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Histopathological findings in celiac disease patients enrolled for duodenal biopsy in Najran, Saudi Arabia: a 5-year retrospective study

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Abstract

Background: Celiac disease is an autoimmune condition characterized by serological and histopathological manifestations associated with gluten ingestion.
Aim: This report investigates histopathological findings in all celiac disease patients of both genders enrolled for duodenal biopsy from June 2015 to May 2020 in four centers in Najran, Saudi Arabia.
Methods: This retrospective study assessed data retrieved from archived histopathology records. The data were analyzed using Prism GraphPad 6. Categorical variables were examined using descriptive statistics, including frequency and percentages. A Chi-square test was used to assess the association between gender and age, clinical presentation, and histopathological changes. $P < 0.05$ was considered as significant.
Results: The study included 150 celiac disease patients, of whom 104 were female (69.3%), with most aged between 31 and 40 years (33.3%). Regarding clinical presentation, the majority of patients (62%) presented with gastrointestinal symptoms. Almost half of the duodenal biopsies (71 cases, 47.3%) showed shortened villi caused by partial atrophy, which is consistent with Grade B1 according to Corazza and Villanaci criteria, and Type 3A and 3B lesions according to the Marsh–Oberhuber classification. The second most frequent histopathological finding was an increased abundance of intraepithelial lymphocytes in the absence of villous atrophy, which was found in 56 biopsies (37.3%) and categorized as Grade A.
Conclusions: Females are affected by celiac disease more than males in Najran and the majority presented as having typical celiac disease with gastrointestinal symptoms. Most of the diagnosed cases of celiac disease ranged between Grades A and B1, with less involvement of the severe degree Grades B2 and 3C, according to Corazza and Villanaci's criteria and the Marsh–Oberhuber classification. Despite the absence of any association between gender, age, or clinical presentation, there were significant associations between gender and histopathological findings, grading, and classification of celiac disease lesions. Finally, the presence of asymptomatic patients (12.7%) indicates the importance of celiac disease screening.
Relevance of Patients: This study might be considered a reference for pathologists assessing the duodenal biopsies for patients screened for celiac disease in Najran.

1. Introduction

Celiac disease is an autoimmune condition characterized by serological and histopathological manifestations associated with the ingestion of gluten, an alcohol-soluble group of proteins present in different cereals such as wheat, barley, and oats [1]. During the last few decades, there have been significant developments in understanding the diagnosis, pathogenesis, and clinical presentation of this condition [2]. Celiac disease associates

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with gastrointestinal and/or extraintestinal symptoms; typical celiac disease is characterized by varying degrees of severity of gastrointestinal symptoms, while atypical presentation of the disease is more frequent, and is characterized by an absence of gastrointestinal symptoms [3,4].

Gastrointestinal findings in typical celiac disease include persistent diarrhea, abdominal pain, distension, vomiting, and weight loss. The extraintestinal findings are variable and might be non-specific, including chronic fatigue, skin inflammatory disorders, joint pain, anemia, migraines, psychiatric disorders, epilepsy, osteoporosis, infertility, frequent fetal loss, short stature, failure to thrive, dental abnormalities, multiple vitamin deficiencies, and autoimmune disorders [5]. In addition, a latent form of celiac disease is characterized by the presence of predisposing genetic factors such as the presence of human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8, normal intestinal mucosa, and the usual positive profile of celiac serology [6].

Early diagnosis and treatment of celiac disease are essential mainly in the pediatric age group. This is because certain complications of celiac disease may be irreversible, such as growth retardation, abnormal teething, and osteoporosis. Several studies in the literature suggest prolonged breastfeeding and a delayed gradual introduction of gluten in the 1st year of life to reduce the risk of celiac disease development [7]. The diagnosis of celiac disease is based on the presence of a predisposing genetic factor, positive histopathological biopsy, and the presence of serological antibodies that are released on gluten ingestion [2]. The most available and effective treatment for celiac disease patients is a lifelong gluten-free diet [8]. This generally leads to improvements in patients within weeks, and normal mucosal histology is regained after several years [9]. However, Vitamin B deficiency may affect patients because of long gluten-free diets, and patients are advised to take gluten-free multivitamins [10]. In this context, despite a lack of reports which link the consumption of milk and dairy products to the progression of celiac disease [11], celiac disease patients are advised to avoid such staples because of abnormal intestinal absorption [12].

