described, including diabetes and thyroiditis[16-19]. In addition, co-existence of primary biliary cirrhosis and celiac disease has not only been reported in Europe and the Americas, but also in migrants from South Asia[20] and the Coast Salish, an aboriginal population inhabiting the west coast of Canada thought to be of Asian descent[16]. To date, however, a definitive genetic predisposition or specific immunological alteration has not been clearly identified. Loss of weight, malabsorption, osteopenic bone disease, steatorrhea and elevated alkaline phosphatase activities are common features of both diseases, so that early in their coexistence, celiac disease or primary biliary cirrhosis may not be easily appreciated. In patients reported with both disorders, regardless of geographical origin or race, restriction of dietary gluten may have improved the diarrhea, but abnormal liver chemistry tests were usually not significantly altered with a gluten-free diet.

Some more recent studies have explored serological testing in primary biliary cirrhosis or celiac disease. Kingham and Parker[21] used a patient registry in the United Kingdom and defined the prevalence of primary biliary cirrhosis 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 antimitochrondrial antibodies in celiac disease was recommended, while in primary biliary cirrhosis, serological screening with gliadin antibodies or small intestinal biopsy was suggested. Dickey et al[22] found similar findings of 7% (4/57) primary biliary cirrhosis patients based on initial evaluation using endomysial antibodies (11% positive), followed by later duodenal biopsy confirmation. Despite 12 to 24 mo 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 8 000 patients with celiac disease, Sorensen et al[23] also suggested an increased risk of primary biliary cirrhosis. Using stored sera from 378 Canadian patients with primary biliary cirrhosis, Gillett et al[24] found that screening for IgA antibodies to endomysium and primary biliary cirrhosis were both positive in 10 (2.6%) patients and 5 patients had small intestinal biopsies confirming celiac disease. Intertestingly, however, another 44 primary biliary cirrhosis patients had raised IgA tissue transglutaminase antibodies but were negative for IgA endomysium antibody. In 255 patients with autoimmune cholestatic liver disorders, including 173 with primary biliary cirrhosis, Volta et al[25] found 9 with celiac disease (including 7 in those with primary biliary cirrhosis, 4%). In some recent studies, however, the importance of biopsy confirmation in patients with primary biliary cirrhosis has been demonstrated in sero-positive patients as false-positive IgA or IgG tTG antibodies may occur in primary biliary cirrhosis[26,27].

In a recent study using a general practice longitudinal database from the United Kingdom[28], an overall 3-fold risk of primary biliary cirrhosis was demonstrated in 4 732 patients diagnosed with celiac disease as compared with 23 620 age- and sex-matched controls.

Primary sclerosing cholangitis

Primary sclerosing cholangitis was first found to be associated with celiac disease in 1988 in 3 patients with diarrhea and steatorrhea[29]. Two also had concomitant "ulcerative colitis" (one with "inactive" quiescent disease and one with "mild" or "minimal change" colonic disease), a disorder known to be associated with primary sclerosing cholangitis. Although hepatobiliary tract changes were defined by cholangiography and liver biopsy, these did not respond to a gluten-free diet. Later, other cases were reported[10,25,30]. In one, the predominant lymphocytic nature of the portal inflammatory process was emphasized with increased intra-epithelial lymphocytes in biliary ductal epithelium[30], an observation also noted in gastric and colonic epithelium of celiac patients[31,33]. To date, despite some case report data[33], it has been difficult to show good evidence for a response of the hepatobiliary tract disease to a gluten-free diet. This may, in part, reflect sampling difficulties associated with liver biopsy as well as the response or lack of response of relatively non-specific liver chemistry test markers of cholestasis (e.g., serum alkaline phosphatase). Indeed, the origin of alkaline phosphatase activities measured in serum include the hepatobiliary tract and other tissues that may be substantially altered in celiac disease (i.e., bone and the intestine); conceivably all might be improved with a gluten-free diet.

