Original paper

The role of antral histopathology in diagnosing paediatric celiac disease

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The aim of this study was to evaluate the diagnostic potential of gastric antrum histology in children suspected of having celiac disease (CD).
The present retrospective study was performed on 224 patients who were suspected of having CD and had several duodenal and one gastric antrum biopsies. They were divided into 2 groups based on the definite diagnosis of CD. The statistical analysis was performed using SPSS version 22 software. Receiver operating characteristic (ROC) curves were drown and the area under the curves (AUCs) was calculated.
Based on MARSH criteria, out of 224 patients, 124 were diagnosed as definite CD and 100 patients comprised the non-celiac group. The AUC for the mean of all pathological tests was estimated to be 0.90 ($p < 0.001$). The pooled AUC for the combination of 3 pathologic findings with the highest AUCs (cell, crypt, and gland size) was estimated to be 0.89 ($p < 0.001$).
We observed that the histological changes we found in the gastric antrum were identical to those found in the duodenum of paediatric CD patients. Because providing a biopsy from the gastric antrum is easier than getting multiple biopsies from the duodenum, we suggest using the criteria mentioned in this study in other studies with larger sample sizes.

Key words: celiac disease, antrum biopsy, histological features, stereology.

Introduction

Celiac disease (CD) is an autoimmune disease characterized by damage to the tissues of the small intestinal mucosa following the consumption of gluten-containing foods [1]. CD is one of the most common chronic diseases of the gastrointestinal tract, with a prevalence of 1–3% [2–4]. Most patients with CD are either completely asymptomatic or show nonspecific gastrointestinal symptoms such as dyspepsia, abdominal pain, bloating, and disorders of bowel movements, which make it difficult to diagnose [5]. Because the proximal part of the small intestine is the main site of CD, the diagnosis is made by histopathological examination of duodenal biopsies; hence, sampling is considered as a gold standard of CD diagnosis [6, 7]. Because intestinal involvement in CD is patchy, the location, number, and quality of sampling affect the diagnostic performance. Therefore, to maximize diagnostic accuracy, more than 5 duodenal biopsies should be collected, which can be highly invasive, especially in children [8]. Histolo-

gical features of this disease include an increase in intraepithelial lymphocytes, with or without villi atrophy [7]. However, in several studies, signs of gastritis and lymphocytic gastritis have been observed in patients with celiac disease [9]. Studies have shown that about 16% of patients with celiac disease have lymphocytic gastritis that had not been related to *Helicobacter pylori* infection [10]. The presence of lymphocytic gastritis is associated with the severity of the disease (in terms of clinical symptoms and laboratory findings) and the severity of duodenal lesions, especially villous atrophy [11, 12]. Therefore, because the diagnosis of CD is challenging, collecting multiple biopsies is invasive, and taking biopsies from the duodenum is difficult in some children, it seems that if gastric antrum biopsy has the required accuracy, it could be used as a replacement in these cases. Therefore, in this study, we decided to investigate the histological features of antral biopsy specimens of children suspected of having celiac disease.

Material and methods

In this retrospective cross-sectional (descriptive-analytical) study all endoscopic biopsy samples from 300 patients who were suspected of having CD based on clinical manifestations were obtained from the pathology archives of Ali Ibn Abitaleb Hospital, Zahedan University of Medical Sciences, Zahedan, Iran. Gastric and duodenal biopsy specimens were taken at the time of the CD diagnosis by both a paediatric gastroenterologist and hepatologist during the period 2017–2019. Histological endoscopy specimens from all patients were re-examined, and the appropriate samples were selected. Celiac diagnosis was done based on histological changes in the duodenum. Appropriate gastric antral specimens were available for 224 patients. Based on these results the patients were divided into 2 groups including celiac patients ($n = 124$) and non-celiac ones ($n = 100$). Inclusion criteria included age under 18 years and diagnosis based on at least one measured antibody (anti endomysium) (EMA and/or anti-transglutaminase 2 [TTG]), and individuals with systemic disorders, family history of inflammatory diseases, and a history of gluten-free diet were excluded from the study.

Histological parameters that were associated with specific duodenal alterations at biopsy, such as increased intraepithelial lymphocytes (IELs), crypt hyperplasia, and villous atrophy, according to Marsh classification were considered as follows: type 1 – increased IELs, type 2 – increased IELs and crypt hyperplasia, type 3 – villous atrophy with increased IELs and crypt hyperplasia [13, 14]. Patients without these findings were classified as having normal duodenal biopsies and entered into our non-celiac group.

