Journal of Clinical and Translational Hepatology **2025** vol. 13(10) | 869–877
DOI: 10.14218/JCTH.2025.00153

Review Article

Autoimmune Hepatitis Associated with Other Autoimmune Diseases: A Critical Review

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Received: April 09, 2025 | **Revised:** June 27, 2025 | **Accepted:** July 07, 2025 | **Published online:** August 27, 2025

Abstract

Autoimmune hepatitis (AIH) is an inflammatory liver disease influenced by genetic, environmental, and immunologic factors. Individuals diagnosed with AIH may exhibit concurrent autoimmune manifestations affecting multiple organ systems. The prevalence of AIH associated with other autoimmune diseases has been reported to range from 20% to 40%. This review indicates that the associations between AIH and autoimmune thyroiditis, type 1 diabetes mellitus, ulcerative colitis, Crohn disease, and celiac disease appear to be significant. However, the associations between AIH and primary sclerosing cholangitis, primary biliary cholangitis, rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, and vitiligo are not well-supported. The aim of this review is to evaluate the strength of the reported associations between AIH and other autoimmune diseases, and to update and present the available evidence on their prevalence, proposed underlying pathogenic mechanisms, diagnostic considerations, and treatment approaches.

Citation of this article: Zhao D, Wu GY. Autoimmune Hepatitis Associated with Other Autoimmune Diseases: A Critical Review. J Clin Transl Hepatol 2025;13(10):869–877. doi: 10.14218/JCTH.2025.00153.

Introduction

Autoimmune hepatitis (AIH) is an inflammatory liver disease influenced by genetic, environmental, and immunologic factors. Individuals diagnosed with AIH may exhibit concurrent autoimmune manifestations affecting multiple organ systems. It is classified into type 1 (AIH-1) and type 2 (AIH-2) based on the presence of specific antibodies. AIH-1 is associated with antinuclear antibody (ANA) and anti-smooth muscle antibody (ASMA) seropositivity, whereas AIH-2 is characterized by the presence of anti-liver kidney microsome type 1 antibody (LKM1) antibodies or anti-liver cytosol type 1 antibodies.[1] The prevalence of AIH is higher in females (3.5:1 female-to-male ratio),[2–4] although male cases are reportedly increasing.[5,6] A recent global meta-analysis of 22 studies reported an annual incidence of 1.37 per 100,000 and a prevalence of 17.44 per 1,000,000 across Asian, European, and American populations. Regionally, the prevalence of AIH in the USA was 22.8 per 100,000.[7] In a US cohort study, the prevalence rate of AIH diagnosis was 31.2 per 100,000, with higher rates in Caucasians, females, and those over 65 years.[8]

The prevalence of AIH-associated autoimmune diseases has been reported to range from 20% to 40% (Table 1).[4,6–41] In this review, we define the term "associated" as the prevalence of two conditions appearing together at a frequency greater than would be expected based on the individual prevalence of either condition alone. Proposed pathogenetic mechanisms of AIH-associated autoimmune diseases include genetic factors, immune dysregulation, and molecular mimicry (Fig. 1).[9,42] Because the organ and tissue involvement vary so widely, the question arises as to whether the associations are real and, if so, whether there are pathogenetic autoimmune bases in common that underlie the development of these associated diseases.

The aim of this review is to update and present the supporting data on the prevalence, proposed pathogenetic mechanisms, diagnostic considerations, and specific treatment approaches for AIH-associated autoimmune diseases.

AIH-associated endocrine autoimmune diseases

AIH-associated autoimmune thyroid disease (ATD)

Supportive evidence and epidemiology: A recent national US population study involving over 37 million individuals reported that patients with AIH were more likely to have a history of AITD than those without AIH ($P < 0.0001$). However, two-thirds of the AIH cases in this study were diagnosed without liver biopsy. AIH-ATD is among the most common AIH-associated autoimmune diseases, affecting 6% to 23% of patients with AIH. Hashimoto thyroiditis (HT) is the most prevalent, followed by Graves disease (GD), with a reported prevalence of 6% for GD in AIH.[10,11] A study of 163 patients with AIH and 1104 age- and gender-matched controls found a significantly higher prevalence of hypothyroidism in AIH patients (17.7% compared to 5%, $P < 0.001$).[12] These studies overall suggest a strong association between AIH and ATD.[8]

Proposed pathogenic mechanisms: Proposed pathogenetic mechanisms of AIH-associated autoimmune diseases

Keywords: Autoimmune hepatitis; Autoimmune diseases; Immune system diseases; Genetic predisposition to disease; Prevalence; Diagnostics; Treatment.