Autoimmune hepatitis and cholangitis

This has been evaluated in only a limited numbers of case reports and survey studies. Unfortunately, many appeared before hepatitis C testing[13,35]. Jacobsen et al[10] performed liver biopsies in 37 of 171 celiac patients and found changes of "chronic active hepatitis" in 5 (2.3%) patients. Using antibodies to endomysium and gliadin, Volta et al[36] surveyed 157 patients with type 1 autoimmune hepatitis and 24 with type 2 autoimmune hepatitis for celiac disease. They found that 8 of these 181 (4%) patients were positive for endomysial antibodies, including 6 (4%) with type 1 disease and 2 (8%) with type 2 disease. Five of the 8 patients had a duodenal biopsy, most being asymptomatic, and all showed changes of subtotal villous atrophy, consistent with untreated celiac disease. The effects of steroid with or without azothioprine treatment on the underlying small intestinal histological changes were considered and also may have masked intestinal symptoms. Unfortunately, in this study, the effects of gluten-free

diet administration on the hepatic and intestinal changes were not reported. Recently, Villalta et al[37] evaluated 47 consecutive patients with autoimmune hepatitis, including 39 with type 1 disease and 8 with type 2 disease. Anti-IgA tissue transglutaminase and endomysial antibodies were positive in 3 (6.4%) patients and small intestinal biopsies confirmed the presence of the celiac disease histological changes[37].

Finally, celiac disease and other types of autoimmune liver and biliary tract disease may coexist. A case report of autoimmune cholangitis[38], a cholestatic liver disorder with biochemical evidence of cholestasis, histological evidence of inflammatory bile duct damage and an absence of anti-mitochondrial antibodies, was has been 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 an another case, Sedlack et al[39] reported an improvement in hepatic biochemistries without use of immunosuppressive agents.

HEMOCHROMATOSIS OR IRON OVERLOAD LIVER DISEASE

Celiac disease has been associated with hemochromatosis, which is not surprising, since both are relatively common disorders based on a common Celtic ancestry, so any association could be coincidental[40-42]. 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 clinically occult 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 one of these early case reports, treatment of celiac disease and improvement in the pathological small intestinal changes led to worsening liver chemistry test values and recognition of occult iron overload liver disease (C282Y-negative), presumably related to improved intestinal uptake of dietary iron[41]. Another similar case of C282Y-positive hemochromatosis presented with diarrhea, positive anti-gliadin and endomysial antibodies. Subsequent small bowel biopsies showed villous atrophy[42]. Interestingly, in this latter case, phlebotomy therapy had to be terminated early because of an unexpectedly rapid fall in the serum ferritin measurement. A genetically-based linkage was also suggested since both diseases are associated with the HLA-region on chromosome 6. Later investigations have sought to resolve this possible relationship. Butterworth et al[43] observed that HFE (hemochromatosis susceptibility gene) locus mutations are common in celiac disease patients from the United Kingdom and may be important in protecting the celiac from iron deficiency, while others suggested that the significance of these observations may be controversial[44]. More recent studies in an Italian population with untreated celiac disease found that HFE mutations failed to protect against the development of iron deficiency[45]. Interestingly, in a recent case study of a patient with homozygous C282Y and celiac disease[46], reduced expression of the divalent metal transporter 1

(DMT1) was observed, but not ferroportin 1 (FP1) or transferrin receptor 1 (TfR1).

OTHER LIVER DISORDERS IN CELIAC DISEASE

Hepatic steatosis

Common causes of hepatic steatosis include alcohol-induced steatosis, diabetes mellitus, NASH syndromes and some forms of drug therapy, including corticosteroids. In some countries, dietary protein deficiency and kwashiorkor are important causes. Intestinal malabsorption is often associated with hepatic steatosis in patients with a prior jejunoileal bypass procedure for morbid obesity[47,48] and, sometimes, in those with inflammatory bowel disease, particularly after extensive intestinal resections[49]. 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 fatty infiltration of the liver, often massive, have been described in adults with celiac disease[50-53]. Presumably, lesser degrees of hepatic fat deposition may occur. Most often if massive steatosis is evident, elevated transaminase and alkaline phosphatase activities have been documented 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[52], a gluten-free diet for about 1 year also resulted in histological improvement in the fatty changes detected in the liver.

