Review Article

Celiac Disease and Elevated Liver Enzymes: A Review

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Abstract

Aminotransferases are commonly found to be elevated in patients with celiac disease in association with two different types of liver dysfunction: cryptogenic liver disorders and autoimmune disorders. The purpose of this review is to discuss the mechanisms by which aminotransferases become elevated in celiac disease, clinical manifestations, and response to gluten-free diet. Many studies have shown that celiac patients with cryptogenic liver disease have normalization in aminotransferases, intestinal histologic improvement and serologic resolution after 6–12 months of strict gluten-free diet. In patients with an underlying autoimmune liver disease, simultaneous treatment for both conditions resulted in normalized elevated aminotransferases. The literature suggests that intestinal permeability may be at least one of the mechanisms by which liver damage occurs. Patients with celiac disease should have liver enzymes routinely checked and treated with a strict gluten-free diet if found to be abnormal. Lack of improvement in patients who have strictly adhered to gluten-free diet should prompt further workup for other causes of liver disease.

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Introduction

Aminotransferases are commonly found to be elevated in patients with celiac disease, due to multiple reasons. The purpose of this review is to discuss the mechanisms by which aminotransferases become elevated in celiac disease, clinical manifestations, and response to gluten-free diet (GFD).

Celiac disease

Celiac disease (or gluten-sensitive enteropathy) is an autoimmune condition triggered by consumption of the gliadin fraction of gluten and other cereals.[1] The prevalence is around 0.5–1% in the general population.[2,3] The small bowel is primarily affected, causing symptoms such as diarrhea, flatulence and weight loss from malabsorption. However, celiac disease is a systemic disorder that can be associated with diseases of organs other than the small intestine, such as the colon, thyroid, skin, pancreas, and liver. For instance, the prevalence of celiac disease among children with type 1 diabetes is high, likely related to expression of HLA risk genotypes (DQ2 or DQ8) in up to 90% of patients with type 1 diabetes.[4] The prevalence of celiac disease in patients with autoimmune thyroid conditions, such as Grave's disease and Hashimoto's thyroiditis, has been found to be around 2–7%, while the risk of thyroid disease in celiacs has been estimated at 3-fold higher compared to controls.[4] Similar associations have been made with Sjogren's syndrome, psoriasis, microscopic colitis and dermatitis herpetiformis.[4] In regards to the liver, the common hepatic manifestation is isolated aminotransferase elevations.[3]

The pathogenesis of celiac disease is not entirely understood, but it is thought to be due to the combination of genetic, environmental and immunological factors. The strongest genetic susceptibility factors are HLA-DQ2 and HLA-DQ8 from the HLA class II genes. However, the presence of these alone is insufficient for disease development. Gluten is the primary trigger of an immune response in the gut epithelium.[5] Intestinal enzyme tissue transglutaminase (tTG) 2 modifies gluten peptides, which bind to HLA-DQ2 or HLA-DQ8 on the surface of antigen-presenting cells. These trigger a T-cell response, with release of proinflammatory cytokines that lead to mucosal inflammation and damage to epithelium. These can also induce a B cell response, leading to production of anti-tTG antibodies as well. Peptides are capable of directly activating epithelial cells to produce cytokines, such as IL-15. This enhances cytolytic activity of intraepithelial lymphocytes and ultimately disrupts the lining and increases the intestinal permeability.[6]

It has also been proposed that infections are related to development of celiac disease.[7] Beyerlein *et al*.[8] studied infants born between 2005 and 2007 retrospectively. Based on a search for ICD codes for infections and celiac disease, they found that risk of developing celiac disease was higher in children with a gastrointestinal infection during the first year of life (hazard ratio of 1.32). There was a weaker association with respiratory infections in the first year of life (hazard ratio 1.22). As the authors did not have information on how celiac disease was diagnosed or whether it was confirmed with biopsy, these results were limited. However, Marild *et al*.[9] showed similar results with increased risk of development of celiac disease in children with 10 or more infections before 18 months of age, compared to those with 4 or less infections. That study was prospective, making the results more convincing.

Keywords: Celiac disease; Gluten free diet; Celiac hepatitis; Autoimmune liver disease.

Abbreviations: AIC, autoimmune cholangitis; AIH, autoimmune hepatitis; AILDs, autoimmune liver diseases; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; GFD, gluten-free diet; GGT, gamma-glutamyl transferase; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SIBO, small intestinal bacterial overgrowth; tTG, tissue transglutaminase.

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Liver damage in celiac disease

Liver dysfunction in patients with celiac disease was first described in studies from the 1970s.[10] Celiac disease is associated with two different types of liver dysfunction: cryptogenic liver disorders, usually with positive response to GFD; and autoimmune disorders.

