High prevalence of celiac disease in autoimmune hepatitis: Systematic review and meta-analysis

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Abstract

Background: Previous studies investigating the prevalence of celiac disease (CD) in individuals with autoimmune hepatitis (AIH) have shown highly variable results. We therefore aimed to examine the prevalence of CD in individuals with AIH.

Methods: Two professional librarians searched PubMed, EMBASE, Cochrane and Web of Science Core Collection up until 7 February 2020. The search terms included 'celiac disease', 'celiac', 'transglutaminases', 'gluten', 'gliadin', 'EMA', 'TTG' and 'villous' combined with 'autoimmune', 'hepatitis', 'ANA', 'SMA' and 'LKM'. This search yielded 2419 unique publications. A systematic review based on the PRISMA guidelines resulted in 31 articles eligible for full text review. Fifteen articles were deemed relevant, with 8 being included in our main analysis. A fixed-effect inverse variance-weighted model was used, and heterogeneity was calculated.

Results: Our main analysis included 567 individuals with AIH from eight studies, where biopsy-verified CD (equivalent to Marsh III) was seen in 23 individuals (4.1%). The pooled prevalence of CD in AIH was 3.5% (95% CI = 1.6%-5.3%) (heterogeneity: \( P = .874; I^2 = 0.0% \)), which is clearly higher than the 1% CD seen in most general populations. When also including studies where CD had been diagnosed through positive serology without biopsy (15 studies: \( n = 1817 \) individuals with AIH), the pooled prevalence of CD was 2.9% (95% CI = 2.1%-3.8%) (heterogeneity: \( P < .001; I^2 = 66.8\% \)).

Conclusion: Our results demonstrate a higher prevalence of CD in individuals with AIH compared to the general population. CD screening may be considered in patients with AIH.

Keywords

AIH, autoimmune hepatitis, celiac disease, coeliac disease, meta-analysis, prevalence

Abbreviations: AIH, autoimmune hepatitis; CD, celiac disease; CI, confidence interval.
Autoimmune hepatitis (AIH) is a severe chronic and progressive autoimmune liver disorder characterized by immune-mediated inflammation of the liver that may proceed to cirrhosis and liver failure. The incidence of AIH ranges between 0.85 and 1.68 per 100,000 person-years, predominantly affecting women. AIH may have a multifactorial pathogenesis, where both genetics, immune response regulation and environmental factors play a crucial role.

AIH have been linked to several extrahepatic autoimmune disorders, including autoimmune thyroiditis, diabetes, rheumatoid arthritis, inflammatory bowel disease and potentially also to celiac disease (CD). CD is an immune-mediated enteropathy triggered by gluten in genetically susceptible individuals and is characterized by circulating celiac-specific autoantibodies and gastrointestinal symptoms including malabsorption caused by small intestinal villous atrophy but also extraintestinal symptoms. In prior studies, the prevalence of CD has ranged from 2% to 20% in children and adults with AIH. While the prevalence of CD in AIH individuals seems to be higher than in the general population (~1%), prior studies have been small, mostly single-centre studies resulting in large variability in results and lack of precise estimates.

It is known that CD is associated with various types of liver diseases and that the use of a gluten-free diet has been shown to improve liver injury in CD-associated hepatopathy, autoimmune cholangitis and non-alcoholic fatty liver disease (NAFLD). Although the data is more sparse in those who have AIH, there is one report that indicated that, in individuals with AIH, the use of a gluten-free diet for CD improved liver injury, whereas the AIH treatment alone had not been satisfying in liver recovery. However, it remains unknown whether CD worsens AIH activity or causes separate liver injury in addition to AIH.

Because of the highly varying CD prevalence data in AIH in earlier studies, we performed a meta-analysis and investigated the prevalence of CD in AIH.

