

# World Journal of *Hepatology*

*World J Hepatol* 2023 May 27; 15(5): 585-724



## REVIEW

- 585 Current and novel modalities for management of chronic hepatitis B infection  
*Salama II, Sami SM, Salama SI, Abdel-Latif GA, Shaaban FA, Fouad WA, Abdelmohsen AM, Raslan HM*
- 609 Noninvasive biomarkers in pediatric nonalcoholic fatty liver disease  
*Jayasekera D, Hartmann P*

## MINIREVIEWS

- 641 Hypothyroidism and non-alcoholic fatty liver disease: A coincidence or a causal relationship?  
*Janota B, Szczepańska E, Adamek B, Janczewska E*
- 649 Sarcopenia in chronic viral hepatitis: From concept to clinical relevance  
*Coelho MPP, de Castro PASV, de Vries TP, Colosimo EA, Bezerra JMT, Rocha GA, Silva LD*
- 666 Fatty liver and celiac disease: Why worry?  
*Narciso-Schiavon JL, Schiavon LL*
- 675 Current guidelines for diagnosis and management of hepatic involvement in hereditary hemorrhagic teleangiectasia  
*Ielasi L, Tonnini M, Piscaglia F, Serio I*

## ORIGINAL ARTICLE

## Clinical Trials Study

- 688 Respiratory muscle training with electronic devices in the postoperative period of hepatectomy: A randomized study  
*Pereira MG, Silva AMO, Galhardo FDM, Almeida BDM, Lopes RL, Boin IFSF*

## Observational Study

- 699 Liver steatosis in patients with rheumatoid arthritis treated with methotrexate is associated with body mass index  
*Castiella A, Lopez-Dominguez L, Sanchez-Iturri MJ, Urreta I, De Diego A, Belzunegui J, Zapata E*

## CASE REPORT

- 707 Giant cavernous hemangioma of the liver with satellite nodules: Aspects on tumour/tissue interface: A case report  
*Fischer AK, Beckurts KTE, Büttner R, Drebber U*
- 715 Cerebrospinal fluid liver pseudocyst: A bizarre long-term complication of ventriculoperitoneal shunt: A case report  
*Yousaf MN, Naqvi HA, Kane S, Chaudhary FS, Hawksworth J, Nayar VV, Faust TW*

**ABOUT COVER**

Editorial Board Member of *World Journal of Hepatology*, Maria Jesus Citores, BSc, PhD, Research Scientist, Teaching Assistant, Laboratory of Internal Medicine, Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda 28222, Madrid, Spain. mariajesus.citores@salud.madrid.org

**AIMS AND SCOPE**

The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJH* mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

**INDEXING/ABSTRACTING**

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 Journal Citation Indicator (JCI) for *WJH* as 0.52. The *WJH*'s CiteScore for 2021 is 3.6 and Scopus CiteScore rank 2021: Hepatology is 42/70.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Yi-Xuan Cai; Production Department Director: Xiang Li; Editorial Office Director: Xiang Li.

**NAME OF JOURNAL**

*World Journal of Hepatology*

**ISSN**

ISSN 1948-5182 (online)

**LAUNCH DATE**

October 31, 2009

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Nikolaos Pylsopoulos, Ke-Qin Hu, Koo Jeong Kang

**EDITORIAL BOARD MEMBERS**

<https://www.wjnet.com/1948-5182/editorialboard.htm>

**PUBLICATION DATE**

May 27, 2023

**COPYRIGHT**

© 2023 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## Fatty liver and celiac disease: Why worry?

Janaina Luz Narciso-Schiavon, Leonardo Lucca Schiavon

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B  
Grade C (Good): C  
Grade D (Fair): 0  
Grade E (Poor): 0

**P-Reviewer:** Kotlyarov S, Russia; Sahin Y, Turkey

**Received:** January 17, 2023

**Peer-review started:** January 17, 2023

**First decision:** February 21, 2023

**Revised:** February 27, 2023

**Accepted:** April 18, 2023

**Article in press:** April 18, 2023

**Published online:** May 27, 2023



**Janaina Luz Narciso-Schiavon, Leonardo Lucca Schiavon**, Department of Internal Medicine, Gastroenterology Division, Federal University of Santa Catarina, Florianópolis 88040-900, Santa Catarina, Brazil

**Corresponding author:** Janaina Luz Narciso-Schiavon, PhD, Associate Professor, Department of Internal Medicine, Gastroenterology Division, Federal University of Santa Catarina, Rua Maria Flora Pasewang S/N – Hospital Universitário 3º andar – Depto Clínica Médica - Trindade, Florianópolis 88040-900, Santa Catarina, Brazil. [janaina.narciso@uol.com.br](mailto:janaina.narciso@uol.com.br)

### Abstract

Celiac disease (CD) is a chronic inflammatory intestinal disorder mediated by the ingestion of gluten in genetically susceptible individuals. Liver involvement in CD has been widely described, and active screening for CD is recommended in patients with liver diseases, particularly in those with autoimmune disorders, fatty liver in the absence of metabolic syndrome, noncirrhotic intrahepatic portal hypertension, cryptogenic cirrhosis, and in the context of liver transplantation. Non-alcoholic fatty liver disease is estimated to affect approximately 25% of the world's adult population and is the world's leading cause of chronic liver disease. In view of both diseases' global significance, and to their correlation, this study reviews the available literature on fatty liver and CD and verifies particularities of the clinical setting.

**Key Words:** Fatty liver; Non-alcoholic fatty liver disease; Celiac disease; Transaminases; Aspartate aminotransferase; Alanine aminotransferase

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** In view of fatty liver and celiac disease (CD) global significance, and to their correlation, this study reviews the available literature on fatty liver and CD and verifies particularities of the clinical setting.