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Table 1. Reported AIH-associated autoimmune diseases

AIH-associated autoimmune diseases	Prevalence of AIH-associated autoimmune diseases in AIH (%)	References
Endocrine		
Autoimmune thyroiditis (Hashimoto thyroiditis and Graves disease)	6–23*	6,10–12,35
Diabetes (Type 1)	1–10*	10,19,33,35
Hepatobiliary		
Primary biliary cholangitis	2.1–19‡	9,20–22,36,37
Primary sclerosing cholangitis	2–10‡	11,13–15,23,24,36,37
Gastrointestinal		
Inflammatory bowel disease (Ulcerative colitis and Crohn disease)	2–16*	8,10,25,35,38–41
Celiac disease	2.8–6.4*	26–28,35
Rheumatologic		
Systemic lupus erythematosus	1.6–15†	16,17,29,31,35
Rheumatoid arthritis	1.6–7.8‡	4,7,8,30,32,33,35
Sjögren syndrome	4.9‡	8
Dermatologic		
Vitiligo	1–4†	18,33,34

*Statistical significance (*P*-value < 0.05 was considered statistically significant). †Lack of statistical significance. ‡Statistical significance was not specified in the studies. AIH, autoimmune hepatitis.

include genetic factors, immune dysregulation, and molecular mimicry.[9,42] AIH-1 is strongly associated with the human leukocyte antigen (HLA)-DRB1 (DR3) locus,[13] which encodes the class II human major histocompatibility complex responsible for presenting antigens to $CD4^+$ T-helper cells (Th) and $CD8^+$ cytotoxic T lymphocytes. A study of 649 AIH-1 patients found that 75% were positive for HLA DRB1*03 and DRB1*04 ($P < 0.001$), suggesting a significant prevalence in Caucasian European and North American populations.[13] DRB1*04:05 has also been significantly associated with AIH in Japanese cohorts (OR = 3.47, 95% CI: 2.34–5.14, $P = 4.0 \times 10^{-9}$).[14] AIH-2 susceptibility has been shown to be significantly associated with HLA-DRB1*03, as shown in a study of 60 Caucasian patients with AIH-2 and 313 control subjects (RR = 4.25, $P < 0.0001$).[43,44] Whole-genome sequencing has further identified several gene variants associated with AIH-ATD, particularly within the HLA-DR gene loci.[15,45] HLA-DR3, specifically the DRB1*03 allele, is significantly associated with AITD, especially GD (RR = 3.4, $P = 0.00032$).[46] However, there is a discrepancy regarding the strength of association between HT and HLA-DR3.[46,47]

Regulatory T cells have been reported to play a pivotal role in maintaining immune tolerance and preventing the activation of autoreactive T cells. When the function of regulatory T cells is impaired, autoreactive T cells target tissue-specific antigens, resulting in liver injury in AIH and thyroid damage in AIH-ATD. Immune dysregulation in AIH and AIH-ATD is further driven by expansion of Th cell subsets, particularly Th17 and Th22, which secrete IL-17 and IL-22, thereby amplifying thyroid cell injury and perpetuating inflammation in HT.[48] Th1, Th2, and Th17 activity are also increased in GD and AIH, producing cytokines involved in inflammation and collagen production in GD orbitopathy.[49] Similarly, in AIH, Th1 and Th17 cytokines contribute to inflammation, fibrosis, and collagen deposition in the liver, exacerbating the autoimmune response.

A case–control study of 163 patients with AIH and 1104 age- and gender-matched healthy controls proposed that the association between AIH and AITD may be mediated in part by the presence of serum anti-thyroid peroxidase antibodies.[12] These were significantly more prevalent in AIH cohorts compared to controls (OR = 1.32, 95% CI: 0.87–1.98), suggesting shared immune pathways, although this particular study did not include the analysis of other autoantibody levels.[12]

Diagnostics: Elevated liver enzymes are usually the initial sign of AIH. This is often accompanied by elevated serum IgG levels. Other causes of elevated liver enzymes, such as viral hepatitis, drug-induced liver injury, metabolic dysfunction-associated steatotic liver disease (MASLD), primary sclerosing cholangitis (PSC), and primary biliary cholangitis (PBC), should be excluded. According to the guidelines from the American Association for the Study of Liver Diseases, ANA and ASMA antibodies should be checked in adults, while in children, LKM1 and antibodies against soluble liver antigen and liver cytosol 1 should also be tested.[50] If these antibodies are positive, a liver biopsy can confirm the diagnosis of AIH with histologic evidence of interface hepatitis with plasma cell infiltration, lobular hepatitis, lymphocytes or plasma cells within the cytoplasm of hepatocytes (emperipolesis), and hepatocyte rosettes.[9,51] If ANA and ASMA are negative, a liver biopsy should be pursued, as up to 20% of AIH cases may be seronegative.[52] The Simplified Diagnostic Criteria from the International Autoimmune Hepatitis Group utilize ANA, ASMA, LKM1, and soluble liver antigen antibodies, IgG levels, liver histology, and exclusion of viral hepatitis to help distinguish probable from definite AIH. Imaging studies are not routinely used to diagnose AIH.[9] Diagnosing AIH with concomitant thyroid dysfunction can be challenging due to overlapping laboratory findings. Hyperthyroidism can cause nonspecific elevation of serum liver enzymes. This may result directly from increased hepatocyte oxygen demand without