2 | MATERIALS AND METHODS

2.1 | Search

Two professional librarians at the University Library of Karolinska Institutet, Sweden, conducted a search of PubMed (Medline), Cochrane, EMBASE and Web of Science Core Collection up until 7 February 2020. Search terms included 'celiac disease', 'celiac', 'coeliac', 'transglutaminases', 'gluten', 'gliadin', 'EMA', 'TTG', 'villus', 'villous' combined with 'autoimmune', 'hepatitis', 'liver', 'ANA', 'SMA' and 'LKM' (Appendix, Tables S1-S4). LH and IG reviewed all the search results. Arbitration was performed by JFL. In order to increase sensitivity, a broad search strategy was used, yielding a total of 3010 publications (after removal of duplicates, 2419 unique publications remained). Some 31 articles were deemed relevant for full-text review.

2.2 | Eligibility criteria

After full-text review, publications with non-English language, poster presentations, conference abstracts, letters to editors, review articles, meta-analyses and publications without sufficient data were excluded (Figure 1). For our main analysis, CD had to be biopsy-proven with villous atrophy (Marsh stage III; 8 studies). In a secondary analysis, a broader definition of CD was used, also including studies where CD was confirmed with at least one positive serological marker (tissue transglutaminase antibody (TTG), endomysial antibody (EMA) or antigliadin antibody (AGA)). The secondary analysis included a total of 15 articles.

2.3 | Data collection process and data items

The PRISMA guidelines were followed, and relevant articles were reviewed in detail by LH and IG. From each article, publication date, country of origin, age of the individuals, CD definition and AIH definition (for further details, see Section 3), number of individuals with AIH, number of AIH individuals with CD, number of controls, number of controls with CD, number with a positive serology, number with a biopsy-proven CD, Marsh grade (III) for the definition of CD and study design, were retrieved.

2.4 | Statistics

In order to reduce the influence of smaller studies on the summary estimate, a fixed effect model was used for the calculation of the weighted prevalence of CD in individuals with AIH. The prevalence was stated with 95% confidence intervals. The heterogeneity was reported with $I^2$ in percentage, and a P-value < 0.05 was considered statistically significant. For detection of potential publication bias, a meta-funnel analysis was carried out (Appendix, Figure S1). The quality of each study was evaluated and commented in Section 3. STATA 13 was used for all statistical analyses.
2.5 | Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

3 | RESULTS

After review of abstracts and titles, 31 papers were eligible for full-text review. Out of these, 15 articles were deemed relevant, and 8 of these had required biopsy with villous atrophy (Marsh III) for the celiac diagnosis, thus included in the main analysis. The reasons for excluding 16 papers were: data only from correspondence/letter to editor (n = 2), conference abstract (n = 3), poster presentation (n = 2), review article (n = 2), meta-analysis per se (n = 1), insufficient/incorrect data (n = 5), and non-English (n = 1). The selection process is illustrated in Figure 1.

3.1 | Study characteristics

For our meta-analysis, 15 papers were deemed relevant, where 8 reported biopsy-proven (with positive serology screening first) CD as the primary outcome and 7 also included serology-proven CD. About half of the studies had a prospective study design (n = 7). The remaining papers were a combination of retrospective and prospective, except 1 study which included both prospective and cross-sectional data. Five studies included their participants consecutively, and 6 studies had control groups. Sixty percent of the publications originated from Europe. In most studies, women made up at least 65% of the study participants (3 studies reported no information on the proportion of females and in 1 study, women made up 46%, Table 1).