**Citation:** Narciso-Schiavon JL, Schiavon LL. Fatty liver and celiac disease: Why worry? *World J Hepatol* 2023; 15(5): 666-674

**URL:** <https://www.wjgnet.com/1948-5182/full/v15/i5/666.htm>

**DOI:** <https://dx.doi.org/10.4254/wjh.v15.i5.666>



## INTRODUCTION

Celiac disease (CD) is a chronic inflammatory intestinal disorder mediated by the ingestion of gluten in genetically susceptible individuals. It is relatively common and affects 0.7%–1.4% of the global population[1]. Its diagnosis relies on a combination of serologic testing for anti-tissue transglutaminase, anti-endomysial, and/or anti-deamidated gliadin peptide antibodies, as well as typical findings of villous atrophy and intraepithelial lymphocytosis in duodenal biopsies[2]. The classical clinical manifestations of CD, related to the gastrointestinal tract, are seen in 50%–60% of all cases. Non-classical CD accounts for 40%–50%, and is characterized by systemic involvement including musculoskeletal, neurological, endocrine, kidney, heart, lung, and liver manifestations, concomitant with other autoimmune diseases and malignancies[3]. Liver involvement in CD has been widely described in case reports and case series in the past fifty years. Presently, active screening for CD is recommended in patients with liver diseases, particularly in those with autoimmune disorders, fatty liver in the absence of metabolic syndrome, noncirrhotic intrahepatic portal hypertension, cryptogenic cirrhosis, and in the context of liver transplantation[4]. Non-alcoholic fatty liver disease (NAFLD), estimated to affect approximately 25% of the world's adult population, is the world's leading cause of chronic liver disease [5]. Due to both diseases' global significance, and to their correlation[6], this study aims to review the available literature on fatty liver and CD, and verify what has already been published on this subject in order to define the clinical particularities of their coexistence.

## CELIAC DISEASE IN PATIENTS WITH FATTY LIVER

NAFLD refers to a spectrum of diseases of the liver ranging from simple steatosis (fatty infiltration of the liver) to nonalcoholic steatohepatitis (steatosis with inflammation and hepatocyte necrosis) to cirrhosis[7]. Massive hepatic steatosis complicating adult celiac has been described since the 1980s. These cases had a marked increase in aminotransferases, sometimes coursing with jaundice and transitory liver failure, presenting complete resolution of the liver condition after a gluten-free diet (GFD)[8–11]. A few authors have investigated the diagnosis of CD in patients with fatty liver by employing different screening methods (Table 1)[12–18]. The methodologies differ between the studies, both with regard to the diagnosis of fatty liver and the serological and histological diagnosis of CD. The prevalence of reactive celiac antibodies varies from 2% to 13%[12–16]. CD has been described as more prevalent in NAFLD patients with body mass index value < 27 kg/m<sup>2</sup>[16] and < 25 kg/m<sup>2</sup>[17].

A clinical picture of undiagnosed chronic diarrhea, bloating, refractory anemia, dermatitis herpetiformis, suboptimal body mass index (< 24) or nutritional deficiency (vitamin B12, vitamin D or folic acid) in patients with NAFLD are associated with high likelihood of CD[18]. Liver biochemistry and celiac antibodies become normal after a GFD[12,14,16]. When either abdominal ultrasound or liver biopsy are performed after treatment, steatosis resolution is observed[12,16]. Concerning this topic, controversy persists as to whether the presence of fatty liver is a hepatic manifestation of CD[19]. Some claim that the hepatic manifestation of CD would be a nonspecific chronic hepatitis[13], called by some authors celiac hepatitis[20]. Furthermore, it is not known whether liver disease associated with CD has the potential to progress to liver cirrhosis, although it has been reported that CD is associated not only with cirrhosis of various etiologies, but also with cryptogenic cirrhosis[21–24]. The association between metabolic cirrhosis and refractory CD has also been reported[25].

## FATTY LIVER IN PATIENTS WITH CELIAC DISEASE

Zali *et al*[30] followed up on 98 patients with CD, and observed that 2% of the patients with CD fulfilled the diagnostic criteria for metabolic syndrome at diagnosis, while 29.5% of the patients met the criteria after 12 mo of GFD ( $P < 0.01$ ; OR: 20). Agarwal *et al*[26] evaluated 44 naïve patients with CD, and observed that patients having fatty liver increased from 6 patients (14.3%) at baseline to 13 (29.5%) after one year of GFD ( $P = 0.002$ ). Ciccone *et al*[27] evaluated the incidence of hepatic steatosis at diagnosis and during follow-up of 185 patients with CD. Hepatic steatosis was found by ultrasound in three patients (1.6%) at CD diagnosis. At the end of the follow-up period (median = 7 years; range 1–36), the prevalence of hepatic steatosis was significantly higher than at the time of CD diagnosis ( $n = 20$ ; 11.0%) ( $P < 0.001$ ). A Swedish nationwide study of over 26000 patients with CD demonstrated an increased risk of NAFLD in both children and adults with CD. The relative risk was highly increased in the first year of follow-up, but remained statistically significant even 15 years after CD diagnosis[28]. Tovoli *et al*[29] evaluated 202 celiac patients under a GFD and evidenced the diagnosis of NAFLD in 34.7% when compared with 21.8% in 333 controls. Curiously, in normal-weight patients the higher prevalence of NAFLD was even more evident than in the controls (20% *vs* 5.8%,  $P = 0.001$ ). On the other hand, this difference was not observed in the overweight population (67.8% *vs* 55.4%,  $P = 0.202$ ), suggesting that traditional metabolic risk factors may mask the effects of the GFD in these patients. Due to the above stated evidence, monitoring aminotransferases levels periodically in celiac patients under GFD is

**Table 1** Celiac disease in patients with fatty liver

Ref.	Country	Patients	Ultrasound	Liver biopsy	AGA	tTG	EmA	Duodenal biopsy	Response with GFD
Grieco <i>et al</i> [12], 2001	Italy	30	(+)	(+)	N/A	N/A	4	Negative	Complete
Nehra <i>et al</i> [13], 2001	United States	47	N/A	(+)	N/A	N/A	1	N/A	N/A
Bardella <i>et al</i> [14], 2004	Italy	59	N/A	(+)	N/A	6	2	2/6	Partial
Lo Iacono <i>et al</i> [15], 2005	Italy	121	N/A	(+)	N/A	20	4	4/4	Partial
Rahimi <i>et al</i> [16], 2011	Iran	316	Either/or	Either/or	N/A	8	7	7/8	Complete
Bakhshipour <i>et al</i> [17], 2013	Iran	403	(+)	N/A	N/A	14	N/A	12/14	Partial
Kamal <i>et al</i> [18], 2018	Egypt	613	(+)	(-)	N/A	160	68	181	Partial

GFD: Gluten-free diet; N/A: Not available; AGA: Anti-gliadin antibody; tTG: Tissue transglutaminase antibody; EmA: Endomysial antibody; Complete response to GFD: Normalization of liver enzymes, celiac antibodies and normal abdominal ultrasound; Partial response to GFD: Normalization of liver enzymes and celiac antibodies.

recommended, especially in patients gaining weight[30].