The mechanisms involved in fat deposition in the liver are not defined. Interestingly, after jejunoileal bypass, reduced serum levels of some essential and nonessential amino acids may be observed[47,48]. In addition, changes in serum amino acids have been recorded in patients with starvation-associated kwashiorkor[54,55]. Based on these nutritional disorders, it has been suggested that malabsorption in celiac disease might lead to chronic deficiency of a lipotropic factor (e.g., choline), with an associated pyridoxine deficiency, hepatic steatosis might occur[52]. Further studies are needed to define the precise pathogenetic mechanism or mechanisms for fatty liver in celiac disease.

Gallstone disease

Several studies have focused on gallbladder function in celiac patients. In some studies, slow emptying of the gallbladder has been documented[56,57], along with impaired contraction response to fat[56]. Studies of enteric endocrine cells showed significant quantitative changes in celiac patients, including complete absence of mucosal secretin cells[59]. In addition, studies with test meals have suggested impaired secretion of cholecystokinin in patients with celiac disease[59] or, possibly, impaired gallbladder responsiveness to cholecystokinin[56].

In spite of these physiological alterations, there does not appear to be a significant predisposition to gallstones in celiac disease. Only 9 of 350 patients had a cholecystectomy for gallstone disease[60]. However, in a

survey of elderly celiacs initially diagnosed after the age of 60 years, 6 of 30 (20%) had gallstone disease[61].

Hepatic vein obstruction

Although mesenteric vascular ischemia[62] and vasculitis[63-66] 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[67,68]. Hepatic vein obstruction has also been documented in 3 adults[69]. Deficiencies in protein C and antithrombin III are detected, and malabsorption of vitamin K in celiac disease has been proposed to cause transient protein C or protein S deficiencies. Further studies are needed to identify possible factors, either dietary or environmental agents, that may be important. 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 has been reported[70].

Hepatic malignancies

While hepatocellular cancer has been reported in 1 patient, cirrhosis was also present[71]. Occasionally, the liver may be involved with lymphoma, the most frequently detected malignant disorder in celiac disease patients[72]. In some patients with celiac disease, lymphomatous deposits have been detected in the liver, presumably as metastatic lesions[71]. For example, lymphoma in the liver is apparently secondary to jejunal lymphoma, complicating celiac disease[71]. 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, a fulminant cholestatic syndrome has been described in a celiac disease patient, resulting in hepatic failure[73]. Later investigations have shown widespread hepatic involvement with an unusual lymphoid neoplasm classified as a hepatosplenic lymphoma, a rare type of peripheral T-cell lymphoma with rearrangement of the gamma-delta T-cell receptor[74,75].

Liver failure

In patients with severe liver failure from a variety of causes in celiac disease, dietary treatment reverses hepatic dysfunction, even in patients with consideration for possible liver transplantation[76].

PANCREATIC DISEASE

While celiac disease is associated with insulin-dependent diabetes[77], pancreatic exocrine insufficiency and celiac disease have only occasionally been recorded[78-84]. Pancreatic calcification is most often associated with chronic or persisting pancreatic inflammation which is usually due to excessive consumption of alcoholic beverages. Atrophy, fibrosis and altered pancreatic function have been observed in experimental animals treated with diets deficient in protein, in adults with protein-energy malnutrition, in children with kwashiorkor and in some early autopsy studies of patients with celiac disease. In addition, pancreatic calcification has been reported with chronic protein malnutrition in the Indian subcontinent

and in some African countries. Finally, a patient with celiac disease and pancreatitis with calcification has been described[83].

