Original Article

High Frequency of Fatty Liver in Ultrasonography of Patients with Celiac Disease in Northeast Iran

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ABSTRACT

Background:
Celiac disease (CD), or as it is called gluten enteropathy, could result in various complications such as liver abnormalities. Non-alcoholic fatty liver disease (NAFLD) affects 25.2% of individuals worldwide and has become one of the most common causes of cirrhosis. This study aimed to report the frequency of fatty liver in ultrasonography of patients with CD in Golestan province, Northeast Iran.

Materials and Methods:
In this cross-sectional study, patients diagnosed with CD based on a positive anti-tTG Ab and proved by small bowel biopsy were recruited between March 2018 and March 2020 (N=80), through the registry system located in Golestan Research Center of Gastroenterology and Hepatology, Northeast Iran. Ultrasonography was performed and the fatty liver diagnosis was done based on attenuation of the liver itself (less than 40 Hounsfield Unit (HU)) or in comparison with the spleen (liver attenuation≤10, than spleen).

Results:
Among 80 patients with CD (46 women, mean age 39.13±12.5 years), fatty liver was reported in 34 (43.5%), which was mild in 31 (39%), moderate in 2 (2.5%), and severe in 1 (1.3%) patients. One cirrhosis and no hepatomegaly were found.

Conclusion:
In the present study, fatty liver was seen in 43.5% of our patients, which is a large amount. It may be suggested to do a closer follow-up of the complications of CD.

Keywords: Celiac disease, Fatty liver disease, Gastroenterology

Please cite this paper as:
Heydarpour H, Norouzi Z, Rashidian Z, Isapanah Amlashi F, Livani S, Besharat S. High frequency of fatty liver in ultrasonography of patients with celiac disease in Northeast Iran. *Govaresh* 2023;28: 36-41.

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Received: 6 Sep. 2022
Revised: 23 Feb. 2023
Accepted: 24 Feb. 2023

INTRODUCTION

Celiac disease (CD), a well-known small bowel disorder associated with permanent intolerance to gluten-containing food, affects 0.5–1% of the worldwide population. CD is characterized by, specific autoantibodies (anti-tissue transglutaminase antibody [anti-tTG Ab], anti-endomysial antibodies (EMAs), or anti-Gliadin Ab (AGA)). Heterogeneous clinical manifestations include intestinal symptoms (abdominal pain, weight loss, steatorrhea, and diarrhea) and extra-intestinal symptoms (anemia, liver disorders, osteoporosis, and depression)(1–3). CD diagnosis depends on both positive serology and the presence of villous atrophy in small intestinal biopsy (4). To date; the only available treatment for patients affected with CD is a gluten-free diet (GFD) (5).

The wide spectrum of liver abnormalities in patients with CD ranges from severe liver disease to mild alterations in transaminases (6). Some studies have reported a high frequency of CD in patients with liver abnormalities (7–10). So, active screening for CD in patients suffering from liver disease is recommended (7).

On the other hand, a Swedish large population study reported that CD is associated with a 2-6 fold risk increase for later liver disease. In addition, the study revealed that patients with prior liver disease have a 4-6 fold risk increase for future CD (11). Even more, CD may increase the risk of death from liver cirrhosis 8 times higher (12).

Non-alcoholic fatty liver disease (NAFLD), characterized by excessive liver fat accumulation (13), affects 25.2% of individuals worldwide and has become one of the most common causes of cirrhosis (14,15). NAFLD is strongly associated with chronic conditions such as type 2 diabetes (T2DM), obesity, and hypertension (16). In the past four decades, studies documented a clinical relationship between CD and NAFLD (8). Presented as Abnormal liver function tests were noted in both CD and NAFLD (6). The prevalence of CD in patients suffering from NAFLD is 3-7% (17). CD is commonly seen in patients with NAFLD even with a normal body mass index (BMI). Also, some evidence showed an increased risk of NAFLD in CD, especially during the first year of follow-up, and the remaining 15 years after CD diagnosis (10,18). The pathogenesis of NAFLD in CD is poorly understood, but it seems there are links between CD and NAFLD (10).

This study aimed to report the frequency of fatty liver, in ultrasonography of patients with CD in Golestan province, Northeast Iran.