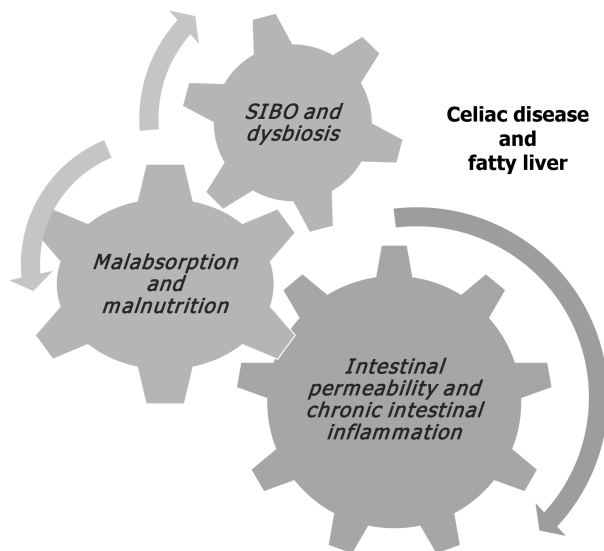
Long-term treatment with proton pump inhibitors (PPI) is associated with excessive weight gain[31, 32]. Imperatore *et al*[33] evaluated 301 patients with newly diagnosed CD, where 4.3% were diagnosed with metabolic syndrome and 25.9% presented with hepatic steatosis at the time of CD diagnosis; 32.8% had long-term exposure to PPI during the study period. After one year, 23.9% of the patients had developed metabolic syndrome and 37.2% had developed hepatic steatosis. Upon multivariate analysis, HOMA-IR (OR: 9.7;  $P = 0.001$ ) and PPI exposure (OR: 9.2;  $P = 0.001$ ) were the only factors associated with the occurrence of hepatic steatosis in celiac patients.

## PATHOPHYSIOLOGICAL MECHANISMS THAT LINK DISEASES

The mechanisms leading both CD and GFD to the metabolic alterations such as the increase in body weight and body mass index, blood triglyceride and cholesterol levels and blood glucose levels, as well as the development of NAFLD remain to be clarified[34]. In non-celiac patients, insulin resistance leads to fat accumulation resulting in steatosis and oxidative stress, determines lipid peroxidation and increases cytokine production, that results in inflammation and necrosis[35]. In celiac patients, malabsorption and long-standing malnutrition, increased intestinal permeability, chronic intestinal inflammation, small intestinal bacterial overgrowth and/or dysbiosis have been suggested to have possible roles in establishing celiac hepatitis in CD (Figures 1 and 2)[36,37].

### Malabsorption and long-standing malnutrition

At diagnosis, CD patients have lower body mass index than the general population due to malabsorption[38,39]. Kwashiorkor and dietary protein deficiency may occur associated with fatty liver on liver biopsy[40]. In patients with significantly reduced intestinal absorptive surface, the ability to assimilate dietary protein may be severely reduced; intestinal malabsorption per se has been associated with hepatic steatosis after jejunoileal bypass in patients with morbid obesity[41,42] and also in patients with inflammatory bowel disease, specially after extensive intestinal resections[43]. It has been hypothesized that malabsorption in CD might lead to chronic deficiency of a lipotropic factor, and that fatty liver may occur with an associated pyridoxine deficiency[44]. In addition to malnutrition itself, qualitative and quantitative changes in the intestinal microflora occur in protein-energy malnutrition [45], however the subject of dysbiosis will be addressed below. Weight changes are common in patients suffering from CD after commencing a GFD[46,47], and the GFD dietary behavior of CD patients correlates with NAFLD[48]. A possible explanation would be the ingestion of gluten substitute products paired with the hyperphagic compensatory status that usually follows malabsorption inducing weight gain[29]. There is evidence that GFD can determine a higher intake of simple sugars, proteins and saturated fat and a lower intake of complex carbohydrates and fibers[49,50]. These changes can contribute to the development of hypertension, dyslipidemia, diabetes mellitus, metabolic syndrome



DOI: 10.4254/wjh.v15.i5.666 Copyright ©The Author(s) 2023.

**Figure 1** Pathophysiological mechanisms associated with fatty liver in patients with celiac disease. SIBO: Small intestinal bacterial overgrowth.

and hepatic steatosis[51].