Although the frequency of pancreatic disease in celiac patients is not known, impaired pancreatic function occurs and may be a cause of persistently impaired nutrient assimilation and malnutrition. It has been estimated that over 20% of children with celiac disease have defective exocrine pancreatic function[85]. This may be related to several factors. Impaired secretion and/or release of pancreatic stimulating hormones from the diseased proximal small intestine may be important[60]. Immunohistochemical studies have demonstrated alterations in enteric endocrine cells, and in biopsies from patients with untreated celiac disease, an absence of secretin cells has been reported[59]. Studies with test meals in celiac patients have suggested impaired secretion of cholecystokinin-pancreozymin resulting in reduced pancreatic exocrine cell stimulation[81]. In addition, a deficiency of amino acids may result from impaired small intestinal amino acid uptake, leading to a reduction in precursors for pancreatic enzyme synthesis[55,80]. Also, protein malnutrition may lead to structural changes in the pancreas, including atrophy of acinar cells and pancreatic fibrosis[55], resulting in impaired pancreatic exocrine function. In a more recent study[86], pancreatic enzyme measurements were reduced with mucosal atrophy and could be inversely correlated with the degree of intestinal damage.

REFERENCES

1   **Freeman HJ.** Adult celiac disease and the severe "flat" small bowel biopsy lesion. *Dig Dis Sci* 2004; **49**: 535-545
2   **Hagander B,** Berg NO, Brandt L, Norden A, Sjolund K, Stenstam M. Hepatic injury in adult coeliac disease. *Lancet* 1977; **2**: 270-272
3   **Dickey W,** McMillan SA, Collins JS, Watson RG, McLoughlin JC, Love AH. Liver abnormalities associated with celiac sprue. How common are they, what is their significance, and what do we do about them? *J Clin Gastroenterol* 1995; **20**: 290-292
4   **Gillett HR,** Freeman HJ. Serological testing in screening for adult celiac disease. *Can J Gastroenterol* 1999; **13**: 265-269
5   **Dieterich W,** Ehnis T, Bauer M, Donner P, Volta U, Riecken EO, Schuppan D. Identification of tissue transglutaminase as the autoantigen of celiac disease. *Nat Med* 1997; **3**: 797-801
6   **Freeman HJ.** Inflammatory bowel disease with cytoplasmic-staining antineutrophil cytoplasmic antibody and extensive colitis. *Can J Gastroenterol* 1998; **12**: 279-282
7   **Ishiyama Y.** The present and future of neurophysiological examination. *Rinsho Byori* 1998; **46**: 879-886
8   **Bardella MT,** Vecchi M, Conte D, Del Ninno E, Fraquelli M, Pacchetti S, Minola E, Landoni M, Cesana BM, De Franchis R. Chronic unexplained hypertransaminasemia may be caused by occult celiac disease. *Hepatology* 1999; **29**: 654-657
9   **Signoretti A,** Roggini M, Bonamico M, Nigro G, Lionetti P, Falconieri P. Interstitial pneumonitis during Kawasaki disease associated with herpes simplex infection. *Minerva Pediatr* 1986; **38**: 589-593
10 **Jacobsen MB,** Fausa O, Elgjo K, Schrumpf E. Hepatic lesions in adult coeliac disease. *Scand J Gastroenterol* 1990; **25**: 656-662
11 **Bardella MT,** Fraquelli M, Quatrini M, Molteni N, Bianchi P, Conte D. Prevalence of hypertransaminasemia in adult celiac patients and effect of gluten-free diet. *Hepatology* 1995; **22**: 833-836
12 **Logan RF,** Ferguson A, Finlayson ND, Weir DG. Primary biliary cirrhosis and coeliac disease: an association? *Lancet* 1978; **1**:

230-233

13   **Behr W,** Barnert J. Adult celiac disease and primary biliary cirrhosis. *Am J Gastroenterol* 1986; **81**: 796-799

14   **Olsson R,** Kagevi I, Rydberg L. On the concurrence of primary biliary cirrhosis and intestinal villous atrophy. *Scand J Gastroenterol* 1982; **17**: 625-628

15   **Iliffe GD,** Owen DA. An association between primary biliary cirrhosis and jejunal villous atrophy resembling celiac disease. *Dig Dis Sci* 1979; **24**: 802-806

16   **Freeman HJ**. Celiac disease associated with primary cirrhosis in a Coast Salish native. *Can J Gastroenterol* 1994; **8**: 105-108