To be eligible for our main analysis (n = 8), we required that the authors stated that Marsh III (villous atrophy) was needed for the CD diagnosis. Diagnosis criteria for AIH in each paper are listed in Table 1. AIH was diagnosed in the majority of papers using either the original 1993 score, revised 1999 score or the 2008 simplified score created by the International Autoimmune Hepatitis Group, all of which are acceptable criteria to diagnose AIH by societal guidelines. Missoum et al utilized serologic markers, but did not provide further diagnosis details. Rubio-Tapia et al diagnosed AIH in liver transplant recipients using chart review, in which, in the US, explant pathology information is available for confirming diagnosis and the United Organ Sharing Network (UNOS) tracks liver transplant diagnoses. While Sjoberg et al did not use a particular score system, they utilized liver biopsy and serology to diagnose AIH, which is also accepted per society guidelines.
| Study (year) | Country         | Consecutive | Consecutive AIH | Female (%) | CD (N) | Percentage with CD (%) | CD biopsy-verified (Marsh III) | Reference # for the basis of AIH diagnosis | Additional exclusion criteria | CD screening at AIH diagnosis |
|-------------|----------------|-------------|----------------|------------|--------|------------------------|-------------------------------|----------------------------------|-------------------------------|-------------------------------|
| Drastich (2012) | Czech Republic | No          | 77             | 50 (65)   | 4      | 5.2                    | Yes                           | Revised 1999 International Autoimmune Hepatitis Group Score⁷ | No                            | No                            |
| El-Shabrawi (2011) | Egypt         | No          | 26             | 12 (46)   | 3      | 11.5                   | Yes                           | Simplified 2008 International Autoimmune Hepatitis Group Score⁷ | Yes                           | Yes                           |
| Germenis (2005) | Greece         | Yes         | 38             | 33 (87)   | 0      | 0                      | No                            | Revised 1999 International Autoimmune Hepatitis Group Score⁷ | No                            | No                            |
| Mirzaagha (2010) | Iran           | No          | 51             | 38 (75)   | 1      | 2.0                    | Yes                           | Revised 1999 International Autoimmune Hepatitis Group Score⁷ | No                            | No                            |
| Missoum (2019) | Morocco        | Yes         | 25             | 21 (84)   | 2      | 8.0                    | No                            | Serological markers, no reference | No                            | Yes                           |
| Muratori (2015) | Italy          | No          | 327            | 254 (78) | 12     | 3.7                    | No                            | Revised 1999 International Autoimmune Hepatitis Group Score⁷ | Yes                           | No                            |
| Najafi (2014)  | Iran           | No          | 64             | 56 (88)   | 3      | 4.7                    | Yes                           | Revised 1999 International Autoimmune Hepatitis Group Score⁷ | Yes                           | No                            |
| Nastasio (2013) | Italy          | Yes         | 79             | 52 (66)   | 15     | 19.0                   | No                            | Revised 1999 International Autoimmune Hepatitis Group Score⁷ | Yes                           | No                            |
| Rubio-Tapia (2008) | USA           | No          | 43             | No data¹ | 15     | 34.9                   | No                            | AIH identified in liver transplant recipients using chart review and explant information | No                            | No                            |
| Sima (2010)    | Iran           | Yes         | 84             | 75 (89)   | 2      | 2.4                    | Yes                           | Revised 1999 International Autoimmune Hepatitis Group Score⁷ | No                            | No                            |
| Sjoberg (1997) | Sweden         | No          | 37             | No data¹ | 2      | 5.4                    | Yes                           | Serological markers and liver biopsy⁸⁹ | No                            | No                            |
| Teufel (2010)  | Germany        | No          | 278            | 229 (82) | 3      | 1.1                    | No                            | Original 1993 International Autoimmune Hepatitis Group Score⁹⁰ | No                            | No                            |
| van Gerven (2014) | Netherlands    | No          | 460            | 375 (82) | 16     | 3.5                    | No                            | Revised 1999 International Autoimmune Hepatitis Group Score⁷ | Yes                           | No                            |

(Continues)
Eighty-seven percent of the publications did not screen for CD at the time of AIH diagnosis. Participant age varied between the studies, where 9 had a combination of children and adults, 2 consisted exclusively of children and 4 consisted of adults. Only 3 studies stated specifically that they followed-up their individuals.

### 3.2 | Prevalence of biopsy-verified CD in AIH

The 8 identified studies for our main analysis contained 567 individuals with AIH. Of these, 23 (4.1%) had a diagnosis of CD. After waiting for study size and using a fixed-effect model, we demonstrated a pooled prevalence of CD of 3.5% (95% CI = 1.6%-5.3%) (Figure 2), with a low heterogeneity of 0.0% (.874). The CD prevalence was similar in adults (3.3%) and in studies of both children and adults (3.5%). Restricting data to studies where ≥75% of AIH participants were women, we found a CD prevalence of 2.9%.