#### ***Intestinal permeability and chronic intestinal inflammation***

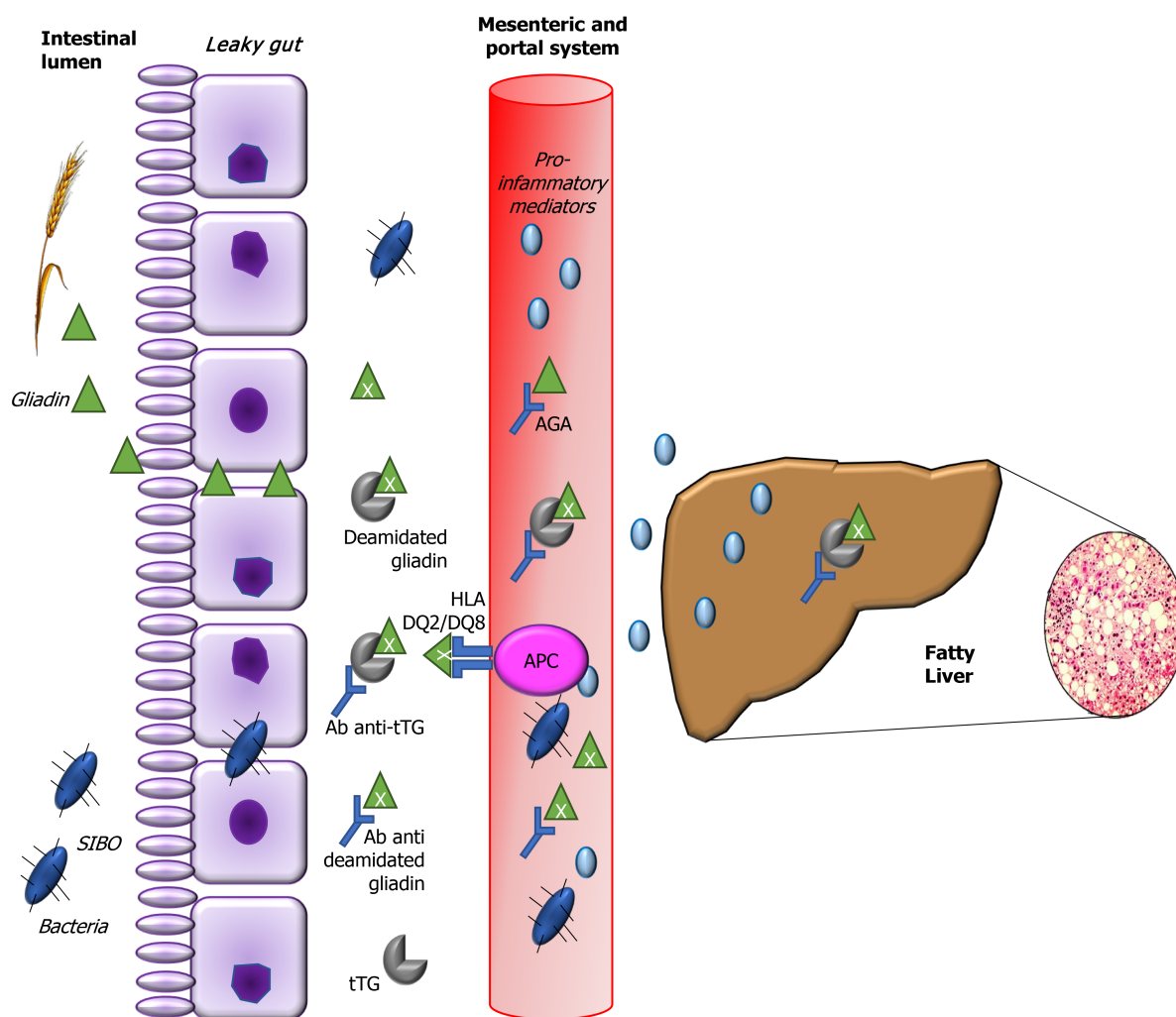
Intestinal permeability is increased in CD[52] and may favor the absorption of antigens by the intestine, *via* the portal circulation[53]. It is known that intestinal permeability is increased in NAFLD, as is bacterial overgrowth in the small intestine, and that these factors are associated with the severity of hepatic steatosis. The increase in intestinal permeability appears to be the key in the contribution of the gut-liver axis to the development of NAFLD[54]. The term gut-liver axis refers to a close anatomical, metabolic, and immunologic link between the gut and liver. The liver and intestine are tightly connected *via* the mesenteric and portal system, which supplies the liver not only with nutrients but also with gut derived food, bacterial antigens, and bacterial metabolic products. The liver portal circulation, derived from the mesenteric vessels, are the afferent part of the gut-liver axis[55]. Patients with concomitant NAFLD and CD present advanced intestinal inflammation and villous atrophy and higher levels of proinflammatory cytokines than those with CD alone, which suggests advanced intestinal injury when both diseases are present in one individual[18]. Moreover, the intestines and the liver are characterized by shared lymphocyte homing and recruitment pathways. Gut-derived T-lymphocytes may also contribute to hepato-biliary inflammation[56]. Additionally, patients with concomitant NAFLD and CD reveal higher levels of hepatic steatosis, liver stiffness, hepatic fibrosis progression rates and profibrotic mediators compared with those with either NAFLD or CD alone[18].

#### ***Small intestinal bacterial overgrowth and/or dysbiosis***

The diagnostic standard for small intestinal bacterial overgrowth (SIBO) is the detection of  $> 10^5$  colony forming units of bacteria per ml of jejunal fluid. The difficulty in collecting jejunal fluid has led to the development of new diagnostic methods, one of them being the hydrogen breath test[57]. Wigg *et al*[58] observed that small intestinal bacterial overgrowth was present in 50% of patients with NAFLD and 22% of control subjects ( $P = 0.048$ ), while intestinal permeability and serum endotoxin levels were similar in the two groups. For the CD patients, gliadin may impair the balance between intestinal microflora and the human body. Through digestive process, large quantity of undegraded gliadin reaches the intestines, delivers abundant substrates for different bacteria, contributes the reproduction of gliadin-degrading bacteria and breaks the steady state of intestinal microbiota[59]. Rubio-Tapia *et al* [60] observed a prevalence of SIBO of 9.3% diagnosed by quantitative culture of intestinal aspirate in CD patients. The association between SIBO and CD occurs mainly in patients who are newly diagnosed and beginning a GFD, and specially in those with nonresponsive CD[61,62].

## **WHEN TO INVESTIGATE**

Screening all patients with NAFLD for CD is controversial. Nonetheless, clinical suspicion may arise from the presence of classical malabsorption symptoms or low body mass index, leading to active