Cryptogenic liver disorders can range from mild to severe hepatitis, and usually present with isolated increase in aminotransferases.[11,12] Histology of the liver typically shows preserved architecture with a mild mononuclear infiltrate of the portal and lobular tract, and hyperplasia of the Kupffer cells. Intraepithelial lymphocytes can be seen in interlobular bile ducts as well as small bowel.[13] Hyperplasia of Kupffer cells is typical of nonspecific reactive hepatitis, also known as celiac hepatitis.[11,12,14] The term 'celiac hepatitis' specifically refers to liver injury in patients with confirmed celiac disease that resolves after introduction of GFD.[3]

Conversely, in autoimmune liver diseases (AILDs), histology of the liver shows mononuclear and eosinophilic infiltration of the portal tract in the presence of characteristic circulating autoantibodies (anti-nuclear ANA, anti-smooth muscle antibody (ASMA), anti-liver kidney microsomal LKM1), suggestive of autoimmune disease. AILDs usually require combination of GFD and immunosuppressive therapy as treatment. It is unknown whether cryptogenic and autoimmune liver disorders have different pathogeneses or constitute a spectrum of the same disorder.[11]

Liver dysfunction in celiac disease can manifest with nonspecific symptoms of hepatitis, such as malaise and fatigue. However, patients are usually asymptomatic and may not have any celiac disease manifestations or symptoms.[3,15] Elevations in aminotransferases are usually mild to moderate, with an aspartate aminotransferase (AST):alanine aminotransferase (ALT) ratio usually less than 1. Alkaline phosphatase (ALP) can be normal or elevated in around 4–20% of cases. Bilirubin and gamma-glutamyl transferase (GGT) are often normal, but prothrombin time and albumin levels are nonspecific and could be altered due to malabsorption.[3] Signs such as jaundice, ascites, encephalopathy or portal hypertension usually indicate advanced liver disease, which can be from another co-existing liver condition.

Wakim-Fleming *et al*.[16] tested for celiac disease in 204 patients with biopsy-proven cirrhosis. Five patients showed positive for celiac disease with duodenal biopsy. These patients had cirrhosis secondary to non-alcoholic steatohepatitis, cryptogenic liver disease, primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), and alcoholic liver disease. Four of these patients were started on GFD and followed for 2 years, the last patient with alcoholic liver disease passed away. Only the patient with AIH received additional treatment with prednisone. All experienced biochemical/serological resolution and normalization of small bowel histology after treatment. Model for end-stage liver disease scores improved in three of the patients.[16] That study suggested that liver damage from celiac disease can be simultaneous to liver damage from another pathology, and biochemical abnormalities can be corrected after GFD incorporation. However, it cannot be determined whether GFD alone would have corrected the elevated aminotransferases. Other measures could have played a role, such as weight loss in the non-alcoholic steatohepatitis patient or cessation of alcohol or hepatotoxic drugs.

Cryptogenic liver disease

Celiac disease has been found in up to 9% of patients with elevated liver enzymes.[3,17] Vajro *et al*.[15] studied six pediatric patients with long-standing aminotransferase elevations. One of them had presented with fatigue, another with hepatomegaly, while the others had incidental findings of elevated aminotransferases. Workup was negative for infectious, infiltrative and toxic causes of liver injury. Other liver tests, including those for alkaline phosphatase, gamma-glutamyl transpeptidase and bilirubin, were normal. However, they tested positive for anti-gliadin serum antibodies, and histological findings from intestinal biopsies were consistent with celiac disease. Liver biopsies in five of the patients yielded nonspecific results (Table 1).[14,15,18–23] All of them experienced biochemical resolution after implementation of GFD, and two of the patients with repeat liver biopsy had histological resolution as well. Three patients received a gluten challenge and experienced elevation of aminotransferases once again, along with increase in anti-gliadin antibodies and histological relapse of intestinal mucosa. After re-introduction of GFD, once again there was biochemical resolution, which persisted at 1–3 year follow-up.[15] The association between isolated elevation of aminotransferases from liver injury and presence of gluten in diet seemed convincing, as other causes of liver damage were ruled out, and there was a positive association between gluten and biochemical/histological abnormalities.

Volta *et al*.[17] evaluated the prevalence of celiac disease in patients with elevated aminotransferases. From 600 mostly asymptomatic patients, 55 (9%) were found to be cryptogenic after other causes of liver disease were ruled out. Viral hepatitis panel, ANA, ASMA, LKM-1, anti-mitochondrial antibody, ceruloplasmin, alpha-1-antitrypsin were negative. Toxins and iron overload were also ruled out.[18] The authors measured IgA anti-endomysial and IgA/IgG anti-gliadin antibodies in the 55 patients with unexplained elevated aminotransferases. Six patients were positive for antibodies, and were offered duodenal and liver biopsies. All five patients (9%) with positivity for IgG anti-gliadin, IgA anti-endomysial and/or IgA anti-gliadin antibodies were diagnosed with celiac disease after duodenal biopsy. Of note, ALP, GGT, serum albumin and prothrombin time were normal in all five patients. The sixth patient with positivity only to IgG to gliadin did not have celiac disease demonstrated on biopsy. Three patients with diagnosed celiac disease had liver biopsies, which showed nonspecific reactive hepatitis. They also performed a liver ultrasonography on all patients, with exception of one patient with hepatic steatosis. After 6 months of GFD, 4 of them (including the patient with fatty liver) experienced histological resolution and normalization of aminotransferases. The remaining patient had persistently elevated aminotransferases, antibodies and villous atrophy, which was thought to be due to poor diet adherence. After correction of diet, they also had biochemical, histological and serological resolution. These results seem convincing, as other causes of liver damage were ruled out and four patients had regularization of aminotransferases after implementation of the GFD. The fifth patient had a delayed recovery with persistently elevated aminotransferases, as well as IgA to endomysium and to gliadin at 6 months. The authors mentioned that presence of these antibodies were suggestive of dietary transgressions. However, testing for gluten immunogenic peptide in urine or stool would have been more reliable detectors of dietary indiscretions.[24,25]