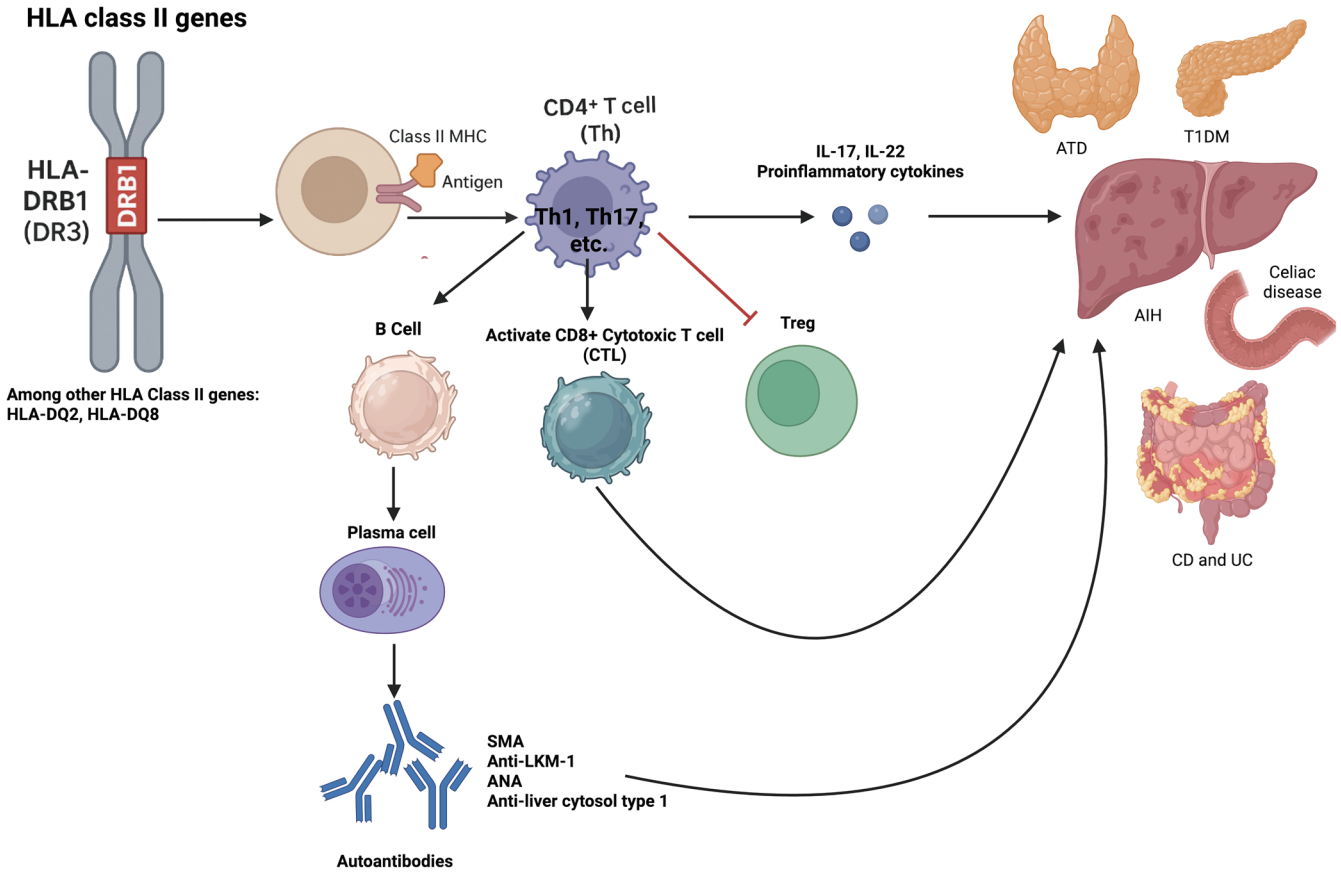

Fig. 1. A diagram showing possible pathogenetic pathways of AIH and associated autoimmune diseases. The leading proposals involve HLA class II gene-mediated antigen presentation through MHC class II, leading to CD4+ T cell activation, such as Th1 and Th17 subsets, among others. These stimulate the production of proinflammatory cytokines IL-17 and IL-22, cytotoxic CD8+ T cells, and autoantibody-producing B cells. Impaired regulatory T cell (Treg) function contributes to immune dysregulation. These shared mechanisms may account for the autoimmune damage to the liver and associated organs, as seen in celiac disease, autoimmune thyroiditis, Crohn disease, ulcerative colitis, and type 1 diabetes mellitus. Created with BioRender. AIH, autoimmune hepatitis; HLA, human leukocyte antigen; MHC, major histocompatibility complex; ATD, autoimmune thyroid disease; T1DM, type 1 diabetes mellitus; CD, Crohn disease; UC, ulcerative colitis; SMA, smooth muscle autoantibody; ANA, antinuclear autoantibody.

increased hepatic perfusion, or indirectly from other organ involvement, such as hyperthyroid-induced heart failure, which may cause hepatic venous congestion and elevation of liver enzymes.[53] In a study of 95 patients with hyperthyroidism, 72 had at least one liver enzyme abnormality, none of which were attributed to viral hepatitis or AIH. This underscores the need for a high index of suspicion when diagnosing concomitant AIH and consideration of liver biopsy in such patients.[16,54] Hypothyroidism may also cause elevated ALT, AST, and GGT levels as a result of impaired lipid metabolism and the development of hepatic steatosis. These nonspecific liver enzyme elevations can mask possible concomitant AIH without liver biopsy.