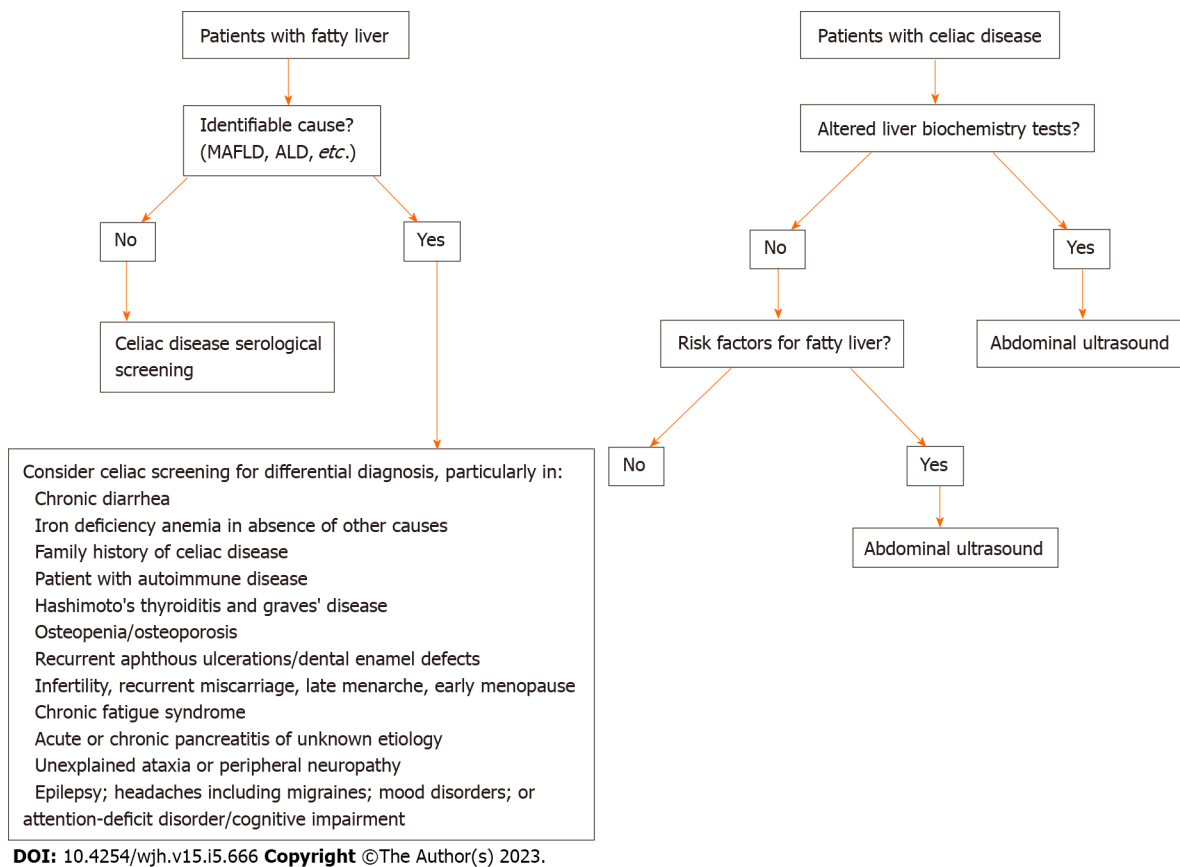


DOI: 10.4254/wjgh.v15.i5.666 Copyright ©The Author(s) 2023.

**Figure 2 Molecular mechanisms that link fatty liver and celiac disease.** Mucosal epithelium of the small intestine is the barrier between gut lumen and microbiota. The intestinal microflora is a primary source of the endotoxins produced by Gram-negative bacteria, normally crossing the mucosa in small amounts and entering the mesenteric and portal system. Celiac patients present increased intestinal permeability. Consequently, there are increased gut derived products and endotoxins in portal stream and increased levels of endotoxin-mediated cytokines in the liver. Ab anti-tTG: Antibody against tissue transglutaminase; AGA: Anti-glutamine antibody; APC: Antigen presenting cells; HLA: Human leukocyte antigen; SIBO: Small intestinal bacterial overgrowth; tTG: Tissue transglutaminase antibody.

screening of celiac antibodies and early diagnosis. The GFD may improve liver tests and liver steatosis in patients with NAFLD and CD, but it remains controversial whether this effect is independent of nutritional factors. Given the biological complexity and clinical heterogeneity of NAFLD and its comorbidities, the identification of the precise drivers of such disease would aid the development of targeted therapeutics[35]. International NAFLD guidelines[63,64] recommend the investigation of other diseases that may occur with liver steatosis and that have a treatment different from NAFLD, even in the presence of metabolic risk factors. From our point of view, CD represents a disease for which diagnosis requires targeted treatment to benefit the patient. This approach not only reduces the risk of developing more severe celiac-related liver injuries, but from a systemic point of view it is known that a GFD can prevent celiac complications such as intestinal malignancies and several autoimmune diseases. Screening for CD is justified in subjects with and without known risk factors for NAFLD. Priority groups include, individuals with chronic diarrhea, iron deficiency anaemia in absence of other causes, family history of CD, patients with autoimmune disease, Hashimoto's thyroiditis and Graves' disease, osteopenia or osteoporosis, recurrent aphthous ulcerations/dental enamel defects, infertility, recurrent miscarriage, late menarche, early menopause, chronic fatigue syndrome, acute or chronic pancreatitis after excluding other known causes and neurological symptoms such as unexplained ataxia or peripheral neuropathy, epilepsy, headaches including migraines, mood disorders, or attention-deficit disorder/cognitive impairment[65]. On the other hand, it is not yet well defined whether it is necessary to investigate fatty liver in all patients with CD, as liver changes may be resolved with GFD. However, it is imperative to investigate fatty liver when liver biochemical tests persist elevated despite GFD. Figure 3 demonstrates an algorithm proposal for CD screening in patients with fatty liver and also for fatty liver screening among celiac patients.





**Figure 3** Proposed screening algorithm for celiac disease in patients with fatty liver and vice versa. MAFLD: Metabolic associated fatty liver disease; ALD: Alcoholic liver disease.

## CONCLUSIONS AND FUTURE DIRECTIONS

CD and NAFLD are a common association and prompt recognition of both diseases is crucial for adequacy of treatment and to improve care. Although a direct cause-effect relationship can be clearly observed in some patients with CD that develop NAFLD as a result of malabsorption; a subtler mechanism, in which CD acts more as a cofactor capable of changing the natural history of NAFLD, has recently been suggested. Therefore, screening for CD should be strongly considered in these patients, although there are no data that exactly define the priority groups. Future investigations focusing on the pathophysiological mechanisms, particularly on the role of changes in the microbiota and intestinal permeability, may help in understanding the interference of one disease on the other. In addition, longitudinal studies evaluating the progression of these patients, particularly the impact of the GFD on NAFLD outcomes, are essential to support the clinical decision-making process.

## FOOTNOTES

**Author contributions:** Narciso-Schiavon JL designed the research, collected clinical data, analyzed the data and wrote the paper; Schiavon LL designed the research and reviewed the paper; all authors have read and approved the final version of the manuscript.

**Conflict-of-interest statement:** All authors do not have any conflicts of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

**Country/Territory of origin:** Brazil

**ORCID number:** Janaina Luz Narciso-Schiavon 0000-0002-6228-4120; Leonardo Lucca Schiavon 0000-0003-4340-6820.

**Corresponding Author's Membership in Professional Societies:** Asociación Latinoamericana para El Estudio del Hígado; Federação Brasileira De Gastroenterologia; Sociedade Brasileira de Hepatologia; Associação Catarinense para o Estudo do Fígado.