MATERIALS AND METHODS

Study participants

In this cross-sectional study, patients diagnosed with CD based on a positive anti-tTG Ab and proved in small bowel biopsy (4) were recruited between March 2018 and March 2020, through the registry system located in Golestan Research Center of Gastroenterology and Hepatology, Northeast Iran.

Study design

All confirmed celiac cases registered in the Golestan Research Center of Gastroenterology and Hepatology (N=120) were asked to participate in this study. All registered patients were on a Gluten-free diet (GFD) immediately after the diagnosis. Among them, 80 agreed to participate in the project.

Inclusion criteria

Celiac cases were confirmed with pathology and a biopsy taken from the duodenum who agreed to participate in the project.

Exclusion criteria

Prior liver disease and alcohol consumption or no tendency to participate were among the most common exclusion criteria. Also having a history of viral hepatitis like Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) was considered as an exclusion criterion.

Overall, 80 participants were recruited and a checklist was used to record demographic characteristics, alcohol ingestion, and history of liver disease through a face-to-face interview after taking the informed consent and being referred to an experienced radiologist. Ultrasonography (ultrasound: Samsung ws80 A Ultrasound Machine; Korea) was performed for the diagnosis of NAFLD, all by

a single radiologist in a certain center. The diagnosis was based on the attenuation of the liver itself (less than 40 Hounsfield Unit (HU)) or in comparison with the spleen.

Ethics

The local ethics committee of the Golestan University of Medical Sciences approved the protocol (IR.GOUMS.REC.1398.382). Informed consent was obtained from all participants. Information was made anonymous and kept confidential before the analyses.

Statistical Analysis

Data were analyzed using SPSS software version 16. Continuous and categorical data were expressed as a median.

RESULTS

Among 80 patients with CD (46 women, mean age 39.13±12.5 years) NAFLD was reported in 34 (43.5%), which was mild in 31(39%), moderate in 2 (2.5%), and severe in 1 (1.3%) patients (Table 1). One case with cirrhosis and no hepatomegaly was found. Data about disease duration were just available for 45 participants and the mean (standard deviation) was 8.4 (±5.6) years (Table 1).

Table 2 shows ultrasonographic features of the hepatobiliary system in patients with CD.

There were no significant differences in the mean age, mean celiac disease duration, and sex between patients with fatty liver and those with non-fatty liver disease (P=0.66, 0.60, 0.64) (Table 3)

DISCUSSION

In the present study, the prevalence of fatty liver was investigated in patients with CD in Gorgan city, Iran. These results further support the finding of other studies, in which patients with CD were at a high risk of NAFLD. However, a notable finding in this study was the higher frequency of NAFLD in our patients (43.5%) compared with most similar studies.

In an Indian study, the prevalence of NAFLD in 44 newly diagnosed patients with CD was 14.3%, and after one year of follow-up, 29.5% of patients developed NAFLD (19).

Table 1. Basic demographic data in patients with celiac disease (N=80)

Variables		
Age (year), Mean (SD)	39.17 (12.5)	
Duration of disease (year), Mean (SD)	8.40 (5.63)	
Sex, N (%)	Male	34 (42)
	Female	46 (57.5)
Fatty liver, N (%)	Absent	46 (57.5)
	Mild	31 (38.8)
	Moderate	2 (2.5)
	Severe	1 (1.3)

Table 2. Ultrasonic features of the hepatobiliary system in patients with celiac disease (N=80)

	Mean (SD)
Liver sagittal diameter (mm)	122.87 (14.9)
Portal vein diameter (mm)	7.95 (1.6)
Common Bile Duct (CBD) diameter (mm)	2.82 (0.5)
Spleen size (mm)	101.37 (120.4)

*mm=millimeter

Table 3. Results of liver ultrasonography in patients with celiac disease regards the demographic data

		Liver ultrasound		*P* value*
		Fatty liver	Normal	
Age (year), mean (SD)		38.47 (12.35)	39.70 (12.73)	0.66
Duration of disease (year), mean (SD)		8.9 (5.85)	8 (5.530)	0.60
Sex, N (%)	Male	13 (38.2)	21 (45.7)	0.64
	Female	21 (61.8)	25 (54.3)	

