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Original Article

# Gallstone Frequency in Adults With Celiac Disease: Results of a Population-Based Celiac Disease Registry From West Azerbaijan, IRAN

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**Abstract**

**Background**: Among people who are genetically predisposed to celiac disease (CD), eating gluten, which is part of the structure of many grains, can lead to intestinal tract damage with an inadequate immune response. The purpose of the present study was to investigate the frequency of gallstones in CD.

**Materials and Methods:** In this analytical cross-sectional study, all CD data were analyzed using the West Azerbaijan Population-Based Celiac Registry (WA-PBCR) database. The mainly evaluated criterion in this study was the frequency of gallstone in samples with CD. For evaluating the results, information related to gender, age, body mass index (BMI), bilirubin, and cholesterol level, anti-transglutaminase antibody level, and the frequency of gallstones were extracted from CD files.

**Results:** Overall, 260 patients with CD were included in the study. The median age of the patients with CD was 33 years, and 66.5% and 33.5% of the patients were females and males, respectively. Gallstones were detected in 11 CD-diagnosed cases (4.23%). There was no significant relationship between the frequency of gallstones and age ($P=0.193$), gender (1.00), and obesity based on the BMI ($P=0.684$) in patients with CD. Finally, 3 (1.15%) of the referred patients with the recognition of gallstones were diagnosed with CD.

**Conclusion:** The prevalence of biliary stones in celiac patients may be higher compared to the normal population. Hypocholesteremia is the predisposing factor for gallstones. In general, a significant relationship was found between the frequency of gallstones and bilirubin levels in patients with CD.

**Keywords:** Celiac disease, Gallstone, Gluten-free diet, Ultrasonography

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## Introduction

Celiac disease (CD) or gluten-sensitive enteropathy is a common autoimmune disorder and is a common cause of absorption disorder (1). This disorder affects people of any age or gender (2). CD has various manifestations, all of which are almost due to an immune response to gluten-containing foods. Contrary to previous studies that merely considered CD a digestive disorder, this disease is a systemic disorder with various demonstrations (1,2,3). Typical symptoms include diarrhea, steatorrhea, weight loss, slimming, and abdominal distension, as well as a series of extraintestinal manifestations and malignancies such as intestinal lymphoma. The serological method is used for disease diagnosis by examining immunoglobulin A (IgA) antibodies against gliadin, anti-endometrial IgA, and IgA anti-transglutaminase.

However, the gold standard for diagnosing CD is small bowel biopsy (4). The main treatment for this disease is the elimination of gluten from the diet, leading to the improvement of many symptoms in patients. Mucosal abnormalities in the small intestine, including villi atrophy, crypt hyperplasia, and increased inflammatory cell density in the epithelium and lamina propria will occur in patients with untreated CD (5). Impaired gallbladder motility has also been reported in patients with CD with reduced secretion of enteric hormones and decreased gallbladder sensitivity to them, increasing the production of stones in the gallbladder (6). If the patient does not eat a gluten-free diet (GFD), enteropathy in the proximal part of the small intestine will reduce the release of cholecystokinin (CCK) from the intestine. Therefore, the gallbladder does not empty quickly after consuming a fatty meal, and gallbladder movements represent a general decrease (7). In other words, if a patient with CD does not eat a GFD, his/her gallbladder becomes large, loose, and lazy. This bile stasis can predispose a person

to gallstones.

In addition to the above-mentioned mechanism, studies have shown that the hepatic production of bile cholesterol, phospholipids, and bile salts, as well as bile flow, increased almost double in patients with CD compared with healthy individuals' bile cholesterol levels, and their bile is supersaturated accordingly (8). These can be logical pathogenesis mechanisms for gallstones in people with CD. However, the recognition and understanding of CD are improving and further people with the disease are receiving positive diagnoses. More than 1 in 10 patients (10%-18%) undergoing cholecystectomy for gallstones have common bile duct stones. Gallstone disease annually affects about 1.8 million outpatients and more than 700 000 cholecystectomy patients in the United States (9). Approximately 60% of CD sufferers are known to have liver, gallbladder, and/or pancreatic problems (10). The cells lining the small intestine (called enterocytes or gut epithelial cells) are less able to release CCK when the gut is damaged whether due to CD or another gut illness. This means that there is not enough signal to the gallbladder indicating that it is the time to release bile salts into the duodenum. CD has been associated with decreased CCK secretion, which could be one of the main causes of gallbladder malfunction (11, 12).