Due to the low heterogeneity in our main analyses (.05), no other subgroup analyses were carried out.

### 3.3 | Prevalence of CD, defined through biopsy or positive serology, in AIH

When allowing cases of CD defined either through biopsy (Marsh III) or celiac serology (TTG, EMA or AGA immunoglobulin G), we identified 15 studies with 1817 individuals (Figure 3). The pooled prevalence of CD according to this definition was 2.9% (95% CI = 2.1%-3.8%) (heterogeneity: P < .001; I² = 66.8%). Restricting the analyses to 2005 and later, when serology was unlikely to include AGA (thereby excluding the studies by Sjöberg et al and Volta et al), did not change the pooled prevalence of CD (2.9%, 95% CI = 2.0%-3.9%). Excluding the Missoum et al paper due to a lack of details on the AIH diagnosis, the pooled prevalence of CD remained 2.9% (95% CI = 2.0%-3.8%).

### 3.4 | Risk of bias across studies

A meta-funnel plot (Appendix, Figure S1) detected signs of publication bias, in that smaller studies were more likely to be published if they showed higher prevalence of CD in AIH than if they showed a lower prevalence.

### 4 | DISCUSSION

Our meta-analysis revealed that the pooled prevalence of biopsy-verified CD in individuals with AIH was 3.5% (95% CI = 1.6%-5.3%) and 2.9% (95% CI = 2.1%-3.8%) if combining both biopsy- or serology-proven CD (95% CIs for the two definitions overlapped). Our main
analysis with biopsy-proven CD consisted of 8 studies comprising 567 individuals, and our second analysis with combined biopsy- or serology proven CD consisted of a total of 15 studies comprising 1817 individuals, including both children and adults. While we are aware of one earlier meta-analysis on CD in individuals with AIH, that meta-analysis only examined children (age 0-18 years), was limited by a smaller number of patients with AIH (n = 206) and mixed biopsy- and serology-proven CD. In addition, it was based on only 3 publications, 2 of which we excluded as these did not meet our inclusion criteria (Caprai: insufficient data; Diamanti: letter to editor, Figure 1). The shared publication included in both meta-analyses was the paper by El-Shabrawi et al.

The 3.5% pooled prevalence of biopsy-proven CD in individuals with AIH was significantly higher than the overall prevalence of around 1% of CD seen in most general populations. AIH and CD may share some gene coding for class II human leukocyte antigens, which may explain their concurrent existence. Volta et al. have described that the presence of CD in AIH individuals was mostly asymptomatic, where only the individuals off AIH therapy had bowel symptoms, which could suggest that the immunosuppressive therapy may disguise CD symptoms and thereby delay crucial diagnosis. Nastasio et al. reported a significantly higher proportion of sustained remission in medication-free AIH individuals who adhered to a gluten-free diet compared to individuals with AIH but no CD. Another study has also suggested that gluten removal may significantly improve liver injury, where AIH treatment alone had not given satisfying results. This effect could be due to an increased intestinal permeability with both circulating and residual tissue transglutaminase antibodies in the liver, modifying self-antigens causing liver injury.