17   **Whitehead EM,** Daly JG, Hayes JR. Renal tubular acidosis in association with Sjogren's syndrome, primary biliary cirrhosis and coeliac disease. *Ir J Med Sci* 1987; **156**: 124-125

18   **Weetman AP.** Non-thyroid autoantibodies in autoimmune thyroid disease. *Best Pract Res Clin Endocrinol Metab* 2005; **19**: 17-32

19   **Fracchia M,** Galatola G, Corradi F, Dall'Omo AM, Rovera L, Pera A, Vitale C, Bertero MT. Coeliac disease associated with Sjogren's syndrome, renal tubular acidosis, primary biliary cirrhosis and autoimmune hyperthyroidism. *Dig Liver Dis* 2004; **36**: 489-491

20   **Anand AC,** Elias E, Neuberger JM. End-stage primary biliary cirrhosis in a first generation migrant south Asian population. *Eur J Gastroenterol Hepatol* 1996; **8**: 663-666

21   **Kingham JG,** Parker DR. The association between primary biliary cirrhosis and coeliac disease: a study of relative prevalences. *Gut* 1998; **42**: 120-122

22   **Dickey W,** McMillan SA, Callender ME. High prevalence of celiac sprue among patients with primary biliary cirrhosis. *J Clin Gastroenterol* 1997; **25**: 328-329

23   **Sorensen HT,** Thulstrup AM, Blomqvist P, Norgaard B, Fonager K, Ekbom A. Risk of primary biliary liver cirrhosis in patients with coeliac disease: Danish and Swedish cohort data. Gut 1999; **44**: 736-738

24   **Gillett HR,** Cauch-Dudek K, Jenny E, Heathcote EJ, Freeman HJ. Prevalence of IgA antibodies to endomysium and tissue transglutaminase in primary biliary cirrhosis. *Can J Gastroenterol* 2000; **14**: 672-675

25   **Volta U,** Rodrigo L, Granito A, Petrolini N, Muratori P, Muratori L, Linares A, Veronesi L, Fuentes D, Zauli D, Bianchi FB. Celiac disease in autoimmune cholestatic liver disorders. *Am J Gastroenterol* 2002; **97**: 2609-2613

26   **Floreani A,** Betterle C, Baragiotta A, Martini S, Venturi C, Basso D, Pittoni M, Chiarelli S, Sategna Guidetti C. Prevalence of coeliac disease in primary biliary cirrhosis and of antimitochondrial antibodies in adult coeliac disease patients in Italy. *Dig Liver Di*s 2002; **34**: 258-261

27   **Bizzaro N,** Villalta D, Tonutti E, Doria A, Tampoia M, Bassetti D, Tozzoli R. IgA and IgG tissue transglutaminase antibody prevalence and clinical significance in connective tissue diseases, inflammatory bowel disease, and primary biliary cirrhosis. *Dig Dis Sci* 2003; **48**: 2360-2365

28   **Lawson A,** West J, Aithal GP, Logan RF. Autoimmune cholestatic liver disease in people with coeliac disease: a population-based study of their association. *Aliment Pharmacol Ther* 2005; **21**: 401-405

29   **Hay JE,** Wiesner RH, Shorter RG, LaRusso NF, Baldus WP. Primary sclerosing cholangitis and celiac disease. A novel association. *Ann Intern Med* 1988; **109**: 713-717

30   **Freeman HJ,** Kwan WC. Occult celiac disease associated with lymphocytic sclerosing cholangitis. *Can J Gastroenterol* 1994; **8:** 249-252

31   **Wolber R,** Owen D, DelBuono L, Appelman H, Freeman H. Lymphocytic gastritis in patients with celiac sprue or sprue-elike intestinal disease. *Gastroenterology* 1990; **98**: 310-315

32   **Wolber R,** Owen D, Freeman H. Colonic lymphocytosis in patients with celiac sprue. *Hum Pathol* 1990; **21**: 1092-1096