**S-Editor:** Xing YX

**L-Editor:** A

**P-Editor:** Xing YX

## REFERENCES

- Dieckman T, Koning F, Bouma G. Celiac disease: New therapies on the horizon. *Curr Opin Pharmacol* 2022; **66**: 102268 [PMID: 35921776 DOI: 10.1016/j.coph.2022.102268]
- Green PHR, Paski S, Ko CW, Rubio-Tapia A. AGA Clinical Practice Update on Management of Refractory Celiac Disease: Expert Review. *Gastroenterology* 2022; **163**: 1461-1469 [PMID: 36137844 DOI: 10.1053/j.gastro.2022.07.086]
- Singh P, Singh AD, Ahuja V, Makharia GK. Who to screen and how to screen for celiac disease. *World J Gastroenterol* 2022; **28**: 4493-4507 [PMID: 36157923 DOI: 10.3748/wjg.v28.i32.4493]
- Narciso-Schiavon JL, Schiavon LL. To screen or not to screen? *World J Gastroenterol* 2017; **23**: 776-791 [PMID: 28223722 DOI: 10.3748/wjg.v23.i5.776]
- Lazarus JV, Mark HE, Villota-Rivas M, Palayew A, Carrieri P, Colombo M, Ekstedt M, Esmat G, George J, Marchesini G, Novak K, Ocama P, Ratzliff V, Razavi H, Romero-Gómez M, Silva M, Spearman CW, Tacke F, Tsochatzis EA, Yilmaz Y, Younossi ZM, Wong VW, Zelber-Sagi S, Cortez-Pinto H, Anstee QM; NAFLD policy review collaborators. The global NAFLD policy review and preparedness index: Are countries ready to address this silent public health challenge? *J Hepatol* 2022; **76**: 771-780 [PMID: 34895743 DOI: 10.1016/j.jhep.2021.10.025]
- Abenavoli L, Luigiano C, Larussa T, Milic N, De Lorenzo A, Stelitano L, Morace C, Consolo P, Miraglia S, Fagoonee S, Virgilio C, Luzzo F, Pellicano R. Liver steatosis in celiac disease: the open door. *Minerva Gastroenterol Dietol* 2013; **59**: 89-95 [PMID: 23478246]
- Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med* 2002; **346**: 1221-1231 [PMID: 11961152 DOI: 10.1056/NEJMr011775]
- Naschitz JE, Yeshurun D, Zuckerman E, Arad E, Boss JH. Massive hepatic steatosis complicating adult celiac disease: report of a case and review of the literature. *Am J Gastroenterol* 1987; **82**: 1186-1189 [PMID: 3314486]
- Lynch DA, Thornton JR, Axon AT. Acute fatty liver complicating coeliac disease. *Eur J Gastroenterol Hepatol* 1994; **6**: 745-747 [DOI: 10.1097/00042737-199408000-00019]
- Cassagnou M, Boruchowicz A, Guillemot F, Gheysens Y, Devisme L, Cortot A, Colombel JF. Hepatic steatosis revealing celiac disease: a case complicated by transitory liver failure. *Am J Gastroenterol* 1996; **91**: 1291-1292 [PMID: 8651214]
- Zippelius A, Diebold J. Images in hepatology. Steatosis hepatitis in celiac disease. *J Hepatol* 1999; **30**: 531 [PMID: 10190740 DOI: 10.1016/s0168-8278(99)80116-0]
- Grieco A, Miele L, Pignaturo G, Pompili M, Rapaccini GL, Gasbarrini G. Is coeliac disease a confounding factor in the diagnosis of NASH? *Gut* 2001; **49**: 596 [PMID: 11589191 DOI: 10.1136/gut.49.4.596]
- Nehra V, Angulo P, Buchman AL, Lindor KD. Nutritional and metabolic considerations in the etiology of nonalcoholic steatohepatitis. *Dig Dis Sci* 2001; **46**: 2347-2352 [PMID: 11713934 DOI: 10.1023/a:1012338828418]
- Bardella MT, Valenti L, Pagliari C, Peracchi M, Farè M, Fracanzani AL, Fargion S. Searching for coeliac disease in patients with non-alcoholic fatty liver disease. *Dig Liver Dis* 2004; **36**: 333-336 [PMID: 15191202 DOI: 10.1016/j.dld.2004.01.012]
- Lo Iacono O, Petta S, Venezia G, Di Marco V, Tarantino G, Barbaria F, Mineo C, De Lisi S, Almasio PL, Craxi A. Anti-tissue transglutaminase antibodies in patients with abnormal liver tests: is it always coeliac disease? *Am J Gastroenterol* 2005; **100**: 2472-2477 [PMID: 16279902 DOI: 10.1111/j.1572-0241.2005.00244.x]
- Rahimi AR, Daryani NE, Ghofrani H, Taher M, Pashaei MR, Abdollahzade S, Kalani M, Ajdarkosh H. The prevalence of celiac disease among patients with non-alcoholic fatty liver disease in Iran. *Turk J Gastroenterol* 2011; **22**: 300-304 [PMID: 21805421 DOI: 10.4318/tjg.2011.0216]
- Bakhshipour A, Kaykhaei MA, Moulaei N, Mashhadi MA. Prevalence of coeliac disease in patients with non-alcoholic fatty liver disease. *Arab J Gastroenterol* 2013; **14**: 113-115 [PMID: 24206739 DOI: 10.1016/j.ajg.2013.08.001]
- Kamal S, Aldossari KK, Ghoraba D, Abdelhakam SM, Kamal AH, Bedewi M, Nabegh L, Bahnasy K, Hafez T. Clinicopathological and immunological characteristics and outcome of concomitant coeliac disease and non-alcoholic fatty liver disease in adults: a large prospective longitudinal study. *BMJ Open Gastroenterol* 2018; **5**: e000150 [PMID: 29503733 DOI: 10.1136/bmjgast-2017-000150]
- Marignani M, Angeletti S, Ruggeri M, Cassetta S, Delle Fave G. Coeliac disease and non-alcoholic fatty liver disease. *Dig Liver Dis* 2004; **36**: 781; author reply 781-781; author reply 782 [PMID: 15571010 DOI: 10.1016/j.dld.2004.07.009]
- Rubio-Tapia A, Murray JA. The Liver and Celiac Disease. *Clin Liver Dis* 2019; **23**: 167-176 [PMID: 30947869 DOI: 10.1016/j.cld.2018.12.001]
- Wakim-Fleming J, Pagadala MR, McCullough AJ, Lopez R, Bennett AE, Barnes DS, Carey WD. Prevalence of celiac disease in cirrhosis and outcome of cirrhosis on a gluten free diet: a prospective study. *J Hepatol* 2014; **61**: 558-563 [PMID: 24842303 DOI: 10.1016/j.jhep.2014.05.020]
- Demir H, Yüce A, Caglar M, Kale G, Kocak N, Ozen H, Gürakan F, Saltik-Temizel IN. Cirrhosis in children with celiac disease. *J Clin Gastroenterol* 2005; **39**: 630-633 [PMID: 16000933 DOI: 10.1097/01.mcg.0000170734.49725.53]
- Duman AE, Oğütmen Koç D, Korkmaz U, Tohumcu A, Celebi A, Sentürk O, Hülalü S, Erçin C. Cirrhosis and intestinal