Treatment: In patients with AIH and associated autoimmune diseases, therapeutic strategies largely involve immunosuppression to control hepatic inflammation while addressing disease-specific manifestations of the coexisting autoimmune condition. Guidelines from the American Association for the Study of Liver Diseases recommend first-line treatment of AIH with prednisone or a combination of prednisone and azathioprine to induce remission.[17,55,56] This combination has shown superior efficacy in maintaining remission compared to monotherapy and is widely accepted in clinical guidelines as the mainstay treatment in AIH with associated autoimmune diseases, although there are specific differences in treatment strategies for each AIH-associated autoimmune disease that will be discussed in this review.[57–61] In patients intolerant to azathioprine, alternatives include 6-mercaptopurine or mycophenolate mofetil, although evidence remains limited and is largely based on observational data. Alternative therapies for treating AIH beyond steroid therapy include cyclophosphamide, methotrexate, and biologics such as rituximab or infliximab. However, the risks and benefits should be discussed due to the risk of infection and other serious complications, particularly in patients with underlying liver dysfunction. Additionally, biologic agents such as infliximab, natalizumab, and adalimumab have been linked to drug-induced AIH.[2,62] The definitive treatment for cirrhotic patients with AIH is liver transplantation.[18]

There are no established guidelines for treating AIH-ATD. Case reports suggest that glucocorticoids may improve liver enzyme and thyroid hormone levels in AIH with coexisting GD, likely due to corticosteroid-mediated suppression of thyroid-stimulating hormone secretion and reduced peripheral conversion of T4 to T3. In one case report, a patient with AIH, HT, and multiple sclerosis showed clinical and laboratory improvement with glucocorticoid and azathioprine therapy.

Another case report demonstrated improved liver function and polyserositis with ursodeoxycholic acid and methylprednisolone in a patient with AIH and HT.[63,64] Sodium L-thyroxine replacement, along with steroids and azathioprine, resulted in normalization of thyroid and serum liver enzyme levels in a case report of a patient with AIH, HT, and vitiligo.[65]

In a review of 11 cases of patients with AIH-GD, radioactive iodine was used in seven cases, two of which developed progression of AIH requiring glucocorticoid therapy. Four patients were treated solely with corticosteroids and achieved sustained remission of both GD and AIH. One patient was initially treated with corticosteroids, which led to remission of AIH but had recurrence of GD with steroid taper. Glucocorticoid therapy remains one of the preferred and effective therapies in AIH-HT. Because of the limited efficacy of glucocorticoids in GD, they may only be effective for their anti-inflammatory properties in AIH. Therefore, separate treatment of GD should not be overlooked.[66]

AIH-associated type 1 diabetes mellitus (T1DM)

Supportive evidence and epidemiology: The prevalence of AIH-T1DM has been reported to range between 1% and 10%.[10] A meta-analysis of 77 studies estimated the pooled prevalence of T1DM in AIH at 3.8%, although statistical significance was not reported.[19] However, heterogeneity among the included studies was high. A large US population database study also found a statistically significant higher likelihood of T1DM in patients with AIH compared to the general population ($P < 0.0001$), supporting an association between AIH and T1DM.[8]

Proposed pathogenic mechanisms: Allelic variants of DR3, such as DRB1*03:01, have been described as risk factors for AIH. These variants are also associated with increased susceptibility to T1DM alone.[19] A genome-wide association study of 649 AIH-1 patients and 13,436 controls identified HLA-DRB1*0301 as the primary susceptibility genotype ($P = 5.3 \times 10^{-49}$) and HLA-DRB1*0401 as a secondary susceptibility genotype ($P = 2.8 \times 10^{-18}$). The strengths of this study include its large sample size and robust statistical significance. Additionally, a meta-analysis of 14 studies (5,196 T1DM cases and 6,359 controls) computed a summary OR of 6.32 for the DR3 homozygous haplotype, suggesting a high risk for T1DM. While HLA-DR3 is associated with increased risk for both AIH and T1DM individually, studies exploring the risk of concurrent disease are limited.[19]

Diagnostics: Elevated liver enzymes commonly observed in AIH can also occur in T1DM patients due to various hepatic complications. For instance, glycogenic hepatopathy, a condition characterized by excessive glycogen accumulation in hepatocytes, is a recognized complication of poorly controlled T1DM and presents with elevated liver enzymes and hepatomegaly. Additionally, MASLD is prevalent among individuals with T1DM and can lead to similar elevations in liver enzymes. These overlapping hepatic manifestations necessitate a careful diagnostic workup to distinguish between liver enzyme elevations due to AIH and those resulting from diabetes-related liver conditions.[67] Leeds *et al*. found that elevated ALT levels were associated with factors such as poor glycemic control, age, and elevated triglycerides. Elevations in ALT can mimic the biochemical profile seen in AIH, complicating a timely diagnosis of autoimmune liver injury.[68] In a cross-sectional study, Jensen *et al*. found that patients with AIH exhibited increased levels of glucagon-like peptide-1 and glucose-dependent insulinotropic peptide hormones, whereas patients with MASLD did not demonstrate significantly altered incretin responses. These findings may help in differentiating AIH from MASLD associated with T1DM.[69]

In patients where AIH and MASLD are difficult to distinguish, obtaining a liver biopsy is essential. MASLD histologically presents with ballooning degeneration of hepatocytes and steatosis-hepatocytes containing large lipid vacuoles that peripherally displace the nuclei. Mallory-Denk bodies may also be seen in the cytoplasm.[70] In contrast, histologic findings in AIH demonstrate interface activity portal tracts with lymphocytic inflammation rich in plasma cells that extends from the portal tract to the lobular parenchyma, characteristic of AIH. Emperipolesis (the presence of lymphocytes or plasma cells within the cytoplasm of hepatocytes) and hepatic rosette formation may also be seen.