33   **Venturini I,** Cosenza R, Miglioli L, Borghi A, Bagni A, Gandolfo M, Modonesi G, Zeneroli ML. Adult celiac disease and primary sclerosing cholangitis: two case reports. *Hepatogastroenterology* 1998; **45**: 2344-2347

34   **Lindberg J,** Ahren C, Iwarson S. Intestinal villous atrophy

in chronic active hepatitis. *Scand J Gastroenterol* 1979; **14**: 1015-1018

35   **Swarbrick ET,** Fairclough PD, Campbell PJ, Levison DA, Greenwood RH, Baker LR. Coeliac disease, chronic active hepatiti, and mesangiocapillary glomerulonephritis in the same patient. *Lancet* 1980; **2**: 1084-1085

36   **Volta U**, De Franceschi L, Molinaro N, Cassani F, Muratori L, Lenzi M, Bianchi FB, Czaja AJ. Frequency and significance of anti-gliadin and anti-endomysial antibodies in autoimmune hepatitis. *Dig Dis Sci* 1998; **43**: 2190-2195

37   **Villalta D,** Girolami D, Bidoli E, Bizzaro N, Tampoia M, Liguori M, Pradella M, Tonutti E, Tozzoli R. High prevalence of celiac disease in autoimmune hepatitis detected by anti-tissue tranglutaminase autoantibodies. *J Clin Lab Anal* 2005; **19**: 6-10

38   **Gogos CA**, Nikolopoulou V, Zolota V, Siampi V, Vagenakis A. Autoimmune cholangitis in a patient with celiac disease: a case report and review of the literature. *J Hepatol* 1999; **30**: 321-324

39   **Sedlack RE,** Smyrk TC, Czaja AJ, Talwalkar JA. Celiac disease-associated autoimmune cholangitis. *Am J Gastroenterol* 2002; **97**: 3196-3198

40   **Morris WE Jr**. Hemochromatosis and celiac sprue. Case report. *J Fla Med Assoc* 1993; **80**: 243-245

41   **Heneghan MA**, Feeley KM, Stevens FM, Little MP, McCarthy CF. Precipitation of iron overload and hereditary hemochromatosis after successful treatment of celiac disease. *Am J Gastroenterol* 2000; **95**: 298-300

42   **Turcu A,** Leveque L, Bielefeld P, Besancenot JF, Hillon P. Adult celiac disease and hemochromatosis. *Am J Gastroenterol* 2000; **95**: 3661-3662

43   **Butterworth JR**, Cooper BT, Rosenberg WM, Purkiss M, Jobson S, Hathaway M, Briggs D, Howell WM, Wood GM, Adams DH, Iqbal TH. The role of hemochromatosis susceptibility gene mutations in protecting against iron deficiency in celiac disease. *Gastroenterology* 2002; **123**: 444-449

44   **Bowlus CL,** Lie BA. Discussion of the role of hemochromatosis susceptibility gene mutation in protecting against iron deficiency in celiac disease. *Gastroenterology* 2003; **124**: 1562-1563

45   **Barisani D**, Ceroni S, Del Bianco S, Meneveri R, Bardella MT. Hemochromatosis gene mutations and iron metabolism in celiac disease. *Haematologica* 2004; **89**: 1299-1305

46   **Geier A,** Gartung C, Theurl I, Weiss G, Lammert F, Dietrich CG, Weiskirchen R, Zoller H, Hermanns B, Matern S. Occult celiac disease prevents penetrance of hemochromatosis. *World J Gastroenterol* 2005; **11**: 3323-3326

47   **Holzbach RT.** Hepatic effects of jejunoileal bypass for morbid obesity. *Am J Clin Nutr* 1977; **30**: 43-52

48   **Moxley RT 3rd,** Pozefsky T, Lockwood DH. Protein nutrition and liver disease after jejunoileal bypass for morbid obesity. *N Engl J Med* 1974; **290**: 921-926

49   **Kern F Jr.** Hepatobiliary disorders in inflammatory bowel disease. *Prog Liver Dis* 1976; **5**: 575-589