- B-cell lymphoma: two entities that are rarely associated with celiac disease. *Turk J Gastroenterol* 2013; **24**: 192-194 [PMID: 23934474 DOI: 10.4318/tjg.2013.0478]
- 24 **Narciso-Schiavon JL**, Schiavon LL. Celiac disease screening in patients with cryptogenic cirrhosis. *World J Gastroenterol* 2023; **29**: 410-412 [PMID: 36687121 DOI: 10.3748/wjg.v29.i2.410]
  - 25 **Hastier A**, Patouraux S, Canivet CM, Lebeaupin C, Tran A, Anty R. Nonalcoholic steatohepatitis cirrhosis and type 1 refractory celiac disease: More than a fortuitous association? *Clin Res Hepatol Gastroenterol* 2016; **40**: 4-5 [PMID: 26526847 DOI: 10.1016/j.clinre.2015.09.006]
  - 26 **Agarwal A**, Singh A, Mehtab W, Gupta V, Chauhan A, Rajput MS, Singh N, Ahuja V, Makharia GK. Patients with celiac disease are at high risk of developing metabolic syndrome and fatty liver. *Intest Res* 2021; **19**: 106-114 [PMID: 32312034 DOI: 10.5217/ir.2019.00136]
  - 27 **Ciccone A**, Gabrieli D, Cardinale R, Di Ruscio M, Vernia F, Stefanelli G, Necozone S, Melideo D, Viscido A, Frieri G, Latella G. Metabolic Alterations in Celiac Disease Occurring after Following a Gluten-Free Diet. *Digestion* 2019; **100**: 262-268 [PMID: 30554200 DOI: 10.1159/000495749]
  - 28 **Reilly NR**, Lebowohl B, Hultcrantz R, Green PH, Ludvigsson JF. Increased risk of non-alcoholic fatty liver disease after diagnosis of celiac disease. *J Hepatol* 2015; **62**: 1405-1411 [PMID: 25617505 DOI: 10.1016/j.jhep.2015.01.013]
  - 29 **Tovoli F**, Negrini G, Fari R, Guidetti E, Faggiano C, Napoli L, Bolondi L, Granito A. Increased risk of nonalcoholic fatty liver disease in patients with coeliac disease on a gluten-free diet: beyond traditional metabolic factors. *Aliment Pharmacol Ther* 2018; **48**: 538-546 [PMID: 29984415 DOI: 10.1111/apt.14910]
  - 30 **Zali MR**, Rostami Nejad M, Rostami K, Alavian SM. Liver complications in celiac disease. *Hepat Mon* 2011; **11**: 333-341 [PMID: 22087157]
  - 31 **Syu YF**, Huang HH, Chen CY. Do proton pump inhibitors contribute to weight gain? *Obes Surg* 2015; **25**: 1071-1072 [PMID: 25845352 DOI: 10.1007/s11695-015-1659-x]
  - 32 **Yoshikawa I**, Nagato M, Yamasaki M, Kume K, Otsuki M. Long-term treatment with proton pump inhibitor is associated with undesired weight gain. *World J Gastroenterol* 2009; **15**: 4794-4798 [PMID: 19824113 DOI: 10.3748/wjg.15.4794]
  - 33 **Imperatore N**, Tortora R, Testa A, Gerbino N, Caporaso N, Rispo A. Proton pump inhibitors as risk factor for metabolic syndrome and hepatic steatosis in coeliac disease patients on gluten-free diet. *J Gastroenterol* 2018; **53**: 507-516 [PMID: 28823009 DOI: 10.1007/s00535-017-1381-7]
  - 34 **Valvano M**, Longo S, Stefanelli G, Frieri G, Viscido A, Latella G. Celiac Disease, Gluten-Free Diet, and Metabolic and Liver Disorders. *Nutrients* 2020; **12** [PMID: 32231050 DOI: 10.3390/nu12040940]
  - 35 **Abenavoli L**, Milic N, De Lorenzo A, Luzzza F. A pathogenetic link between non-alcoholic fatty liver disease and celiac disease. *Endocrine* 2013; **43**: 65-67 [PMID: 22740094 DOI: 10.1007/s12020-012-9731-y]
  - 36 **Marciano F**, Savoia M, Vajro P. Celiac disease-related hepatic injury: Insights into associated conditions and underlying pathomechanisms. *Dig Liver Dis* 2016; **48**: 112-119 [PMID: 26711682 DOI: 10.1016/j.dld.2015.11.013]
  - 37 **Sahin Y**. Celiac disease in children: A review of the literature. *World J Clin Pediatr* 2021; **10**: 53-71 [PMID: 34316439 DOI: 10.5409/wjcp.v10.i4.53]
  - 38 **NCD Risk Factor Collaboration (NCD-RisC)**. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet* 2016; **387**: 1377-1396 [PMID: 27115820 DOI: 10.1016/S0140-6736(16)30054-X]
  - 39 **Cheng J**, Brar PS, Lee AR, Green PH. Body mass index in celiac disease: beneficial effect of a gluten-free diet. *J Clin Gastroenterol* 2010; **44**: 267-271 [PMID: 19779362 DOI: 10.1097/MCG.0b013e3181b7ed58]
  - 40 **Freeman HJ**, Kim YS, Sleisenger MH. Protein digestion and absorption in man. Normal mechanisms and protein-energy malnutrition. *Am J Med* 1979; **67**: 1030-1036 [PMID: 117704 DOI: 10.1016/0002-9343(79)90645-4]
  - 41 **Holzbach RT**. Hepatic effects of jejunoileal bypass for morbid obesity. *Am J Clin Nutr* 1977; **30**: 43-52 [PMID: 831438 DOI: 10.1093/ajcn/30.1.43]
  - 42 **Geier A**, Gartung C, Theurl I, Weiss G, Lammert F, Dietrich CG, Weiskirchen R, Zoller H, Hermanns B, Matern S. Occult celiac disease prevents penetrance of hemochromatosis. *World J Gastroenterol* 2005; **11**: 3323-3326 [PMID: 15929194 DOI: 10.3748/wjg.v11.i21.3323]
  - 43 **Moxley RT 3rd**, Pozefsky T, Lockwood DH. Protein nutrition and liver disease after jejunoileal bypass for morbid obesity. *N Engl J Med* 1974; **290**: 921-926 [PMID: 4206095 DOI: 10.1056/NEJM197404252901701]
  - 44 **Freeman HJ**. Hepatic manifestations of celiac disease. *Clin Exp Gastroenterol* 2010; **3**: 33-39 [PMID: 21694844 DOI: 10.2147/ceg.s7556]
  - 45 **Mata LJ**, Jiménez F, Córdón M, Rosales R, Prera E, Schneider RE, Viteri F. Gastrointestinal flora of children with protein-calorie malnutrition. *Am J Clin Nutr* 1972; **25**: 118-126 [PMID: 4627875 DOI: 10.1093/ajcn/25.10.1118]
  - 46 **Ukkola A**, Mäki M, Kurppa K, Collin P, Huhtala H, Kekkonen L, Kaukinen K. Changes in body mass index on a gluten-free diet in coeliac disease: a nationwide study. *Eur J Intern Med* 2012; **23**: 384-388 [PMID: 22560391 DOI: 10.1016/j.ejim.2011.12.012]
  - 47 **Dickey W**, Kearney N. Overweight in celiac disease: prevalence, clinical characteristics, and effect of a gluten-free diet. *Am J Gastroenterol* 2006; **101**: 2356-2359 [PMID: 17032202 DOI: 10.1111/j.1572-0241.2006.00750.x]
  - 48 **Raiteri A**, Granito A, Faggiano C, Giamperoli A, Catenaro T, Negrini G, Tovoli F. Hepatic Steatosis in Patients with Celiac Disease: The Role of Packaged Gluten-Free Foods. *Nutrients* 2022; **14** [PMID: 35889899 DOI: 10.3390/nu14142942]
  - 49 **Mariani P**, Viti MG, Montuori M, La Vecchia A, Cipolletta E, Calvani L, Bonamico M. The gluten-free diet: a nutritional risk factor for adolescents with celiac disease? *J Pediatr Gastroenterol Nutr* 1998; **27**: 519-523 [PMID: 9822315 DOI: 10.1097/00005176-199811000-00004]
  - 50 **Tortora R**, Capone P, De Stefano G, Imperatore N, Gerbino N, Donetto S, Monaco V, Caporaso N, Rispo A. Metabolic syndrome in patients with coeliac disease on a gluten-free diet. *Aliment Pharmacol Ther* 2015; **41**: 352-359 [PMID: 25581084 DOI: 10.1111/apt.13062]
  - 51 **West J**, Logan RF, Card TR, Smith C, Hubbard R. Risk of vascular disease in adults with diagnosed coeliac disease: a