The current report aims to investigate histopathological findings retrospectively in celiac disease patients enrolled for duodenal biopsy in Najran, since this is considered one of the diagnostic criteria, along with serology and genetic testing.

2. Materials and Methods

A retrospective study was conducted after receiving approval from the Local Ethical Committee at the College of Medicine, Najran University. As mentioned previously, this study aims to investigate histopathological findings in celiac disease patients enrolled for duodenal biopsy. The study included all patients who attended the Departments of Pathology/Histopathology at the King Khalid Hospital, Najran General Hospital, Maternity and Child Hospital, and Najran University Hospital from June 2015 to May 2020, and data were retrieved from the records of confirmed cases. The inclusion criteria comprised all cases that were reported by histopathology, and graded and/or classified according to the Villanaci and Ceppa [13]; Corazza and Villanaci [14]; and/or Marsh–Oberhuber criteria [15]. These criteria were suggested to simplify histopathological reporting and consequently to facilitate communication between pathologists and clinicians. Celiac disease lesions were divided into two categories according to the Corazza and Villanaci criteria, as follows: (1) Grade A non-atrophic lesions, characterized by an increased number of intraepithelial lymphocytes with intact villi and (2) Grade B trophic lesions with further subcategorization into B1, in which villi were still identifiable, and B2, in which villi were totally atrophic [14]. Grade A lesions correspond to Type 1 and Type 2 lesions based on the Marsh–Oberhuber classification and are usually identified by immunohistochemical staining for cluster of differentiation (CD) 3, which is specific for T lymphocytes [2]. Grade B1 lesions correspond to Class 3A and 3B lesions according to the Marsh–Oberhuber classification, while Grade B2 lesions of Corazza and Villanaci correspond to Marsh–Oberhuber class 3C [2].

Crombie's items, the appraisal tool for cross-sectional studies, and the Agency for Health-care Research and Quality methodology checklist for cross-sectional/prevalence studies (Table S1), were used to assess selection bias [16].

Data were analyzed using Prism GraphPad 6 for Windows, version 6.07 (CA, USA). Categorical variables were analyzed using descriptive statistics, including frequency and percentages. A Chi-square test was used to assess the association between gender, age, and clinical presentation. $P < 0.05$ was considered as significant results.

3. Results

This study included 150 celiac disease patients who were diagnosed from June 2015 to May 2020, and no cases have been excluded from the study. As shown in Figure 1 regarding case distribution during this period, most cases were diagnosed in 2019 – 2020 (61, 40.7%). In 2018, there were 51 cases (34%), while there were 18 cases (12%) in 2016 – 2017. The least number of diagnosed cases was in 2015 – 2016 (8 cases, 5.3%), followed by 2017 – 2018 (12 cases, 8%).

As detailed in Table 1, this study included 46 males (30.7%) and 104 females (69.3%), and most of the patients were between 31 and 40 years old (33.3%, 17 males, 33 females). Patients aged between 20 and 30 years comprised 32% (14 males and 34 females) of the diagnosed cases, and those aged between 41 and 50 years accounted for 17.3% (9 males and 17 females) of cases. There were only 15 patients (10%) under 20 years old (three males and 12 females) and 11 patients over 50 years old (6% aged 51 – 60 years, and 1.3% aged more than 60 years). There was no significant association between gender and the different age groups ($P = 0.82$).

Regarding the clinical presentation of the patients, the majority (62%, 28 males, 65 females) presented with gastrointestinal symptoms, including abdominal pain, diarrhea, and abdominal distention. In addition, 20% (10 males and 20 females) of patients presented with anemia, 12.7% (six males and 13 females) were asymptomatic, and 5.3% presented with a history of failure to

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thrive (two males and six females). There was no significant association between gender and the different clinical presentations (P = 0.97).