50   **van Tongeren JH,** Breed WP, Corstens FH, Driessen WM, Flendrig JA, Laar A van't, Schillings PH. Fatty liver and malabosprtion. *Folia Med Neerl* 1972; **15**: 246-258

51   **Capron JP,** Sevenet F, Quenum C, Doutrellot C, Capron-Chivrac D, Delamarre J. Massive hepatic steatosis disclosing adult celiac disease. Study of a case and review of the literature. *Gastroenterol Clin Biol* 1983; **7**: 256-260

52   **Naschitz JE,** Yeshurun D, Zuckerman E, Arad E, Boss JH. Massive hepatic steatosis complicating adult celiac disease: report of a case and review of the literature. *Am J Gastroenterol* 1987; **82**: 1186-1189

53   **Sood A,** Midha V, Sood N. Nonalcoholic steatohepatitis, obesity and celiac disease. *Indian J Gastroenterol* 2003; **22**: 156

54   **Padilla H,** Sanchez A, Powell RN, Umezawa C, Swendseid ME, Prado PM, Sigala R. Plasma amino acids in children from Guadalajara with kwashiorkor. *Am J Clin Nutr* 1971; **24**: 353-357

55   **Freeman HJ,** Kim YS, Sleisenger MH. Protein digestion and absorption in man. Normal mechanisms and protein-energy malnutrition. *Am J Med* 1979; **67**: 1030-1036

56   **Low-Beer TS,** Heaton KW, Read AE. Gallbladder inertia in

adult coeliac disease. *Gut* 1970; **11**: 1057-1058

57 **Low-Beer TS,** Heaton KW, Heaton ST, Read AE. Gallbladder inertia and sluggish enterohepatic circulation of bile-salts in coeliac disease. *Lancet* 1971; **1**: 991-994

58 **Low-Beer TS,** Harvey RF, Davies ER, Read AF. Abnormalities of serum cholecystokinin and gallbladder emptying in celiac disease. *N Engl J Med* 1975; **292**: 961-963

59 **Buchan AM,** Grant S, Brown JC, Freeman HJ. A quantitative study of enteric endocrine cells in celiac sprue. *J Pediatr Gastroenterol Nutr* 1984; **3**: 665-671

60 **DiMagno EP,** Go WL, Summerskill WH. Impaired cholecystokinin-pancreozymin secretion, intraluminal dilution, and maldigestion of fat in sprue. *Gastroenterology* 1972; **63**: 25-32

61 **Freeman H,** Lemoyne M, Pare P. Coeliac disease. *Best Pract Res Clin Gastroenterol* 2002; **16**: 37-49

62 **Upadhyay R,** Park RH, Russell RI, Danesh BJ, Lee FD. Acute mesenteric ischaemia: a presenting feature of coeliac disease? *Br Med J (Clin Res Ed)* 1987; **295**: 958-959

63 **Does WF**, Evans D, Hobbs JR, Booth CC. Celiac disease, vasculitis, and cryoglobulinemia. *Gut* 1972; **13**: 112-123

64 **Meyers S,** Dikman S, Spiera H, Schultz N, Janowitz HD. Cutaneous vasculitis complicating coeliac disease. *Gut* 1981; **22**: 61-64

65 **Alegre VA**, Winkelmann RK, Diez-Martin JL, Banks PM. Adult celiac disease, small and medium vessel cutaneous necrotizing vasculitis, and T cell lymphoma. *J Am Acad Dermatol* 1988; **19**: 973-978

66 **Simila S,** Kokkonen J, Kallioinen M. Cutaneous vasculitis as a manifestation of coeliac disease. *Acta Paediatr Scand* 1982; **71**: 1051-1054

67 **Gentil-Kocher S,** Bernard O, Brunelle F. Budd-Chiari syndrome in children: report of 22 cases. *J Pediatr* 1988; **113**: 30-38

68 **Hamdi A,** Ayachi R, Saad H, Gargouri R, Zouari K, Chebbah MS. Hemiplegie relevant un syndrome de Budd-Chiari associe a une maladie coeliaque chez un nourrisson. *Presse Med* 1990; **19**: 1011-1012