Treatment: Treatment of concomitant AIH and T1DM can be challenging, as steroid therapy in AIH can often lead to hyperglycemia and contribute to worsening diabetes. These patients may require significantly higher doses of insulin than those without AIH.[19]

Therefore, non-steroidal or steroid-sparing maintenance options, including azathioprine, 6-mercaptopurine, or low-dose systemic steroids such as budesonide, should be considered as alternatives. These therapies can reduce risks of hyperglycemia and hyperglycemia-related morbidity. Azathioprine is preferred for AIH remission maintenance therapy but should be used cautiously in acutely jaundiced patients given its potential hepatotoxicity. It is typically started after a response to corticosteroid therapy has been established.[57] 6-mercaptopurine (an azathioprine metabolite) may also be an alternative therapy if azathioprine is not well tolerated. For patients who do not tolerate azathioprine or 6-mercaptopurine, mycophenolate mofetil can be used as a second-line option with similar efficacy. Long-term maintenance therapy includes low-dose corticosteroids alone or in combination with azathioprine.[57]

Identifying the primary autoimmune disease to guide immunosuppressive therapy can be clinically challenging. Immunosuppressive therapies generally target AIH to decrease the risk of progressive liver injury, while the autoimmune-mediated destruction of pancreatic beta cells is largely completed by the time T1DM manifests, thus minimizing the therapeutic benefit of immunosuppressive therapy for T1DM. Treatment of AIH with immunosuppressive therapy should be prioritized, with interdisciplinary support from endocrinology to guide the management of diabetes.[58]

AIH-associated autoimmune hepatobiliary and gastrointestinal diseases

The association between AIH and hepatobiliary diseases such as PSC and PBC, and how they coexist, remains controversial. There are several theories regarding the relationship between AIH and autoimmune hepatobiliary diseases: 1. AIH and PBC/PSC are two separate disease processes that present together. 2. AIH and PBC/PSC represent a "middle ground" on a continuum between AIH and other autoimmune liver diseases. 3. AIH and PBC/PSC together constitute a unique entity of their own. 4. There is a primary disease state with overriding features, such as AIH with biliary features.[71] AIH has also been reported to be associated with several gastrointestinal autoimmune conditions, including inflammatory bowel disease (IBD) and celiac disease.

AIH-PBC

Supportive evidence and epidemiology: The Paris criteria are used to identify patients with overlapping features of AIH and PBC.[9,37] Patients meeting two of the three PBC criteria and two of the three AIH criteria fulfill the Paris criteria, although this approach may underestimate the true

prevalence of AIH-PBC.[20] Historically, prevalence has been reported between 2% and 20%, but recent studies suggest it is lower. One study reviewing data from 609 patients with PBC and/or 15 patients with AIH over six years found that only 1% met the Paris criteria.[21] Statistical significance was not reported. Studies using the revised International Autoimmune Hepatitis Group (IAIHG) criteria for AIH-PBC have reported prevalence ranging from 2.1% to 19%, with a reduction to 4% after excluding "female gender" and the presence of other autoimmune disorders, thus reducing discriminative power.[22] These studies also did not report statistical significance, likely due to the rarity of this presentation, controversial diagnostic criteria, and shared histologic features that complicate diagnosis. Therefore, a significant association has not been established.

AIH-PSC

Supportive evidence and epidemiology: The United Network for Organ Sharing database of patients who underwent liver transplant for PSC identified a higher prevalence of AIH-PSC in patients aged 18–39 years (2.1%, mean age 25) compared to those aged 40–59 years (1%).[71] While AIH alone is more common in females and PSC is more prevalent in males, the sex predominance in AIH-PSC remains controversial.[71,73]

A meta-analysis of population-based studies from North America, Asia, Europe, and Oceania revealed a prevalence of PSC of 13.53 per 100,000 persons (95% CI, 10.20–17.94).[74] AIH alone had a prevalence of 17.44 per 1,000,000. Reported prevalence of AIH-PSC has ranged from 2% to 10%.[71,75] In a study of 79 AIH patients, 10% had evidence of PSC on magnetic resonance cholangiography with minimal interpreter variability (Cohen's kappa = 0.87).[23] A study of 114 PSC patients (confirmed by endoscopic retrograde cholangiopancreatography) found 2% classified as "definite" AIH based on the IAIHG scoring system.[72] Utilizing the modified IAIHG score, a retrospective study found 8% of PSC patients with overlap syndrome.[24] Because this simplified IAIHG criteria have shown higher specificity for AIH,[76] it is currently not recommended to use the original IAIHG scoring system. However, precise diagnostic criteria for AIH-PSC overlap have yet to be established.[71,24] With statistical significance for AIH-PSC overlap unavailable, a significant association, therefore, has not been established.