Bardella *et al*.[26] screened 140 patients in Italy with cryptogenic elevated aminotransferases for subclinical celiac disease, and found 13 (9%) positive for anti-gliadin antibody and anti-endomysial IgA antibody. On endoscopy, three patients were found to have mild villous atrophy with intraepithelial lymphocytes, six to have subtotal villous atrophy, three to have total villous atrophy. It is notable that the screened patients had isolated elevation of aminotransferases on three different occasions. Drug and alcohol abuse, viral hepatitis, iron overload and autoimmune liver diseases were ruled out. The prevalence of ce-

Table 1. Liver biopsy findings in celiac disease patients with elevated aminotransferases

Study	Patients	Histologic findings on liver biopsy	Biopsies	AILD*
Vajro *et al*.[15]	6	Reactive hepatitis	2	(−)
		Chronic persistent hepatitis	2	
		Chronic active hepatitis	2	
Volta *et al*.[18]	5	Reactive hepatitis peri-portal inflammation	2	(−)
		Mild fatty infiltration	1	
Bardella *et al*.[19]	13	Minimal changes	9	(−)
		Fatty infiltration	3	
Bardella *et al*.[20]	67	Chronic active hepatitis	5	(−)
		Fatty infiltration	2	
Hagander *et al*.[21]	74	Reactive hepatitis	5	N/A
		Hepatic injury	7	
Jacobsen *et al*.[22]	62	Nonspecific hepatitis	25	(−)
		Chronic active hepatitis	5	
Kaukinen *et al*.[23]	4	Acute fulminant hepatitis	1	N/A
		Congenital liver fibrosis	1	
		Cirrhotic changes	1	
Mounajjed *et al*.[14]	26	Nonspecific findings	5	N/A

Abbreviations: AILD, autoimmune liver disease; N/A, not applicable.
*Serology for autoimmune liver disease; (−), negative serology; N/A, serology not mentioned or not performed.

liac disease was higher compared to the general population (9.3%), with a relative risk of 18.6; although, these findings might not be reproducible on other countries, as celiac disease prevalence is highest in the European continent.[26] At the 1-year follow up, 12 patients had normal laboratory tests after being on GFD, and all of them had disappearance of celiac antibodies. These results seem to support the fact that celiac hepatitis improves with GFD, but there was no mention of the patient who did not have biochemical resolution and whether an underlying disease was found. In addition to the blood-work, liver biopsies were carried out in nine out of the thirteen patients, and six had minimal changes while three had evidence of steatosis. Documentation of body mass index and possible weight loss resulting in normalization of aminotransferases would have been useful in order to determine if non-alcoholic fatty liver disease was also likely playing a role.[17,19]

Bardella *et al*.[20] had previously also evaluated 158 patients with celiac disease and found that 67 of them had elevated AST and/or ALT. All patients were followed for 1–10 years while on GFD. In patients with elevated aminotransferases, body mass index increased from 18.5 to 21 (p<0.001) and aminotransferases normalized in 60 (95%) after 1 year of GFD adherence. The seven remaining patients were found to have fatty infiltration on liver biopsy (two patients) and chronic active hepatitis (five patients) from HCV, HBV and AIH. Other causes of concomitant liver disease with blood-work, abdominal ultrasound and liver biopsy were only sought in those with persistent elevated aminotransferases at 1 year. Whether testing for other causes of liver disease were done at time of celiac disease in all patients is unknown. Nevertheless, histological and biochemical improvement in those patients with celiac disease was likely due to GFD, as they did not receive any other types of treatment and had higher body mass index at 1 year. Three patients were found to have elevated ALP, attributed to hyperparathyroidism according to elevated bone ALP isoenzymes, hypocalcemia, elevated parathyroid hormone and decreased bone mineral density. The authors raised the question of whether the persistently elevated aminotransferases observed in the seven patients, despite proven improvement (but not normalization) in small intestine histology, was due to the fact that intestinal abnormality might not be the only factor associated with liver injury. However, these patients were found to have other causes for elevated aminotransferases. A lack of improvement of elevated aminotransferases in celiac disease patients adherent to GFD should be an indicator for underlying concomitant liver pathology.[20]

Mechanism of liver dysfunction in celiac disease

The mechanism by which celiac disease patients develop abnormal liver enzymes remains unknown. Predisposition to autoimmunity and systemic effects of abnormal intestinal permeability are thought to play pathogenic roles.[3] Gliadin induces an increase in gut permeability and MyD88-dependent zonulin release by binding to CXCR3 chemokine receptor.[10,27] Zonulin is able to reversibly regulate intestinal permeability by modulation of intercellular tight junctions. It is thought that the increased intestinal permeability allows toxins, cytokines, and antigens to reach the liver through the portal circulation and cause liver injury through release of pro-inflammatory mediators. Toll-like receptors expressed in liver cells (such as Kupffer, endothelial, dendritic, hepatic stellate and hepatocytes) can recognize lipopolysaccharides (present in Gram-negative bacteria) and mount an immune response.[11]