69 **Marteau P,** Cadranel JF, Messing B, Gargot D, Valla D, Rambaud JC. Association of hepatic vein obstruction and coeliac disease in North African subjects. *J Hepatol* 1994; **20**: 650-653

70 **Martinez F,** Berenguer M, Prieto M, Montes H, Rayon M, Berenguer J. Budd-Chiari syndrome caused by membranous obstruction of the inferior vena cava associated with coeliac disease. *Dig Liver Dis* 2004; **36**: 157-162

71 **Pollock DJ.** The liver in coeliac disease. *Histopathology* 1977; **1**: 421-430

72 **Freeman HJ.** Lymphoproliferative and intestinal malignancies in 214 patients with biopsy-defined celiac disease. *J Clin Gastroenterol* 2004; **38**: 429-434

73 **Freeman HJ**. Fulminant liver failure with necrotizing foci in the liver, spleen and lymph nodes in celiac disease due to malignant lymphoma. *Can J Gastroenterol* 1996; **10**: 225-229

74 **Harris NL,** Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, Delsol G, De Wolf-Peeters C, Falini B, Gatter KC. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; **84**: 1361-1392

75 **Farcet JP,** Gaulard P, Marolleau JP, Le Couedic JP, Henni T, Gourdin MF, Divine M, Haioun C, Zafrani S, Goossens M. Hepatosplenic T-cell lymphoma: sinusal/sinusoidal localization of malignant cells expressing the T-cell receptor gamma delta. *Blood* 1990; **75**: 2213-2219

76 **Kaukinen K**, Halme L, Collin P, Farkkila M, Maki M, Vehmanen P, Partanen J, Hockerstedt K. Celiac disease in patients with severe liver disease: gluten-free diet may reverse hepatic failure. *Gastroenterology* 2002; **122**: 881-888

77 **Gillett PM**, Gillett HR, Israel DM, Metzger DL, Stewart L, Chanoine JP, Freeman HJ. High prevalence of celiac disease in patients with type 1 diabetes detected by antibodies to endomysium and tissue transglutaminase. *Can J Gastroenterol* 2001; **15**: 297-301

78 **Benson GD,** Kowlessar OD, Sleisenger MH. Adult celiac disease with emphasis upon response to the gluten-free diet. *Medicine (Baltimore)* 1964; **43**: 1-40

79 **Pink IJ**, Creamer B. Response to a gluten-free diet of patients with the celiac syndrome. *Lancet* 1967; **1**: 300-304

80 **Weinstein LD**, Herskovic T. Rectal seepage of oil in a patient with celiac disease and secondary pancreatic insufficiency. *Am J Dig Dis* 1968; **13**: 762-765

81 **Regan PT,** DiMagno EP. Exocrine pancreatic insufficiency in celiac sprue: a cause of treatment failure. *Gastroenterology* 1980; **78**: 484-487

82 **Pitchumoni CS**, Thomas E, Balthazar E, Sherling B. Chronic calcific pancreatitis in association with celiac disease. *Am J Gastroenterol* 1977; **68**: 358-361

83 **Freeman HJ**, Whittaker SJ. Nonalcoholic chronic pancreatitis with pancreatic calcification: presenting manifestation of occult celiac disease. *Can J Gastroenterol* 1994; **8**: 319-322

84 **Pitchumoni CS**. Pancreas in primary malnutrition disorders. *Am J Clin Nutr* 1973; **26**: 374-379

85 **Carroccio A,** Iacono G, Montalto G, Cavataio F, Di Marco C, Balsamo V, Notarbartolo A. Exocrine pancreatic function in children with coeliac disease before and after a gluten free diet. *Gut* 1991; **32**: 796-799

86 **Nousia-Arvanitakis S,** Karagiozoglou-Lamboudes T, Aggouridaki C, Malaka-Lambrellis E, Galli-Tsinopoulou A, Xefteri M. Influence of jejunal morphology changes on exocrine pancreatic function in celiac disease. *J Pediatr Gastroenterol Nutr* 1999; **29**: 81-85

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