AIH-associated inflammatory bowel disease: Crohn disease and ulcerative colitis (UC)

Supportive evidence and epidemiology of AIH-associated Crohn disease: A US national cohort study found 3.1% of patients with Crohn disease had AIH. This study identified statistically significantly higher odds of Crohn disease in AIH patients compared to those without ($P < 0.0001$).[8] A retrospective study reported that 5% of IBD patients also had AIH, and 28.6% of those had Crohn disease.[25] A Mendelian randomization study observed a significant positive relationship between Crohn disease and AIH with an inverse variance–weighted odds ratio ($P = 0.045$).[25]

Supportive evidence and epidemiology of AIH-UC: A US national cohort study (2014–2019) found that 3.8% of AIH patients had UC, with significantly higher odds of UC observed in AIH patients compared to those without ($P < 0.0001$).[8] Among AIH and IBD patients, 71.4% had UC.[25] A study of 105 patients with severe AIH identified 16% with chronic UC.[77] Mendelian randomization revealed a significant positive relationship between UC and AIH ($P = 0.038$). In the replication analysis, results were conflicting, but a positive association between UC and AIH risk was confirmed ($P = 2.90 \times 10^{-6}$).[25] The Mendelian analysis and replication analysis supported a significant association between UC and AIH risk.

Proposed pathogenic mechanisms: The "leaky gut" hypothesis has been suggested to explain how intestinal barrier disruption in UC and Crohn disease may contribute to the development of AIH. In UC and Crohn disease, intestinal inflammation exacerbates permeability, compromising the mucosal lining and enabling immune responses that affect the liver.[25,78] IL-17, a pro-inflammatory cytokine, plays a key role in inflammation, fibrosis, and collagen production in AIH. Th cells dysregulate IL-17 release, and its reduction through anti-IL-17A therapy has been shown to reduce hepatic fibrosis.[79]

Studies on Lactobacillus suggest that the gut microbiome influences the hepatic autoimmune response.[79,80] One study observed increased serum IL-17 levels and liver inflammatory cell infiltration in mice injected with *Lactobacillus gasseri*. In contrast, reducing serum IL-17 with anti-γδ T-cell receptor therapy mitigated liver fibrosis.[79] The aryl hydrocarbon receptor signaling pathway has also been implicated in AIH-like pathology in mouse models.[81] Lactobacillus was found to release aryl hydrocarbon receptor ligands (indole-3-aldehyde), promoting CD8 T-cell differentiation and contributing to AIH-like pathology.[81] These findings support a role of the gut microbiome in the development of AIH.[81]

Diagnostics: AIH-UC poses diagnostic challenges due to overlapping clinical, serological, and histological features with other autoimmune liver diseases. PSC, a known coexisting hepatobiliary disease with UC, can present with cholestatic liver patterns similar to those seen in AIH.[82] Approximately 10% of patients with AIH can present with histologic features of biliary duct injury.[83] Histologically, AIH presents with significant interface hepatitis, which can also be seen in PSC. PSC shares overlapping serologic patterns of reactivity with AIH, such as ANA and ASMA positivity, making it difficult to distinguish between AIH and PSC, and between AIH-PSC associated with UC.[82] Differentiating between AIH and PSC in patients with UC can be challenging, as the initial clinical presentation, laboratory testing, and histologic findings may not clearly distinguish the two.[77] Pediatric patients with autoimmune liver disease and IBD may initially present with complications of portal hypertension, such as esophagogastric variceal bleeding. A multidisciplinary team is essential for the appropriate management of these patients.[84] Studies have found that 11% to 49% of patients with UC or Crohn disease presented with elevations in serum AST, ALT, and/or ALP.[85]

Treatment of AIH-UC: Treatment for AIH is similar in patients with and without associated UC or Crohn disease.[17] AIH-UC is generally managed in the same way as AIH alone. Data are limited on whether the clinical course of AIH differs between patients with and without IBD.[86]

Treatment of AIH-Crohn disease: There is limited literature on the efficacy and outcomes of treating Crohn disease associated with AIH. One case described a patient with AIH who was maintained on azathioprine and prednisone and subsequently developed PSC and biopsy-proven Crohn disease. She was treated for PSC with mycophenolate mofetil and ursodeoxycholic acid and was temporarily given a TNF blocker and methotrexate for Crohn disease. The patient did not tolerate this regimen, and her liver enzymes rose. She ultimately achieved and maintained remission on 6-mercaptopurine alone. The authors of this case report suggest treating each disease entity separately and adjusting medications based on tolerability, as there are no current guidelines for managing concurrent disease.[87]

AIH-associated celiac disease

Supportive evidence and epidemiology: The prevalence of AIH-associated celiac disease has been reported to range from 3% to 6%.[26] A cohort study of 460 patients with AIH found that 2.8% had celiac disease, based on the presence of IgA tissue transglutaminase and endomysial antibodies, compared to 0.35% in the general population. A meta-analysis of 567 individuals with AIH from eight different studies reported a pooled prevalence of biopsy-verified AIH-associated celiac disease of 3.5% (heterogeneity $P = 0.874$), compared to 1% in the general population. The strengths of this study include its large sample size and low heterogeneity.[27] A separate meta-analysis of nine studies involving 2,046 pediatric patients found a pooled prevalence of 6.35% (95% CI, 3.87–11.7). This study was statistically significant and had a robust sample size.[28] These findings suggest a strong association between AIH and celiac disease.