Novacek *et al*.[13] studied 178 adults with celiac disease and measured serum aminotransferases prior to initiation of GFD, and periodically thereafter for 1 year. They also measured gut permeability to assess the relationship with liver damage prior to start of GFD. Permeability index was

Table 2. Classification of duodenal histologic changes

Classification	Findings
Grade I	Normal, no shortening of villi or lengthening of crypts
Grade II	Slight partial villus atrophy; slight shortening of villi
Grade III	Marked partial villus atrophy; marked shortening of villi
Grade IV	Subtotal villus atrophy; no definite villus structure

Adapted from Scott and Losowsky.[28]

determined from the ratio of percentage of lactulose excreted in urine to the percentage of mannitol excreted. A comparison was made between patients with elevated versus normal aminotransferases, and permeability indexes were found to be higher in those with abnormal aminotransferases ($p<0.0001$). There was no difference in body mass index, duodenal intraepithelial lymphocytes, age, or onset of symptoms between the two groups. The authors screened for other causes of liver disease in patients with elevated aminotransferases (71 patients), and 9 were found to have underlying causes of liver diseases, such as viral hepatitis, autoimmune conditions, and alcohol abuse, amongst others.[9,13]

After 1 year on GFD, 63 patients showed normalization of aminotransferases and significant decrease in intestinal permeability index ($p<0.0001$). These results seem to support the concept that permeability indexes have an association with liver damage, as they correlated with AST and ALT levels, and improved with GFD adherence. However, it would have been helpful to prove that intestinal permeability indexes had not changed in the group with normal aminotransferases. From patients with persistently elevated aminotransferases, some had underlying liver conditions and four were thought to be due to dietary indiscretions disclosed by the patients.[13] It would have been helpful to determine that there was no significant change in the permeability indexes of those who continued gluten consumption. Additionally, lack of antibody testing before and after GFD implementation makes the determination of whether autoimmunity plays a role difficult.

Bardella *et al*.[20] studied 158 patients with known celiac disease and reported duodenal histological changes classified in terms of severity, at the time of diagnosis, and again after 1 year of GFD. The authors used the histologic classification of Scott and Losowsky.[28] Within the group of patients with elevated aminotransferases, the number of grade I-II histological changes increased from 7 to 60 along with a decrease in grade III-IV histological changes from 60 to 31 after 1 year of GFD (Table 2).[28] There was no correlation assessment performed for levels of aminotransferases and severity of histologic changes, which could have been helpful to determine if there is such a relationship between gut and liver damage. There was also no correlation assessment performed for levels of aminotransferases and celiac antibodies, which could have supported the hypothesis of autoimmunity and liver damage. Small intestinal permeability has been used as an indicator for histological recovery in the past, but that study did not test permeability. Even though there were no differences in histological findings seen between patients with and without elevated aminotransferases, the role of gut permeability in liver dysfunction is difficult to assess without permeability tests. Biopsies for celiac activity are notoriously variable, and the specific tissue obtained might not represent mucosal changes adequately along the entirety of the gut. Additionally, histology based on Scott and Losowsky classification is subjective and operator-dependent, making these results less reliable.

Ukabam *et al*.[29] studied 13 patients with celiac disease before starting GFD and during treatment, and compared them with 25 non-diseased adults. The subjects underwent permeability testing with ingestion of mannitol and lactulose, measurement of percentages of the oral dose in urine, and calculation of lactulose/mannitol excretion ratio (LMER). Small bowel biopsies were obtained without knowledge of the group which the patient belonged to or results of permeability testing. The percentage of lactulose excretion was significantly higher in celiacs compared to non-celiacs, while the percentage of mannitol excretion was significantly lower. Intestinal mucosal damage decreases transcellular absorption of small molecules (such as mannitol) and increases larger paracellular pores that allow passive permeation of larger molecules, such as lactulose.[30] Normally, <1% of ingested lactulose permeates the intestinal mucosa and appears in urine.[31] Lactulose excretion improved on GFD, resulting in decreases in LMERs after GFD, but remained significantly higher compared to normal controls. There was also a positive correlation with improvement in severity of histology findings after GFD; patients with lower LMERs after treatment had mostly grade I histological grading (minor abnormalities) and higher ratios of villus height to total mucosal thickness.[29] That study suggested an association between histology changes and permeability. Results are convincing, as the investigators used villus height to total mucosa thickness ratio, which is a more objective measure of gut lining damage.

Greco *et al*.[31] measured intestinal permeability in two groups (27 patients with celiac disease on GFD for 2 years and 19 healthy controls matched by gender and age) before and 6 h after ingestion of gluten. Urinary excretion of lactulose and L-rhamnose (low molecular weight monosaccharide) were quantified. Lactulose/L-rhamnose ratio was unchanged in controls before and after gluten ingestion. In contrast, the same ratio increased in all celiac patients after ingestion of gluten; although, it is worth mentioning that two of the twenty-seven total patients had abnormal permeability at the beginning.[31] Even though the sample size was rather small, the results suggest that gluten causes changes in permeability, even after a single meal. However, this study was carried out in a pediatric population and thus results are not necessarily applicable for adults.