Table 2 illustrates the histopathological findings of duodenal biopsies, grades of celiac disease according to Corazza and Villanaci criteria, and histopathological classification according to Marsh–Oberhuber criteria. Almost half of duodenal biopsies (71 cases, 47.3%) showed shortened villi caused by partial atrophy, which is consistent with Grade B1 according to Corazza and Villanaci criteria, and Type 3A/3B lesions according to Marsh–Oberhuber classification. Interestingly, most of these patients were females (74.6%), while only 18 were males.

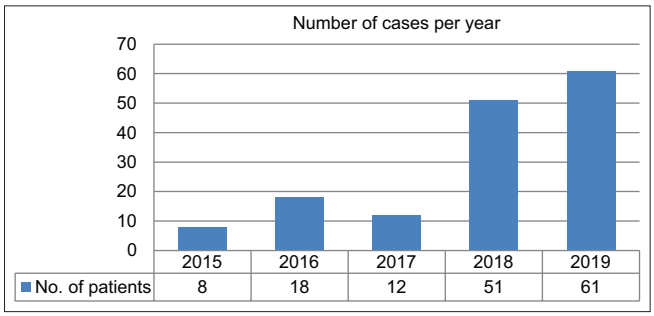

Figure 1. Case distribution of patients diagnosed with celiac disease per year (n = 150).

The second most notable histopathological finding was an increased frequency of intraepithelial lymphocytes without villous atrophy, which was found in 56 biopsies (37.3%) and classified as Grade A according to Corazza and Villanaci criteria, and Type 1/ Type 2 lesions according to the Marsh–Oberhuber classification. In 23 patients (15.3%), there was severe subtotal villous atrophy, assigned as Grade B2 according to Corazza and Villanaci criteria and Type 3C lesions according to the Marsh–Oberhuber classification. This group comprised 13 males (56.5%), compared to only 10 females. Finally, there was a significant association (P = 0.01) between gender and histopathological observations, grading, and classification of celiac disease lesions.

4. Discussion

This 5-year retrospective study aimed to investigate histopathological features in duodenal biopsies from celiac disease patients enrolled in different hospitals in Najran, Saudi Arabia. This work is a continuation of other previously published studies that assessed the histopathological and cytological patterns of different diseases in the region [17,18] and included 150 cases that

Table 1. Gender, age, and presentation of celiac disease patients (n=150)

Parameter	No.	%			
Gender					
Male	46	30.7			
Female	104	69.3			
			Male	**Female**	***P* value (Chi-square, degrees of freedom)**
Age					
<20	15	10	3	12	0.82 (2.22, 5)
20–30	48	32	14	34	
31–40	50	33.3	17	33	
41–50	26	17.3	9	17	
51–60	9	6	3	6	
More than 60	2	1.3	0	2	
Presenting symptoms					
Asymptomatic	19	12.7	6	13	0.97 (0.242, 3)
Gastrointestinal symptoms: abdominal pain, diarrhea, and abdominal distention	93	62	28	65	
Failure to thrive	8	5.3	2	6	
Anemia	30	20	10	20	

Table 2. Histopathological findings, grading, and classification of celiac disease lesions

Histopathological findings	Grade of celiac disease according to Corazza and Villanaci criteria	Histopathological classification according to Marsh–Oberhuber criteria	Number of cases	%	Male	Female	*P* value (Chi-square, degrees of freedom)
Increased intraepithelial lymphocytes without villous atrophy	Grade A/Type 1	Type 1 lesion Type 2 lesion	56	37.3	15	41	*P=0.01 (8.57, 2)
Villi present but shortened as a result of partial atrophy	Grade B1/Type 2	Type 3A lesion Type 3B lesion	71	47.3	18	53	
Subtotal and complete villous atrophy	Grade B2/Type 3	Type 3C lesion	23	15.3	13	10	