CD affects the liver, which is responsible for producing the bile that your gallbladder stores. Even in cases in which liver transplantation is considered, dietary treatment may prevent progression to hepatic failure (13). CD may also be associated with primary sclerosing cholangitis, which is a chronic condition involving gradual damage to the ducts that move bile from the liver to the gallbladder (14). Due to the existence of logical mechanisms for the pathogenesis of gallstones in CD, very few studies have been conducted regarding the frequency of gallstones in these patients. Further, no study has been conducted using this approach in Iran. Accordingly, the present study investigated the prevalence of gallstone in CD according to the results of a population-based CD registry.

## Materials and Methods

In this analytical cross-sectional study, all CD data were analyzed using the database of West Azerbaijan Population-Based Celiac Registry (WA-PBCR), and 260 patients with CD were enrolled in the study. The main criterion for inclusion was the frequency of gallstone and bile ducts in samples with CD. The present study was conducted after obtaining permission from the Ethics Committee of Urmia University of Medical Sciences. All newly diagnosed CD data were available in the WA-PBCR database. All sources of CD-related data collection were reports from pathology laboratories, hospital records, endoscopic centers, and registry databases. The main demographic data were all recorded in the database, including the first and last name, national identification number, date of birth, date of diagnosis, gender, place of birth, sonographic data, body mass index (BMI), cholesterol and anti-transglutaminase antibody levels, and contact information.

All the obtained CD data were analyzed using the WA-PBCR database, which included the definitive diagnoses of CD cases in the entire West Azerbaijan Province. This province is located in the northwest of Iran and has approximately 3.5 million people from the 17 counties, 43 cities, and 40 districts, comprising the largest Azeri Ethnic population in Iran after East Azerbaijan. All patients participating in the celiac registry project were considered in the study. The exclusion criterion included the patients who could not undergo ultrasonography (USG).

USG was performed after fasting for about 8-12 hours and all its procedures were performed by three independent radiologists. The patients for whom the three physicians provided the same reports were included in the study. The definition of cholelithiasis was based on detecting echogenic structures with acoustic shadows in the visible gallbladder. The lumen or hepatocholedochus duct, one or more echogenic structures in the gallbladder (without dorsal shadow), or a structure having echogenicity and a dorsal acoustic shadow in the gallbladder did not show adequate visualization in the lumen. The obtained data were analyzed by SPSS, version 21. Quantitative and qualitative data were reported as mean and standard deviation, as well as percentage and frequency, respectively, and a *P* value of less than 0.05 was considered statistically significant.

Statistical data analysis, as well as quality and consistency checks were performed to ensure clean and non-duplicated data. Most cases provided their address and contact information, and the follow-up data were obtained by contacting the patients' relatives. Researchers at all stages of the study were committed to the principles of the Helsinki Convention and the Ethics Committee of Urmia University of Medical Sciences.

### *Statistical Methods*

Continuous variables were reported as mean ± standard deviation. Categorical variables were expressed as numbers (percentages) and were compared between without and with stone groups using Chi-square or Fisher's exact test. A *P* value of less than 0.05 was considered statistically significant and data analysis was performed using SPSS, version 17.

## Results

The study was conducted on 260 patients with CD who were participating in the celiac registry project. The mean age of patients was 33.15 ± 91.38 years. In addition, the genus distribution of patients included 87 men (33.5%) and 173 women (66.5%) and most patients were in the age range of 21-40 years (Table 1).

Of 260 patients with CD, only 4.23% had gallstones ($P$ = 4.23%, 95% CI = 2.13-7.44 %), and gallstones were not observed in 95.8% of patients. Only 10% of patients had cholesterol above 240 (Table 1). The mean BMI of patients with CD was 23.36 ± 4.67. The lowest and highest BMIs of patients were 11.4 and 37.81, respectively. Therefore, one of the manifestations of CD can be obesity and overweight (Table 1).

Among the studied celiac patients for whom gallstones were reported on ultrasound, 63.6% and 36.4% were females and males, respectively (Table 2).

The age range of 60-41 had the highest percentage of reported gallstones among all age ranges of the studied celiac patients. However, gallstones were not reported in the age range of 20-1 and 100-80 (Table 3).