Lahdeaho *et al*.[32] challenged 21 known celiac disease patients with low (1–3 g) or moderate (3–5 g) doses of gluten daily for 12 weeks and assessed for symptoms, intestinal histology, and celiac serology. These patients were on a strict GFD and in clinical remission. The authors performed morphometric analysis, measuring villus height/crypt depth ratio. A decrease in the ratio of 0.5 or more after gluten challenge was considered gluten sensitivity. A significant decrease in villus height/crypt depth ratio was found in 67% of patients, without correlation with dose of daily gluten intake. There was an increase in CD3 intraepithelial lymphocytes, especially in the group with moderate gluten dose, which in the past has been found to be dose-dependent. There was a serological response in 43% of patients with positivity for EMA and TG2 antibodies.[32] That study suggested an association between gluten and small bowel histological damage, but there is not enough evidence to support association between histological small bowel damage

(or intestinal permeability) and antibody levels.

Lindberg *et al*.[33] prospectively studied 180 children with suspected malabsorption. Ninety-six children with elevated aminotransferases were diagnosed with celiac disease, milk protein and/or multiple protein allergy or were classified as miscellaneous after evaluation of intestinal mucosal morphology. Of 10 children with food allergy and moderate-severe mucosal damage, 6 had elevated ALT and 7 had elevated AST. Those with normal or slight mucosal damage had normal AST and ALT.[33] These findings suggested that mucosal damage is associated with elevation of aminotransferases and not exclusively due to gluten exposure. Nevertheless, these results were limited, as there was no mention of whether other causes of elevated aminotransferases were ruled out. In addition, even though aminotransferases were monitored in some children and normalized after 2–8 weeks of dietary treatment, they did not specify which group of children was followed and what dietary changes were made. For this reason the results are not reliable.

Small intestinal bacterial overgrowth (SIBO)

A study was done to determine the prevalence of SIBO in celiac disease patients who were unresponsive to GFD, symptomatic or asymptomatic on GFD.[34] SIBO was found in 11% of patients unresponsive to GFD and 11% who were symptomatic, while none were found in the asymptomatic group. SIBO was not the only factor associated with persistent symptoms, as 67% of these patients had underlying conditions, such as microscopic colitis. No serologic difference was found between patients with and without SIBO, and serum aminotransferases were not measured. Previous studies have found that prevalence of SIBO is increased in celiacs compared to healthy controls,[35] and that study showed that SIBO can be associated with persistent symptoms in patients adherent to GFD. However, no relationship has been demonstrated between SIBO and elevated aminotransferases. Therefore, an association between bacteria and liver damage in celiac patients remains speculative.

Systemic autoimmunity

The pathogenesis behind extraintestinal manifestations of celiac disease is still not entirely understood, but it is thought to be due to autoantibodies that target transglutaminase 2 (TG2). TG2 is the antigen to which celiac IgA antibody binds *in vitro* in intestinal and extraintestinal tissues. Karponay-Szabo *et al*.[36] performed a study to detect IgA against intestinal and extraintestinal tissues by immunofluorescence. IgA deposition on extracellularly located TG2 was found in jejunal and extrajejunal specimens of all celiac patients. Overexpression of TG2 in liver causing deposition of IgA antibodies could potentially explain liver damage in celiac disease patients.[11] However, it would not explain why some patients have elevated aminotransferases and others do not.

Diagnosis

In the serum of patients with celiac disease, there are various types of antibodies that target gliadin or connective tissue components These include anti-endomysial and anti-tissue transglutaminase antibodies (anti-tTG). Sjoberg *et al*.[37] measured anti-gliadin antibodies (IgA and IgG) in patients with chronic liver disease and compared them to healthy controls. Anti-gliadin IgA positivity was significantly higher in the group with chronic liver disease (particularly patients with PSC) compared to healthy individuals.[37] Further work-up with anti-endomysial antibody was positive in two patients out of four-hundred and sixty-five who were found to have celiac disease based on small bowel biopsy. These results showed that anti-gliadin antibodies can be positive in many chronic liver conditions without celiac disease. Anti-gliadin antibodies are no longer recommended for diagnosis due to low sensitivity and specificity.