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were diagnosed with celiac disease from June 2015 to May 2020. The histopathological grading and classification have clinical importance for clinical follow-up and indicate whether such grades reduce in severity, are maintained, or deteriorate [19]. In this report, according to the criteria of Villanaci and Ceppa [13]; Corazza and Villanaci [14]; and Marsh–Oberhuber [15], Grade A lesions were found in 56 patients (37.3%) as the second most common histopathological pattern after Grade B1 lesions, which were found in 71 patients (47.3%; Table 2). Moreover, only 15.3% of the cases were classified as Grade B2 and Class 3C. This indicates that most of the diagnosed celiac disease cases in Najran range between Grades A and B1, with less involvement of severe Grade B2 and Class 3C. However, despite the absence of any observed associations between gender and age or clinical presentation, contrary to what has been published before [20], there were significant associations between gender and the histopathological findings, grading, and classification of celiac disease lesions. Male patients were diagnosed to have mainly Grades B1 (18 males, 39.1%) and B2 (13 males, 28.3%), while female patients were reported to have mostly Grades A (41 females, 39.4%) and B1 (53 females, 51%) lesions.

The prevalence of celiac disease in Western countries ranges from 1% to 2%. In Saudi Arabia, while there is no clear data regarding the prevalence of celiac disease, studies from different cities and regions have estimated a prevalence range of 1%–3% [21-23]. A meta-analysis conducted in 2018 concluded that the prevalence of histopathology-proven celiac disease cases is about 1.4%, and that seroprevalence is around 2.7% [24]. One of the largest studies in Saudi Arabia was performed in 2013, and included 1167 healthy adolescents for screening in three different regions [25]; this investigation revealed a celiac disease seroprevalence rate of 2.2%. A notable mass screening study to determine the prevalence of celiac disease in Riyadh reported a high prevalence of the disease (1.5%) among Saudi children, which is at least double that in Europe and North America [26]. In this report, the prevalence was not studied in detail and was not one of the objectives. However, during the collection of gastrointestinal cases assessed by histopathology in our 5-year study period, the number of celiac disease cases was noted to be 150 out of 9406 (1.6%), which is consistent with previous reports in other regions of the country.

Regarding celiac disease case distribution through the study period (Figure 1), the highest frequency was in 2019, with 61 cases diagnosed with celiac disease (40.7%). The second highest frequency was in 2018, with 51 cases (34%), followed by 2016 (18 cases, 12%) and 2017 (12 cases, 8%), and the lowest in 2015 (8 cases, 5.3%). Regarding gender differences, males and females are comparable in terms of prevalence and presentation [27]. However, the number of affected females has been reported to be higher than that of affected males [28,29], consistent with the observations of this study (Table 1). Females comprised more than two-thirds of the cases (104 cases, 69.3%). Conversely, gender is not of clinical significance in follow-up, and males and females have comparable disease courses after adhering to a gluten-free diet [20].

Celiac disease patients present with various signs and symptoms, such as abdominal distention, diarrhea, abdominal pain, weight loss, anemia, and bone disease. Despite the increased global prevalence of celiac disease, a significant number of celiac disease patients are still undiagnosed [30]. A variety of reasons for this have been discussed in the literature, including the patchy appearance of mucosal pathology in celiac disease, insufficient or non-representative biopsy for histopathological assessment, variability in histopathology reporting, and the presence of asymptomatic patients [31-34]. The last observation is consistent with the results of this study (Table 1), where the asymptomatic patient group consisted of 19 cases (12.7%). Although typical celiac disease presenting with gastrointestinal symptoms was less common than that presenting with extra-intestinal symptoms [2-4], the former group comprised 93 cases (62%) in this report, and the most affected age group was 31 – 40 years (33.3%), followed by 21 – 30 years (32%). In this report, the atypical extraintestinal celiac disease presentation group [35] included 30 cases of anemia (20%) and 8 cases of failure to thrive (5.3%).

Finally, the pathogenesis of celiac disease has been linked to various microbial species, including *Helicobacter pylori*. In this study, only 2% of the patients had any history of *H. pylori* infection (data not shown). This was contrary to several studies that found a high prevalence of *H. pylori* infection in celiac disease patients [36]. However, some studies have reported no relationship or correlation between the presence of *H. pylori* and pathogenesis of celiac disease [37,38], which may support the observation of this report in this regard.

