Coeliac disease and chronic liver disease: a double-face issue

Marco Vincenzo Lenti,[a,b,*] Paola Ilaria Bianchi,[b] and Antonio Di Sabatino[a,b]

[a]Department of Internal Medicine and Medical Therapeutics, University of Pavia, Italy
[b]Department of Internal Medicine, San Matteo Hospital Foundation, Pavia, Italy

The Lancet Regional Health - Europe 2025;50: 101216

Published Online xxx
https://doi.org/10.1016/j.lanepe.2025.101216

Coeliac disease (CD) is a highly prevalent, immune-mediated, gluten-sensitive enteropathy causing villous atrophy in genetically susceptible individuals.[1] CD exhibits a high clinical variability and a wide spectrum of comorbidities, especially autoimmune, which have been progressively described and better characterised.[2] Among these, abnormalities in liver function tests and even chronic liver disease (CLD) are some of the most intriguing clinical challenges in CD patients, as they may underlie various disorders and prompt recognition is needed to avoid misdiagnoses and serious consequences.

In this issue of *The Lancet Regional Health Europe*, Yao et al.,[3] performed a nationwide (Sweden) cohort study focusing on the development of CLD of various aetiologies or major adverse liver outcomes (MALO) in patients with CD. The authors identified 48,027 patients between 1969 and 2017; patients were matched with up to five general population reference individuals (total n = 231,909) and followed through 2021. Adjusted hazard ratios (aHRs) of any and specific CLD were assessed, including viral hepatitis, metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol-related liver disease, autoimmune liver disease, and MALO (which includes compensated/decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, and liver-related death). Notably, during a median follow-up of 16·0 years, the incidence rate of any CLD in CD patients was 79·4 vs 39·5 per 100,000 person-years in controls. CD patients had a higher risk of developing any CLD (aHR 2·01) compared to controls, up to more than 25 years, though the relative risk was highest soon after CD diagnosis. Regarding specific liver diseases, positive associations were found for autoimmune liver disease (aHR 4·86), MASLD (aHR 2·54), and alcohol-related liver disease (aHR 1·51). The risk of incident MALO was also significantly increased in CD (aHR = 1·54), though modestly. The authors conclude that CD is associated with a persistently increased risk of any incident CLD, although the absolute risk is low.

Such a study was highly anticipated, as it provides a comprehensive and detailed epidemiological picture of the relationship between CD and CLD across an entire European country. The results provide several actionable points aimed at providing an earlier diagnosis of CLD in CD, such as setting up screening strategies, enhancing clinical follow-up, and promoting awareness campaigns. Indeed, since the aetiology of CLD is mostly multi-factorial and highly dependant on several environmental and genetic factors, the results of the study may not be generalisable to other countries or geographical areas. Additionally, prospective studies that explore mechanistic insights into the relationship between CD and CLD are needed.

The relationship between liver abnormalities and CD is certainly double faced. Hypertransaminasemia is very common in untreated or undiagnosed CD, since, according to a review, it has been reported in 13–60% of the cases.[4] In most instances, a gluten-free diet can reverse liver impairment and even histological alterations, when present. This condition is referred to as "coeliac hepatitis",[5] which is why cryptic hypertransaminasemia should prompt suspicion of CD. Though rarely, coeliac hepatitis may even lead to liver failure, which is still reversible after gluten withdrawal.[6] Persistent alteration of liver function tests should instead raise the suspicion of a CLD. Among CLD, autoimmune liver disease has been associated with CD in children, possibly due to shared genetic predisposition, or to persistent liver injury caused by impaired intestinal barrier and microbiome alterations.[7] Primary biliary cholangitis and primary sclerosing cholangitis have also been associated to a certain extent with CD, and they should be suspected in case of laboratory or radiological evidence of cholestatis.[8] Conversely, the association between CD and MASLD or alcohol-related liver injury is more nuanced. The gluten-free diet may potentially lead to a rapid weight gain or be unbalanced, high in fat and sugar, thereby promoting metabolic syndrome.[9] There is a lack of studies on alcohol abuse as either a risk factor for CD or its prevalence among previously diagnosed CD patients. However, there is clear evidence that CD has been associated with lower quality of life and a higher prevalence of psychological morbidity and mood disorders, such as anxiety, panic disorder, social phobia, sleep disorders, and depression.[10] Indeed, psychological morbidity is associated with alcohol abuse and may therefore constitute a risk factor for alcohol-related liver injury.

Abbreviations: aHR, adjusted hazard ratio; CD, coeliac disease; CLD, chronic liver disease; MALO, major adverse liver outcomes; MASLD, metabolic dysfunction-associated steatotic liver disease

DOI of original article: https://doi.org/10.1016/j.lanepe.2024.101201

*Corresponding author. Clinica Medica I, Fondazione IRCCS Policlinico San Matteo, Università di Pavia, Viale Golgi 19, Pavia 27100, Italy.
E-mail address: marco.lenti@unipv.it (M.V. Lenti).

To conclude, the paper by Yao et al.[3] has provided solid background for implementing the care of patients with CD developing liver function test abnormalities, but also constitutes a salutary lesson because it stresses the importance of screening for CD individuals presenting with cryptic hypertransaminasemia. Future studies should focus on early diagnosis of CLD in CD and potential strategies to prevent CLD in these patients.

Contributors
MVL and PIB drafted the manuscript; MVL and ADS revised the manuscript for important intellectual content; all authors approved the final version.

Informed consent
Not applicable.

Declaration of interests
Nothing to disclose.

Acknowledgements
None.
Funding: None.

References
1 Di Sabatino A, Corazza GR. Coeliac disease. *Lancet*. 2009;373:1480–1493.
2 Zingone F, Bai JC, Cellier C, Ludvigsson JF. Celiac disease-related conditions: who to test? *Gastroenterology*. 2024;167:64–78.
3 Yao J, Sun J, Ebrahimi F, et al. Long-term risk of chronic liver disease in patients with celiac disease: a nationwide population-based, sibling-controlled cohort study. *Lancet Reg Health Eur*. 2024. https://doi.org/10.1016/j.lanepe.2024.101201 [Epub ahead of print].
4 Rubio-Tapia A, Murray JA. The liver and celiac disease. *Clin Liver Dis*. 2019;23:167–176.
5 Rubio-Tapia A, Murray JA. Liver involvement in celiac disease. *Minerva Med*. 2008;99:595–604.
6 Kaukinen K, Halme L, Collin P, et al. Celiac disease in patients with severe liver disease: gluten-free diet may reverse hepatic failure. *Gastroenterology*. 2002;122:881–888.
7 Caprai S, Vajro P, Ventura A, Sciveres M, Maggiore G, SIGENP Study Group for Autoimmune Liver Disorders in Celiac Disease. Autoimmune liver disease associated with celiac disease in childhood: a multicenter study. *Clin Gastroenterol Hepatol*. 2008;6:803–806.
8 Abdo A, Meddings J, Swain M. Liver abnormalities in celiac disease. *Clin Gastroenterol Hepatol*. 2004;2:107–112.
9 Defeudis G, Massari MC, Terrana G, Coppola L, Napoli N, Migliaccio S. Gluten-free diet and metabolic syndrome: could Be a not benevolent encounter? *Nutrients*. 2023;15:627.
10 Zingone F, Swift GL, Card TR, Sanders DS, Ludvigsson JF, Bai JC. Psychological morbidity of celiac disease: a review of the literature. *United European Gastroenterol J*. 2015;3:136–145.