Anti-tTG IgA is the serologic test of choice for diagnosis of celiac disease. However, Vecchi *et al*.[38] measured anti-tTG and anti-endomysial antibodies in a group with celiac disease and another group with chronic liver disease (including cirrhosis) and found anti-tTG positivity in the chronic liver disease group. Even though anti-endomysial antibody was negative in all patients within this group, 57.9% of the cirrhotics had positive anti-tTG, likely indicating that chronic liver disease can cause false positives. Similarly, anti-tTG can be falsely positive in diabetes mellitus, Down's syndrome, and inflammatory bowel disease.[38]

Testing for deaminated gliadin peptide IgA or IgG is likely more accurate in children <2 years-old and who are anti-tTG negative.[39] IgA-endomysial antibodies have nearly 100% sensitivity and specificity in untreated celiac patients but testing is expensive and time consuming. Serologies usually normalize after 6–12 months of GFD but mucosal healing is a slower process.[39,40]

Small bowel biopsy remains the gold standard. Pathologic findings in the duodenum can vary in severity and may have a patchy distribution, affecting certain areas more than others. Collection of multiple specimens (four to six) must be submitted to increase sensitivity for diagnosis.[39] Several studies have reported higher diagnostic yields for biopsy of duodenal bulb[39–41] compared to the terminal ileum.[42,43]

Treatment

In the previously mentioned studies performed by Volta *et al*.,[15] Vajro *et al*.[18] and Bardella *et al*.,[19] findings seem convincing that GFD reverses cryptogenic liver disease, as evidenced by normalization of elevated aminotransferases. In the study by Novacek *et al*.,[13] eight patients did not respond to GFD and it was thought to be either due to diet non-adherence or another concomitant liver disease. That study suggested that celiac disease patients with persistently elevated aminotransferases despite GFD could have a second liver pathology non-responsive to GFD. In the study by Bardella *et al*.[20] from 1995, patients who responded to dietary changes were not tested for other underlying liver disease. Thus, it could not be determined if they did have another underlying condition, despite showing improvement with only GFD.

Hagander *et al*.[17,21] first described liver injury in association with celiac disease after they found patients with known celiac disease and elevated liver enzymes. The authors retrospectively studied 74 patients with biopsy-proven celiac disease. Histology sections were available from thirteen patients, of which five showed reactive hepatitis and seven had hepatic injury. Out of 53 patients with measured aminotransferases, 29 had elevations and 19 of them had measurements before and after starting GFD; a significant reduction was found after dietary changes. However, the authors did not mention whether other causes of liver damage were ruled out in the 29 patients and not all patients with elevated enzymes were monitored after GFD; furthermore, the follow-up period was for only 8 weeks. There was also no clarification on whether all 19 patients had reduction in aminotransferase levels after GFD. There may have been cases of non-response to GFD that were undiscovered, but the follow-up period was also too short to determine non-

response. Overall, it is difficult to draw conclusions from this study even though a significant reduction in measured enzymes after start of GFD in certain patients seem to support the previous studies' findings.

Jacobsen *et al*.[22] examined 132 patients with biopsy-proven celiac disease for hepatic involvement and found that 62 (47%) had elevated AST, ALT and ALP. These patients had other causes of liver damage ruled-out. Thirty-seven patients had liver biopsies performed, of which twenty-five showed nonspecific hepatitis and five showed chronic active hepatitis.[17,22] Only 32 patients were rechecked after 2 years on GFD and were found to have significantly lower liver enzymes, while 24 had complete normalization of laboratory values. Four patients with complete normalization of laboratory tests had repeat liver biopsies that showed additional histologic normalization of nonspecific changes. It was not mentioned why only these patients had a repeat liver biopsy, especially after normalization of enzymes. Of 38 patients with small intestine biopsies before and after implementation of GFD, 24 had improvement in gut lining after GFD. The group with intestinal histologic improvement had median duration of symptoms of 11.4 years compared to 21.1 years from those who did not respond to dietary restrictions.[22] This could mean that onset of celiac disease could be a determinant of whether GFD reverses gut permeability and therefore, liver damage. Findings seem convincing that GFD improved liver damage in the study, as seen by significant improvement in aminotransferases. Lack of intestinal histologic improvement in eight patients, however, seemed to contradict these findings. There is no mention, though, of severity of histological findings, whether there was correlation with antibodies or timing of repeat intestinal biopsy, or whether it was carried out concomitantly with repeat blood-work after 2 years. Thirty-eight patients had a repeat small intestine biopsy, while only thirty-two patients with elevated aminotransferases were rechecked at 2 years. This suggests the small intestinal biopsies occurred prior to follow up at 2 years, and there are no data on whether these were the same patients who had aminotransferases rechecked. A longer period of time on GFD could have potentially led to different biopsy results.

Kaukinen *et al*.[23] showed that a GFD could cause reversal of hepatic dysfunction in patients with celiac disease and severe liver disease. The investigators retrospectively studied four patients with untreated celiac disease and severe liver failure. Liver biopsy showed acute fulminant hepatitis in one patient with known celiac disease who was non-compliant with GFD. He had no family history, denied use of drugs/alcohol, and other underlying liver diseases were ruled-out. His liver function initially improved after starting GFD but, unfortunately, he later progressed due to non-adherence to diet. Another patient was diagnosed with congenital liver fibrosis, from a biopsy after presenting with ascites. He was later found to have histologic changes in duodenum consistent with celiac disease. Within 6 months of GFD, his ascites resolved. There were no signs of liver disease and small bowel mucosal biopsy was normal. This patient was considered for liver transplant due to severity of disease but, ultimately, improved with dietary changes and transplant was not needed. Of the two remaining patients, one had other causes of liver disease investigated and ultimately improved with GFD and steroids. The remaining patient had cirrhotic changes on biopsy without clear recovery despite steroid treatment for suspected AIH. Although her lack of improvement was deemed due to poor GFD (and steroid) compliance with persistent mucosal villus atrophy on repeat small bowel biopsy, her persistent liver damage could have been due to autoimmune disorder. It is difficult to determine if GFD improved liver function based on these case reports, especially when two of them were suspected to have autoimmune liver disease and were treated with concomitant steroids. Correlation with celiac antibodies could have been useful to determine whether the persistently elevated aminotransferases was possibly related to higher levels of antibodies.