- population-based study. *Aliment Pharmacol Ther* 2004; **20**: 73-79 [PMID: [15225173](#) DOI: [10.1111/j.1365-2036.2004.02008.x](#)]
- 52 **Corazza GR**, Strocchi A, Gasbarrini G. Fasting breath hydrogen in celiac disease. *Gastroenterology* 1987; **93**: 53-58 [PMID: [3582915](#) DOI: [10.1016/0016-5085\(87\)90313-1](#)]
  - 53 **Novacek G**, Miehsler W, Wrba F, Ferenci P, Penner E, Vogelsang H. Prevalence and clinical importance of hypertransaminasaemia in coeliac disease. *Eur J Gastroenterol Hepatol* 1999; **11**: 283-288 [PMID: [10333201](#) DOI: [10.1097/00042737-199903000-00012](#)]
  - 54 **Miele L**, Valenza V, La Torre G, Montalto M, Cammarota G, Ricci R, Mascianà R, Forgione A, Gabrieli ML, Perotti G, Vecchio FM, Rapaccini G, Gasbarrini G, Day CP, Grieco A. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. *Hepatology* 2009; **49**: 1877-1887 [PMID: [19291785](#) DOI: [10.1002/hep.22848](#)]
  - 55 **Hoffmanová I**, Sánchez D, Tučková L, Tlaskalová-Hogenová H. Celiac Disease and Liver Disorders: From Putative Pathogenesis to Clinical Implications. *Nutrients* 2018; **10** [PMID: [30002342](#) DOI: [10.3390/nu10070892](#)]
  - 56 **Sturgeon C**, Fasano A. Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases. *Tissue Barriers* 2016; **4**: e1251384 [PMID: [28123927](#) DOI: [10.1080/21688370.2016.1251384](#)]
  - 57 **Charlesworth RPG**, Winter G. Small intestinal bacterial overgrowth and Celiac disease - coincidence or causation? *Expert Rev Gastroenterol Hepatol* 2020; **14**: 305-306 [PMID: [32295433](#) DOI: [10.1080/17474124.2020.1757428](#)]
  - 58 **Wigg AJ**, Roberts-Thomson IC, Dymock RB, McCarthy PJ, Grose RH, Cummins AG. The role of small intestinal bacterial overgrowth, intestinal permeability, endotoxaemia, and tumour necrosis factor alpha in the pathogenesis of non-alcoholic steatohepatitis. *Gut* 2001; **48**: 206-211 [PMID: [11156641](#) DOI: [10.1136/gut.48.2.206](#)]
  - 59 **Wu X**, Qian L, Liu K, Wu J, Shan Z. Gastrointestinal microbiome and gluten in celiac disease. *Ann Med* 2021; **53**: 1797-1805 [PMID: [34647492](#) DOI: [10.1080/07853890.2021.1990392](#)]
  - 60 **Rubio-Tapia A**, Barton SH, Rosenblatt JE, Murray JA. Prevalence of small intestine bacterial overgrowth diagnosed by quantitative culture of intestinal aspirate in celiac disease. *J Clin Gastroenterol* 2009; **43**: 157-161 [PMID: [18719514](#) DOI: [10.1097/MCG.0b013e3181557e67](#)]
  - 61 **Losurdo G**, Marra A, Shahini E, Girardi B, Giorgio F, Amoroso A, Pisani A, Piscitelli D, Barone M, Principi M, Di Leo A, Ierardi E. Small intestinal bacterial overgrowth and celiac disease: A systematic review with pooled-data analysis. *Neurogastroenterol Motil* 2017; **29** [PMID: [28191721](#) DOI: [10.1111/nmo.13028](#)]
  - 62 **Tursi A**, Brandimarte G, Giorgetti G. High prevalence of small intestinal bacterial overgrowth in celiac patients with persistence of gastrointestinal symptoms after gluten withdrawal. *Am J Gastroenterol* 2003; **98**: 839-843 [PMID: [12738465](#) DOI: [10.1111/j.1572-0241.2003.07379.x](#)]
  - 63 **Rinella ME**, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, Kleiner DE, Loomba R. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023 [PMID: [36727674](#) DOI: [10.1097/HEP.0000000000000323](#)]
  - 64 **European Association For The Study Of The Liver**. Corrigendum to 'EASL recommendations on treatment of hepatitis C: Final update of the series(') [J Hepatol 73 (2020) 1170-1218]. *J Hepatol* 2023; **78**: 452 [PMID: [36464532](#) DOI: [10.1016/j.jhep.2022.10.006](#)]
  - 65 **Al-Toma A**, Volta U, Auricchio R, Castillejo G, Sanders DS, Cellier C, Mulder CJ, Lundin KEA. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. *United European Gastroenterol J* 2019; **7**: 583-613 [PMID: [31210940](#) DOI: [10.1177/2050640619844125](#)]





Published by **Baishideng Publishing Group Inc**  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