Current guidelines on AIH from the American Association for the Study of Liver Diseases recommend screening AIH individuals for CD at diagnosis. Ours is the largest meta-analysis that includes both children and adults, and the results support the statement of celiac screening in the AIH guidelines and additionally provide a more accurate estimate of the prevalence of CD in AIH. However, the guidelines do not state specifically how the screening for CD should be done. An initial serology-based CD screening could possibly be used as opposed to esophagogastroduodenoscopy with biopsy given that the prevalence of CD using both definitions is very similar with overlapping CIs (biopsy: 3.5% (95% CI = 1.6%-5.3%) vs combining biopsy and serology: 2.9% (95% CI = 2.1%-3.8%)). This would most likely be a more cost-effective and less invasive method for CD screening. CD screening may also possibly be done more than once, not only at AIH diagnosis, as concurrent autoimmune disorders, including CD, could develop over time.
This high rate of CD diagnosis seen in our results could be an underestimate of the prevalence of CD in AIH. This is because the treatment of AIH (steroids, prednisone, budesonide and immunosuppressants) is very effective at treating patients with CD, resolving symptoms, affecting serological tests and improving/resolving biopsies. If testing for CD had been made at diagnosis of AIH in all studies, we would have a better knowledge of CD prevalence. However, the majority of the included publications did not screen for CD at AIH diagnosis and were in the majority of cases carried out before the new guidelines recommending CD screening at AIH diagnosis were published. Performing serological screening for CD after initiation of AIH therapy may falsely lower the diagnostic rate of CD. Ideally, CD testing should be recommended at AIH diagnosis as well as later, if any digestive symptoms or other signs or symptoms of CD are present, similar to current recommendations for type 1 diabetes patients. It was beyond the scope of this study to examine suitable screening intervals, but we encourage future research to explore this topic to benefit patients with AIH.

4.1 | Strengths and limitations

A broad search strategy was used to maximize the sensitivity of our paper, yielding a total of 3010 publications, where 31 articles were deemed relevant for full-text review and 15 were included in our study. To our knowledge, this is the only truly large-scale meta-analysis (567 individuals in our main analysis and 1817 individuals with AIH in our secondary analysis), investigating the prevalence of CD in AIH, including both children and adults. The large sample size allowed us to calculate exact prevalence estimates with narrow CIs. We used two different definitions of CD, one to increase specificity (biopsy only) and another one to reflect the increased use of serology to diagnose CD. Using two definitions of CD were valuable in determining whether a more cost-effective and less-invasive screening for CD using serologies could possibly be used in AIH individuals as opposed to esophagogastroduodenoscopy.

This study has also some limitations. The diagnostic criteria for AIH have changed over time. However, all the included studies were
published in 1996 or later, when viral hepatitis (including hepatitis C virus diagnosed in 1990) could be ruled out, and the scoring systems for AIH diagnosis had been created (although the main revised criteria were made in 1999). Additionally, the diagnostic criteria for CD have changed throughout the years.

Interestingly, the pooled prevalence of biopsy-verified CD was higher in our study than that of serology- or biopsy-verified CD diagnosis, 3.5% (95% CI = 1.6%-5.3%) vs 2.9% (95% CI = 2.1%-3.8%), although the latter is a more liberal set of criteria. Since serology-based CD tends to be more prevalent than biopsy-verified CD (however often preceded by a positive serology), our results do not indicate that serology-positive CD is less common, only that studies based on serological markers found on average lower CD prevalence. Of note, the 95% CI for the two outcomes were overlapping. We included AGA in our search terms for serology-based CD since that antibody was used in older studies of CD; however, AGA may overestimate the prevalence of CD due to false-positive cases. Additionally, we cannot rule out that publication bias has impacted on our results since smaller studies may have been published more often if they showed a higher prevalence of CD (Appendix, Figure S1). Finally, our study had limited power in sub-analyses, and we were unable to calculate, for instance, area-specific prevalence estimates of CD. In a meta-analysis by Singh et al., the prevalence of CD varied between 0.4% in South America and 0.8% in Europe and Oceania (general population), and we cannot rule out that CD is both more and less prevalent in AIH populations in different parts of the world.

4.2 | Clinical implications

The meta-analysis found a high prevalence of CD in patients with AIH. Patients with AIH may benefit from CD screening.

4.3 | Conclusion

This meta-analysis of 567 individuals with AIH revealed a CD diagnosis in every 30 AIH individuals.

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CONFLICT OF INTEREST

Dr Ludvigsson coordinates a study on behalf of the Swedish IBD quality register (SWIBREG). This study has received funding from Janssen Corporation. All other authors declare that they have no conflict of interest and nothing to declare.

DISCLAIMER

This manuscript represents the views of the authors.

FUNDING AND ROLE OF THE FUNDING SOURCES

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DETAILS OF ETHICS APPROVAL

Not relevant.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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