Celiac disease and autoimmune liver diseases

Liver involvement in celiac disease can coexist with other autoimmune conditions, such as primary biliary cholangitis (PBC) or PSC.[13] Many of the aforementioned studies showed cases of patients with celiac disease who had persistently elevated aminotransferases despite GFD and who were ultimately found to have an autoimmune liver condition. Another study found a 3% prevalence of PBC in 143 patients with celiac disease, and there have been similar findings in other studies in Denmark and Sweden.[44] Schrumpf *et al*.[45] found a 3% prevalence of celiac disease in patients with PSC. The prevalence of celiac disease in AIH was reportedly higher compared to the general population (around 3–6%).[45] Mounajjed *et al*.[14] studied 30 patients with celiac disease who had liver biopsies and found 9 patients with AIH, 3 with PBC and 7 with PSC.

AIH and celiac disease

Celiac disease has a strong HLDA-DQ association. Approximately 95% of patients with celiac disease express HLA-DQ2, which has a strong association with HLA-DR3 expressed in autoimmune hepatitis.[1] Prevalence of celiac disease in AIH is higher compared to that in the general population and is thought to be around 4-6.4%.[1]

Iqbal *et al*.[1] presented the case of a patient with known AIH on azathioprine with flares of elevated aminotransferases. The patient was not taking any supplements or over-the-counter medications and denied drug/alcohol use. ASMA, alpha-1 antitrypsin antibody and anti-mitochondrial antibody were negative, as well as hepatitis panel and antibodies against cytomegalovirus and Epstein-Barr virus. Ceruloplasmin, thyroid stimulating hormone and iron were normal. A liver biopsy showed grade 3 portal fibrosis. The patient was started on steroids, without improvement. He was further investigated for anti-tTG and endomysial immunoglobulin A antibody, the results of which seemed consistent with celiac disease. A small bowel biopsy revealed flattening of villi with intraepithelial lymphocytes, confirming diagnosis. He had normalization of aminotransferases and bilirubin with GFD.[1] The fact that aminotransferase elevations did not improve despite being on treatment for AIH but normalized after initiation of GFD seems to suggest that persistent elevated aminotransferases was due to celiac disease.

Volta *et al*.[46] studied a case of a celiac patient who had persistently elevated aminotransferases after 1 year on GFD. She also had elevated bilirubin, high albumin and low platelets. Eventually, the patient was investigated for autoimmune conditions and was found to have positive ANA, ASMA and anti-dsDNA. On GFD, celiac disease-related antibodies were negative, while small bowel biopsy showed normal findings, suggesting adherence. Liver biopsy showed chronic active hepatitis with lymphocytic and plasma cell periportal infiltration. She was started on azathioprine and methylprednisolone, in addition to GFD, and had normalization of laboratory tests at the 18-month follow up visit.[46] Although this was a single reported case, it suggests that combination therapy for both celiac disease and AIH normalized aminotransferases.

Additionally, Di Biase *et al*.[47] studied seven children with known celiac disease on GFD and AIH diagnosed by liver his-

tology and serology. They had mild fibrosis and necrosis in all cases. They were treated with steroids and azathioprine for 5 years, with biochemical and ultrasound tests every 3 months. All patients had normalized aminotransferases at 5 years. Six underwent liver biopsy, which revealed no interface hepatitis, and only two had (minimal) inflammation. Even though there was no mention found of aminotransferases levels prior to addition of AIH therapy, the results of liver biopsies suggest that treatment for both conditions led to improvement in liver histology.[47] There is no evidence to suggest liver damage from AIH-celiac disease is reversible with GFD only.

PBC and celiac disease

The prevalence of PBC has been reported to be 3- to 2-fold higher in celiac disease patients, while celiac disease prevalence in PBC patients ranged from 3–7%.[48] Kingham *et al*.[49] determined the relative prevalences of PBC and celiac disease in a population of around 250,000 over 12 years. They found 143 patients with celiac disease (biopsy-proven and responsive to GFD) and 67 with PBC (proven with liver biopsy). In patients with celiac disease, four were found to have concomitant PBC. Of all patients with PBC, 11 underwent duodenal biopsy and 1 was diagnosed with celiac disease. Approximately 3% of patients with celiac disease might develop PBC, while around 6% of patients with PBC might have celiac disease.[49] Many cases of simultaneous PBC and celiac disease have been reported in multiple studies but a common causal association has not been proven.[50,51] Conversely, Chatzicostas *et al*.[52] screened 62 patients with PBC and 17 with autoimmune cholangitis (AIC) for celiac disease by testing for anti-gliadin, anti-reticulin, anti-endomysial and anti-tTG antibodies. They also tested 100 random donated serum samples and 18 biopsy-proven uncontrolled celiac disease patients as controls. Anti-gliadin and anti-tTG antibodies were significantly higher in patients with PBC and AIC compared to the healthy controls, but none were positive for anti-reticulin or anti-endomysial antibodies. However, duodenal biopsies in 15 out of 24 patients with PBC or AIC and positive antibodies did not show histologic features suggestive of celiac disease. The study had a small sample size, and did not establish an increased risk for celiac disease in PBC patients.