Proposed pathogenic mechanisms: The pathogenic mechanisms of AIH-associated celiac disease remain poorly understood. Celiac disease shares genetic risk factors with AIH, particularly the presence of HLA class II genes (HLA-DQ2 and HLA-DQ8).[88] In celiac disease, DQ2 and DQ8 on antigen-presenting cells bind gluten peptide complexes, activating T cells specific to the small intestinal mucosa. This triggers both Th1 and Th2 responses, with IFN-γ production and B-cell clonal expansion, resulting in the production of anti-gliadin and anti-tissue transglutaminase antibodies.[88] Gluten itself does not appear to have a direct effect on the pathogenesis of AIH-associated celiac disease.[17]

Korponay-Szabo *et al*. investigated the interaction of celiac IgA autoantibodies with transglutaminase 2 *in vivo*. The study demonstrated that celiac IgA autoantibodies also bind to transglutaminase 2 in extraintestinal tissues, including the liver, lymph nodes, and muscles, potentially contributing to the extraintestinal manifestations of celiac disease.[89]

Diagnostics: The primary diagnostic challenge in AIH-associated celiac disease is distinguishing liver abnormalities related to celiac disease itself (celiac hepatitis) from those resulting from autoimmune liver disease. Elevated aminotransferase levels in celiac disease can be related to gluten exposure and may improve with a gluten-free diet (GFD). Persistently elevated liver enzymes despite strict avoidance of gluten suggest a concurrent autoimmune liver process, which complicates the diagnosis.[90]

Re-evaluation of liver enzymes six to twelve months after initiating a strict GFD can aid in diagnosis, as persistent elevation may indicate coexisting autoimmune liver disease and warrant further evaluation. Liver biopsy can help differentiate AIH from celiac hepatitis, as the latter typically shows steatosis, Kupffer cell hyperplasia, or mild lobular and portal tract inflammation without plasma cell infiltration. Response to dietary treatment may require up to 12 months. Failure to improve with diet suggests an alternative diagnosis.[90]

Treatment: A GFD is recommended for AIH-associated celiac disease, but its effect on AIH itself remains unclear. Nastasio *et al*. studied 79 patients with AIH, 15 of whom had celiac disease and were treated with prednisone and either azathioprine or cyclosporine in addition to a GFD. Of these 15 patients, 33% achieved sustained immunosuppressant-free remission of AIH compared to 8% of AIH patients without celiac disease ($P < 0.05$).[60]

Volta *et al*. presented a case of a patient with celiac disease and persistently elevated aminotransferases despite being on a GFD for one year. Small bowel biopsies revealed no active celiac disease, and celiac disease-related antibodies were negative, suggesting adherence to the GFD. Despite this, liver biopsy continued to show active chronic hepatitis with lymphocytic and plasma cell periportal infiltration. She was started on methylprednisolone and azathioprine and achieved normalization of aminotransferases at 18 months.[91]

Di Biase *et al*. studied seven children with AIH and celiac disease on a GFD treated with steroids and azathioprine for five years and observed normalization of aminotransferases. Six of these patients underwent repeat liver biopsy, which revealed no interface hepatitis, and only two showed evidence of mild inflammation, suggesting improved liver histology.[92] These studies suggest benefits from treating AIH-associated celiac disease with a combination of steroids and azathioprine rather than GFD alone.

In a study of 166 patients diagnosed with AIH, 5.4% had histologic confirmation of celiac disease. Patients with AIH-associated celiac disease required significantly lower doses of prednisone at two-year follow-up (2.5 vs. 5 mg/day, $P = 0.007$) and were more likely to discontinue steroid therapy by three years (83% vs. 1%, $P = 0.007$) compared to AIH patients without celiac disease. Long-term observation revealed higher rates of immunosuppressive therapy withdrawal in AIH-associated celiac disease patients (44% vs. 13%, $P = 0.01$).[61]

AIH-associated rheumatologic disease

AIH-associated systemic lupus erythematosus (SLE)

Supportive evidence and epidemiology: AIH-SLE must fulfill the American College of Rheumatology criteria for SLE and the IAIHG criteria for AIH.[29] The reported prevalence of AIH-SLE varies widely, ranging from 1.6% to 15%.[30,93] A retrospective analysis found that 72.3% of 147 SLE patients met the IAIHG criteria for AIH; however, only 13.8% had liver biopsies consistent with AIH, suggesting potential overestimation of AIH-SLE cases.[30]

A 10-year retrospective analysis identified 805 patients with SLE, of whom only five (0.6%) had coexisting AIH. These patients, all female, were diagnosed between ages 22 and 57 years.[31] Similarly, among 562 patients with AIH in another study, 3.3% with AIH-1 and 3.1% with AIH-2 had concomitant SLE, although this was not statistically significant. However, a US national population study reported a significant association between SLE and AIH ($P < 0.0001$),[8] with a greater frequency than expected from the prevalence of the individual diseases. This suggests an association between AIH and SLE, although the clinical relevance remains uncertain given the variable prevalence estimates. As available data are limited to low-evidence studies, the association remains speculative.