Most celiac patients had a normal BMI, and only two of these patients had gallstones. In addition, of 71 overweight celiac patients, gallstones were reported for 4 patients on ultrasound. Therefore, the highest number of celiac patients with gallstones was reported in the range of 25 ≤ BMI ≤ 29.9 (Table 4).

Of ten patients with cholesterol above 240, 7 and 3 patients were reported with CD without stones and with gallstones, respectively (Table 5).

Of 24 celiac patients with bilirubin above 0.9, 8 patients had gallstones, and only 3 out of 229 patients with bilirubin less than 0.9 had stones (Table 6).

**Table 1.** Demographic, Laboratory Results of the Celiac Disease

| Characteristics | Number | Percent |
|---|---|---|
| Gender | | |
| Female | 173 | 66.5 |
| Male | 87 | 33.5 |
| Presence of gallstone | 11 | 4.2 |
| Cholesterol level | | |
| Cholesterol < 200 | 199 | 54.76 |
| 00 < Cholesterol < 239 | 51 | 62.19 |
| Cholesterol >239 | 10 | 3.84 |
| BMI | | |
| Lean body (BMI < 20) | 64 | 24.6 |
| Normal (20 ≤ BMI ≤ 24.9) | 98 | 37.7 |
| Overweight (25 ≤ BMI ≤ 29.9) | 71 | 27.3 |
| Obese (BMI > 30) | 27 | 10.4 |

*Note*. BMI: Body mass index.

**Table 2.** Correlation Between Gallstone and Genus

| Characteristics | Gallstone | | *P* Value[a] |
|---|---|---|---|
| | Without Stone | With Stone | |
| Gender, No. (%) | | | |
| Female | 166 (66.7) | 7 (63.6) | 1.000 |
| Male | 83 (33.3) | 4 (36.4) | |

[a] Chi-square test.

**Table 3.** Gallstone Frequency and Age of Celiac Patients

| Characteristics | Gallstone | | *P* Value[a] |
|---|---|---|---|
| | Without Stone | With Stone | |
| Age range, No. (%) | | | |
| 1-20 | 29 (6.11) | 0 (0) | 195 |
| 21-40 | 116 (6.46) | 4 (4.36) | |
| 41-60 | 83 (3.33) | 6 (5.45) | |
| 61-80 | 18 (2.7) | 1 (1.9) | |
| 81-100 | 3 (2.1) | 0 (0) | |

[a] Fisher's exact test.

## Discussion

It has been a matter of discussion whether CD is responsible for gallstone disease. Approximately 60% of patients with CD are diagnosed with liver, gallbladder, or pancreas problems. Although some of these conditions may result from malnutrition or a direct link to intestinal damage occurring in CD, others are thought to have common genetic factors or a common immunopathogenesis (10). The plasma levels of hormones such as neurotensin, CCK, and somatostatin have been reported to be altered in patients with CD due to proximal intestinal enteropathy, which impairs fasting gallbladder volume and gallbladder contraction and secretion (15-18). Previous research has reported that the hormone neurotensin increased in untreated CD. It has also been reported that an increase in this hormone may delay gastric emptying and impair

**Table 4.** Frequency of Gallstone and BMI in Celiac Patients

| Characteristics | Gallstone | | *P* Value[a] |
|---|---|---|---|
| | Without Stone | With Stone | |
| BMI, No. (%) | | | |
| Lean body (BMI < 20) | 63 (24) | 3 (30) | 0.684 |
| Normal (20 ≤ BMI ≤ 24.9) | 107 (41) | 2 (20) | |
| Overweight (25 ≤ BMI ≤ 29.9) | 71 (28) | 4 (40) | |
| Obese (BMI > 30) | 19 (7) | 2 (10) | |

[a] Fisher's exact test; BMI: Body mass index.

**Table 5.** Gallstone Frequency and Cholesterol Level in Celiac Patients

| Characteristics | Gallstone | | *P* Value[a] |
|---|---|---|---|
| | Without Stone | With Stone | |
| Total cholesterol level, No. (%) | | | |
| Cholesterol < 200 | 197 (12.97) | 2 (18.18) | 0.044 |
| 200 < cholesterol < 239 | 45 (7.18) | 6 (7.18) | |
| Cholesterol > 240 | 7 (81.2) | 3 (27.27) | |

[a] Chi-square test.