In conclusion, females are affected by celiac disease more than males and most of the patients are aged between 31 and 40 years. Regarding the clinical presentation of the patients, the majority (62%) presented with typical celiac disease with gastrointestinal symptoms, including abdominal pain, diarrhea, and abdominal distention. Most of the diagnosed cases of celiac disease in Najran range between Grades A and B1, with less involvement of the severe degree Grade B2 and Class 3C, according to Corazza and Villanaci criteria and the Marsh–Oberhuber classification, respectively. Despite the absence of any association between gender and age or clinical presentations, there was a significant association between gender and the histopathological findings, grading, and classification of celiac disease lesions. Finally, the presence of asymptomatic patients (12.7%) may indicate the importance of celiac disease screening.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Ethics Approval and Consent to Participate

The study was conducted after receiving approval from the Local Ethical Committee at the College of Medicine, Najran University. Consents have been obtained from the human subjects prior to this study.

Consent to Publication

Not applicable.

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Supplementary File

Table S1. Checklist for bias assessment

Major components	Response options		
The Appraisal tool for Cross-Sectional Studies (AXIS tool; last introduced on December 8, 2016)			
Introduction			
1. Were the aims/objectives of the study clear?	Yes	No	Do not know/comment
Methods			
2. Was the study design appropriate for the stated aim (s)?	Yes	No	Do not know/comment
3. Was the sample size justified?	Yes	No	Do not know/comment
4. Was the target/reference population clearly defined? (Is it clear who the research was about?)	Yes	No	Do not know/comment
5. Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?	Yes	No	Do not know/comment
6. Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?	Yes	No	Do not know/comment Not applicable
7. Were measures undertaken to address and categorise non-responders?	Yes	No	Do not know/comment Not applicable
8. Were the risk factor and outcome variables measured appropriate to the aims of the study?	Yes	No	Do not know/comment Not applicable
9. Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialed, piloted or published previously?	Yes	No	Do not know/comment Not applicable
10. Is it clear what was used to determined statistical significance and/or precision estimates? (e.g., *P* values, CIs)	Yes	No	Do not know/comment
11. Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	Yes	No	Do not know/comment
Results			
12. Were the basic data adequately described?	Yes	No	Do not know/comment
13. Does the response rate raise concerns about non-response bias? Not applicable	Yes	No	Do not know/comment
14. If appropriate, was information about non-responders described? Not applicable	Yes	No	Do not know/comment
15. Were the results internally consistent?	Yes	No	Do not know/comment
16. Were the results for the analyses described in the methods, presented?	Yes	No	Do not know/comment

(*Contd...*)

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Table S1. (*Continued*)

Major components	Response options		
The Agency for Healthcare Research and Quality (AHRQ) Methodology Checklist for Cross-Sectional/Prevalence Study Website: http://www.ncbi.nlm.nih.gov/books/NBK35156/			
1. Define the source of information (survey, record review)	Yes	No	Unclear
2. List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	Yes	No	Unclear
3. Indicate time period used for identifying patients	Yes	No	Unclear
4. Indicate whether or not subjects were consecutive if not population-based	Yes	No	Unclear
5. Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	Yes	No	Unclear
6. Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements) Not applicable	Yes	No	Unclear
7. Explain any patient exclusions from analysis	Yes	No	Unclear
8. Describe how confounding was assessed and/or controlled Not applicable	Yes	No	Unclear
9. If applicable, explain how missing data were handled in the analysis Not applicable	Yes	No	Unclear
10. Summarize patient response rates and completeness of data collection Not applicable	Yes	No	Unclear
11. Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained Not applicable	Yes	No	Unclear
Crombie's items			
1. Appropriateness of design to meet the aims	Yes (1 point)	Unclear (0.5 point)	No (0 point)
2. Adequate description of the data	Yes (1 point)	Unclear (0.5 point)	No (0 point)
3. Report the response rates: not applicable	Yes (1 point)	Unclear (0.5 point)	No (0 point)
4. Adequate representativeness of the sample to total	Yes (1 point)	Unclear (0.5 point)	No (0 point)
5. Clearly stated aims and likelihood of reliable and valid measurements	Yes (1 point)	Unclear (0.5 point)	No (0 point)
6. Assessment of statistical significance	Yes (1 point)	Unclear (0.5 point)	No (0 point)
7. Adequate description of statistical methods	Yes (1 point)	Unclear (0.5 point)	No (0 point)

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