Liver involvement by SLE remains controversial. "Lupus hepatitis" has been suggested as a mild disease process that is often asymptomatic, characterized by elevated transaminase levels that respond to corticosteroids during SLE flares.[94] Zheng *et al*. reported mostly mild to moderate aminotransferase elevations, while alkaline phosphatase and gamma-glutamyl transferase elevations were rarer. Anti-ribosomal *P* levels were also higher in patients with lupus hepatitis.[95] Diagnostic findings of lupus hepatitis are usually distinct from the diagnostic criteria and typical histologic features of AIH.[94]

AIH-associated rheumatoid arthritis (RA)

Supportive evidence and epidemiology: Among patients with AIH, 1.6% to 5.4% have been reported to have concomitant RA.[30] Teufel *et al*. analyzed 278 patients diagnosed with AIH, of whom 1.8% had concomitant RA.[35] Al-Chalabi *et al*. identified RA in 4.4% of AIH patients under 60 years old

and 7.8% of individuals over 60 years, although statistical significance was not established.[32] Similarly, a retrospective study of 562 patients with AIH found RA in 3.9% of patients with AIH-1, but this lacked statistical significance and was limited by low-level evidence. Therefore, an association is not supported.[33]

Differentiating AIH from RA-related liver involvement can be challenging, although histologic findings in RA-related liver damage are usually distinct from AIH, including centrilobular lipofuscin deposits, granulomas, regenerative Kupffer cell hyperplasia, portal inflammation, and fibrosis. Vascular involvement may also be present in rheumatoid vasculitis, which can affect hepatic vessels and rarely lead to intrahepatic hemorrhage.[96]

AIH-associated Sjögren syndrome (SS)

Supportive evidence and epidemiology: There are few reported cases of AIH-SS and limited literature on SS in AIH.[97–99] A US national cohort study (2014–2019) found a 4.9% prevalence of SS among individuals with AIH, although statistical significance was not provided. AIH patients had significantly higher odds of SS compared to patients without AIH ($P < 0.0001$).[8] This study had notable limitations: liver biopsy confirmation of AIH was documented in only one-third of patients, raising concerns about diagnostic accuracy. Additionally, patients treated at multiple healthcare institutions may have been counted multiple times, leading to a false representation of the true population. Given these limitations, reliance on a single population study, and the low-evidence nature of available cases, an association between AIH and SS cannot be conclusively established. Matsumoto *et al*. compared AIH patients with and without primary SS and found a significantly higher degree of portal inflammation in those with primary SS ($P = 0.006$).[100]

AIH-associated dermatological disease

Vitiligo is one of the most commonly seen autoimmune skin disorders in patients with AIH.[18] Less common skin conditions with probable associations include psoriasis and alopecia areata. Studies of psoriasis and its association with AIH are limited in accuracy due to suboptimal methodology for diagnosing AIH and failure to exclude anti-TNF agents (used to treat psoriasis) as triggers for developing AIH. While liver disease has been analyzed in psoriasis, limited literature exists specifically regarding psoriasis in AIH.

AIH-associated vitiligo

Supportive evidence and epidemiology: A study in India examining 41 AIH cases found a 5% prevalence of concomitant vitiligo, which was ten times higher than in the general population. However, not all patients underwent liver biopsy, limiting the accuracy of AIH diagnosis. In a case series of 143 patients, 82% had pediatric-onset AIH; vitiligo was reported in 1% of AIH-1 cases and 4% of AIH-2 cases.[18] In another study from Western India, vitiligo was present in one (1.2%) of 79 patients with AIH.[34] These studies are limited by small sample sizes, low-evidence case reports, and lack of specified statistical significance, leaving the association between vitiligo and AIH uncertain.

Other rare extrahepatic autoimmune diseases of unclear significance

Other rarer extrahepatic autoimmune diseases have been observed in AIH, including hematologic disorders (idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, pernicious anemia, and antiphospholipid syndrome), neurologic disorders (multiple sclerosis, mononeuritis multiplex), and pulmonary disorders (fibrosing alveolitis, pulmonary fibrosis, sarcoidosis). However, these are scarce, with a reported prevalence of 1% or less, and lack statistical significance to suggest a true association.[10]

Outcomes

In a study of 2,479 patients with AIH, nearly 20% had at least one extrahepatic autoimmune disease. Patients with extrahepatic autoimmune comorbidities had higher mortality compared to those without [hazard ratio 1.3 (95% CI: 1.12–1.52)], with even higher mortality observed in those with more than one extrahepatic autoimmune disease. These findings highlight the importance of not only treating the underlying AIH but also adopting an interdisciplinary approach to address concomitant disease processes.[101]

Conclusions

Our review indicates that associations of AIH with AITD, T1DM, UC, Crohn disease, and celiac disease appear to be significant. However, associations between AIH and PSC/PBC, RA, SLE, SS, and vitiligo are not well-supported. Diagnostic criteria in some cases are based on scoring systems, but most depend on the established criteria of each individual disease. Treatment of combined AIH and other diseases in most reports resembles treatment of AIH alone, typically including corticosteroid therapy, often in combination with purine analogs. However, a multidisciplinary approach to managing multi-organ involvement is highly recommended.

Acknowledgments

This work was made possible by the Herman Lopata Chair in Hepatitis Research.

Funding

None to declare.

Conflict of interest

GYW has been an Editor-in-Chief of the *Journal of Clinical and Translational Hepatology* since 2013. He has no role in the publisher's decisions regarding this manuscript. DZ has no conflicts of interest related to this publication.

Author contributions

Review concept (GYW), information collection, drafting of the manuscript (DZ), and revision of the manuscript (GYW, DZ). All authors have approved the final version and publication of the manuscript.

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