**Table 6.** Gallstone Frequency and Bilirubin Level in Celiac Patients

| Characteristics | Gallstone | | *P* Value[a] |
|---|---|---|---|
| | Without Stone | With Stone | |
| Total bilirubin level, No. (%) | | | |
| Bilirubin > 0.9 | 16 (6.4) | 8 (72.7) | 0.039 |
| Bilirubin < 0.9 | 233 (93.6) | 3 (27.3) | |

[a] Chi-square test.

gallbladder motility directly or indirectly (18). In their study, Das et al reported that gallbladder levels and plasma somatostatin levels were higher in CD patients compared to controls at the time of diagnosis, and these findings were completely confirmed after the GFD (7). In patients with CD, postprandial CCK levels are low despite the increased number of cells secreting duodenal CCK. Due to impaired exogenous lipolysis, CCK-secreting cells are not sufficiently stimulated to secrete CCK (12). Gastrointestinal hormone abnormalities and their effects on the gallbladder become normal following a GFD (11, 15).

In recent decades, clinical studies and basic research have extensively examined the pathogenesis of CD with a strong emphasis on immune system enteropathy, which is accelerated by dietary gluten (19). According to numerical data, gallbladder abnormalities are common in patients with CD. The results of James et al indicated that the prevalence of gallstone in CD was about 20%, which is higher than the general population, namely 12% (20, 21). These classic observations show that patients with CD are prone to gallstone formation before the onset of a GFD. In the present study, gallstones were detected in eleven patients with CD diagnosis (4.23%). Based on the analysis of the findings, the mean age of patients was 33.15 ± 91.38 years. Additionally, no significant relationship was found between serum gallstone and age ($P > 0.05$) and genus ($P > 0.05$).

According to this study, most celiac patients had normal weight or were overweight, and on the other hand, most gallstones were observed in the overweight range. However, there was no significant relationship between BMI and gallstones in these patients ($P = 0.68$). Mean cholesterol levels in celiac patients with gallstones were significantly higher in comparison with patients without gallstones ($P = 0.44$). It is not clear if patients with gallstones diagnosed with USG or undergoing cholecystectomy had celiac-caused stones. On the other hand, most cases of celiac have not been diagnosed due to the asymptomatic nature of the CD, and the prevalence of CD and gallstones cannot be estimated appropriately (22).

Similar to fatty acids, phosphate, carbonate, and other anions, unconjugated bilirubin tends to form insoluble precipitates with calcium, and calcium bilirubinate may then crystallize from the solution, and eventually, form stones (23). In another study, Stender et al reported a causal association between extreme levels of plasma bilirubin and increased risk of symptomatic gallstone (24). The findings of this study showed a significant relationship between the frequency of gallstones and bilirubin levels in patients with CD ($P = 0.039$). The results of another study conducted by Zamani et al demonstrated that the overall prevalence of gallstones was estimated at 0.8% of the patients (25). According to findings, it can be hypothesized that the prevalence of biliary stones is higher in celiac patients compared to the normal population.

## Conclusion

In general, a significant relationship was found between the frequency of gallstones and bilirubin levels in patients with CD. The prevalence of biliary stones in celiac patients may be higher in comparison with the normal population. Celiac patients should be followed up with ultrasound for gallstones both at the diagnosis and follow-up. Further research is needed to determine whether CD is a risk factor for gallstones. It is hoped that the present study can take a step toward recognizing the prevalence of CD and gallstones and lead to a better diagnostic and therapeutic orientation.

## Limitations of the Study

This study has been conducted during a short period and with a limited number of cases, thus it is better to extend the time and increase the number of cases. We were unable to enter all celiac patients in the West Azerbaijan province into the celiac ridge project, which will be gradually performed over time.

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### Authors' Contributions

MRP: Study validation and supervision; KS: Literature review and English editing; FHS: Literature review, data collection, and interpretation of the results; MRP, KS, and FHS: Writing and reviewing.

### Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

### Ethical Statement

The study received ethics approval from the Ethics Committee of Urmia University of Medical Sciences (IR.UMSU.REC.1398.223). Patients' information was kept confidential through all research procedures.

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### Informed Consent

Not applicable due to the data collection from files.

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