Ginn *et al*.,[53] Neuberger *et al*.[54] and Logan *et al*.[55] reported cases of patients with concomitant celiac disease and PBC where GFD alone did not normalize aminotransferases. There was a lack of evidence to prove that GFD is sufficient for histological and biochemical resolution of liver damage in patients with both conditions. Additionally, whether GFD slows down progression of liver damage is difficult to prove.

PSC and celiac disease

Brazier *et al*.[56] reported a case of a patient with elevated AST, ALT and ALP and moderate dilation of the common bile duct on ultrasound. He had an ERCP, which showed diffuse narrowing and irregularity of the intrahepatic bile ducts without any obstruction. In the absence of secondary causes of PSC, diagnosis of primary PSC was suggested. On liver biopsy, he was found to have onionskin fibrosis and mononuclear infiltrate. Colonoscopy showed findings consistent with ulcerative colitis, while upper endoscopy showed findings consistent with celiac disease. Anti-reticulin antibodies and anti-endomysial antibodies were positive. He was treated only with GFD for 14 months, with improvement in duodenal histology, normalization of antibody levels and of AST, ALT and ALP. Repeat liver biopsy showed improvement from histological stage 2 to stage 1. Although treatment with only GFD showed improvement in liver histology and normalization of laboratory tests, it is difficult to draw conclusions from a single case report.

Nonalcoholic fatty liver disease (NAFLD) and celiac disease

Reilly *et al*.[57] studied the risk of NAFLD in celiac disease patients with matched healthy controls. They ruled out patients with previous liver disease and those with lifetime diagnosis of alcohol-related conditions. They found that patients with celiac disease had an increased risk of developing NAFLD compared to healthy controls, with a hazard ratio of 2.8.[57] Similar findings were concluded by Tovoli *et al*.[58] after studying a celiac disease group of patients compliant with GFD with matched controls. It has been shown that NAFLD patients have increased intestinal permeability and greater association with SIBO.[35,59] The increased risk for developing NAFLD in celiac disease patients might be explained by these pathogenic mechanisms in common.

Miele *et al*.[35] investigated intestinal permeability in patients with NAFLD (biopsy-proven), assessed correlation with liver damage, integrity of tight junctions and prevalence of SIBO, and compared to a group of celiacs and group of healthy controls. They found that patients with NAFLD had a higher prevalence of SIBO and increased permeability compared to healthy patients, but lower compared to the celiac patients. Increased intestinal permeability and SIBO prevalence correlated with severity of steatosis in patients with NAFLD. This group also had lower intensity of duodenal ZO-1 staining, suggesting less intact tight junctions, possibly causing increased permeability. These findings suggest that bacterial translocation may be related to increased gut permeability and steatosis; although, the mechanism remains unproven.

Conclusions

Patients with celiac disease should have liver enzymes routinely checked. If abnormal laboratory tests are found, it is reasonable to implement a strict GFD and monitor for response with repeat testing over the next 6–12 months. Many studies have shown improvement or normalization in aminotransferases with GFD and relapse with a gluten challenge. Lack of improvement should prompt a search for evidence of dietary transgressions. Following IgA anti-endomysial and IgA anti-gliadin levels might be useful in assessing compliance with diet, but if the patient is strictly adherent to GFD, further workup for other causes of liver disease and/or liver biopsy should be considered.[18]

On the other hand, patients with elevated liver enzymes without known history of celiac disease should be screened for this disease, regardless of symptoms, as the evidence shows most patients are asymptomatic.[17] These patients should be screened with celiac disease serology, and if found to be positive, undergo a confirmatory small-bowel biopsy. If diagnosed with celiac disease, implementation of GFD is recommended, with follow-up testing in 6-12 months.

In patients with known celiac disease and an autoimmune liver disorder, treatment of concomitant autoimmune hepatobiliary disease is suggested in addition to GFD, as there is insufficient evidence to suggest biochemical or histological normalization with GFD only. Previous studies do show that GFD can improve aminotransferase levels in patients with PBC and PSC. These enzymes might help in slowing down progression of disease, but further longitudinal studies are needed to prove this hypothesis. Assuming systemic auto-

immunity is the main mechanism of liver damage in celiac disease, assessing response to steroids alone in patients with simultaneous AIH and correlating aminotransferase levels and antibodies could be useful.

The mechanism of liver damage in celiac disease patients is likely multifactorial. It is possible that gut lining damage in general, and not exclusively due to gluten-induced damage, could cause elevated aminotransferases. SIBO and local (rather than systemic) endotoxemia could be related to increased intestinal permeability and liver damage. However, this specific association remains speculative and further studies would be needed to determine if there is a significant association.

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Conflict of interest

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Author contributions

Wrote the manuscript (JVK), proposed the idea for the review and revised the manuscript with critical revisions (GYW).

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