*Significant at P<0.05

In addition, in an Italian study, the prevalence of NAFLD in 221 newly diagnosed patients was 29.4%, and after two years of follow-up, 46.6% of the patients developed NAFLD (20). A population-based cohort study of more than 26,000 patients with CD in Sweden demonstrated an increased risk of NAFLD in both children (HR=4.6; 95% CI=2.3-9.1) and adults (HR=2.8; 95%CI=2.0-3.8) with CD (10). Also, another Swedish study among 8513 individuals with CD finds an increased risk of fatty liver (HR, 6.06; 95% CI, 1.35–27.16; P .018) with a prevalence of 0.029%(11). On the other hand, the prevalence of CD

in patients with NAFLD is 3-7% (17). Most authors suggest a serological screening for CD in all patients with NAFLD (21,22).

Further research should be done to find the precise pathogenesis of NAFLD in patients with CD. However, some investigations have suggested the following mechanisms as mechanisms underlying liver injury in such patients: The liver and intestine have a tight connection via the portal system (known as the gut-liver axis). Impairment or dysregulation in the gut–liver axis components (intestinal barrier, gut microbiota, several hepatic receptors, shared lymphocyte homing, and bile) can cause hepatic innate immune response activation which, leads to liver injury (23,24). Gluten exposure in patients with CD cause either intestinal mucosa inflammation or increased expression of zonulin (modulator of small-intestinal tight junctions (TJs)). TJs disruption and intestinal mucosa inflammation may describe increased intestinal permeability leading to intestinal barrier damage in patients with CD (25–27). In addition, long-standing intestinal transit time in poor control CD patients can cause small intestinal bacterial overgrowth (SIBO) (9,28). SIBO changes the microbiota with a consequent increased intestinal permeability and portal endotoxemia, which leads to liver damage (25). Some research demonstrated increased intestinal permeability and SIBO in patients with NAFLD, and this can be commonly shared pathomechanisms between NAFLD and CD (29–31). Furthermore, impaired gut mucosa integrity can cause malabsorption, and then malnutrition, which currently is a rare feature of CD, can lead to hepatic dysfunction (32). There is no doubt that genetics can have a crucial role in liver injury in patients with CD. Some studies have demonstrated a shared inherited predisposition (HLA-DQ2) between CD and some liver disorders (autoimmune hepatitis and primary sclerosing cholangitis) (9). Also, Antonio Rispo and colleagues performed a genotyping assay for evaluating the role of PNPLA3 rs738409 variants in the development of NAFLD in Italian patients with CD. The results demonstrate no differences among patients with different polymorphisms and NAFLD at the time of CD diagnosis. However, after two years of follow-up, patients with NAFLD showed a higher rate of heterozygosis or homozygosis polymorphisms compared with patients without NAFLD (P=0.03 and 0.02, respectively)(20). Further research is needed to prove the genetic link between CD and NAFLD.

Possible explanations for the high prevalence of NAFLD in our patients can be due to genetic variation or can be due to the high frequency of both diseases in the general population (33). The global prevalence of NAFLD is approximately 10-25% (34,35). Therefore, a high prevalence of NAFLD in patients with CD is likely to be coincidental rather than a well-defined association. Obesity, a high-fat diet, lifestyle, and metabolic syndrome, as well as mechanisms that alter intestinal permeability, are potential triggers for NAFLD, which may be found in CD (10,36–38). Evaluating these factors in further research is needed to accurately determine the main reason for the high prevalence of NAFLD in patients with CD.

LIMITATIONS

As previous studies showed trans-abdominal ultrasound (TUS) has a low value for the diagnosis of liver fibrosis in patients with NAFLD and for predicting the prognosis (39). TUS has a good correlation with fibroscan in grades 0 and 1 of fatty liver, but in grades 2 and 3 of fatty liver, we can not rely on TUS for accurate grading.

CONCLUSION

In the present study, the prevalence of fatty liver in our patients with CD was 43.5% (39% mild, 2.5% moderate, and 2.5% severe), and this result supports the findings of earlier studies that patients with CD are at risk for NAFLD.

ACKNOWLEDGMENTS

Authors tend to thank the deputy of research, Golestan University of Medical Sciences for the financial support. And also thank all of our patients and staff in GRCGH, Mrs.Mirkrimi, Mrs. Salamat, and Mrs.Shokouhifar.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest related to this work.

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