In this morphometric study, antrum microscopic slides that were stained with haematoxylin eosin, from celiac and non-celiac specimens, were analysed by an expert histologist (Z.H.). She examined all the slides under a light microscope at high-power magnification (400×). In each slide, 5 fields were selected using systematic uniform random sampling (SURS) method by moving the microscope's stage in the X and Y directions with the aid of a vernier scale in the tissue section, as described previously [15–17]. To count the intraepithelial and lamina propria lymphocytes, a frame of 70 × 69 mm was superimposed onto the histologic images on the computer monitor in the SURS fields, with a 40× magnification objective lens and 1130× linear magnification. Lymphocytes were recognized by their basophilic nuclear chromatin pattern, irregular nuclear outline, and clear perinuclear halo. All lymphocyte cells were counted in the corresponding frame area in the gastric antrum epithelium and then in connective tissues. Image analysis software (Digimizer 5.3.5) was used on a Leica digital photomicroscope (ICC50 HD, Wetzlar Germany), for cell counting and for measurement of epithelial cell and gland dimensions. To measure the size of the epithelial cells a 100× objective lens was used. The dimension of the longest gland in the frame was also measured on the same frame with a magnification of 280×. These results were entered into a data sheet for each patient. This project was approved by the Ethics Committee of Zahedan University of Medical Sciences (IR. ZAUMS. REC.1397.23).

Receiver operating characteristic (ROC) curves were used to assess which test is more useful in predicting whether patients have celiac disease. The area under the curve (AUC) for all continuous tests were designed and compared with each other. The greater the area under the ROC curve, the more useful the test was in predicting the patients who had celiac disease. We also determined the optimal cut-point for each test for predicting celiac disease with the highest sensitivity and specificity. In addition, the cut-off values with highest sensitivity and cut-off values with the highest specificity were calculated to select the best cut-off points for screening and diagnosis of celiac disease, respectively. In the next step, new measurements were designed using the average of all pathological tests as well as the 3 pathological tests with the highest AUC. Then, the results of the ROC curves of these new measurements were compared with those of the other pathological tests. We also converted the continuous pathological tests to categorical measurements using the optimal cut-off values. Then, a new measurement was designed, which was defined as positive (when all pathological tests were positive) or negative (when at least one of the pathological tests was negative). Finally, sensitivity, specificity, and positive and negative predictive values

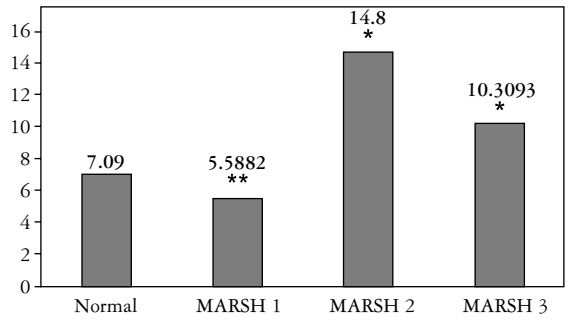

Fig. 1. Comparison of lymphocyte infiltration in the antral epithelial tissue of the celiac children based on MARSH classification

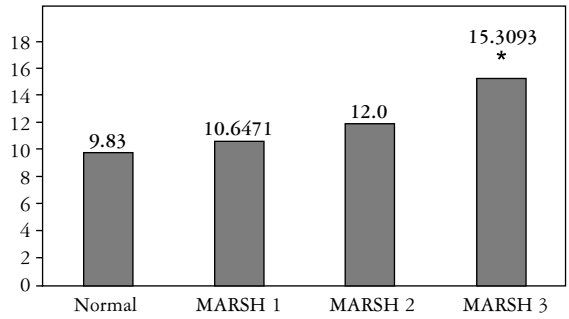

Fig. 2. Comparison of lymphocyte infiltration in the antral lamina propria in celiac patients based on MARSH classification

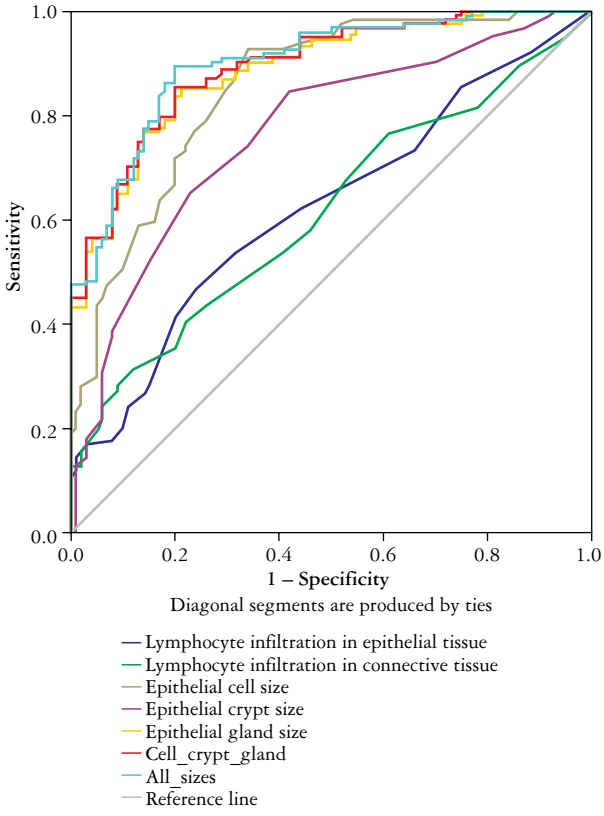

Fig. 3. ROC curves for different pathological measurements of the antrum

for the new test were calculated. The correlation between categorical variables was estimated using the Spearmen correlation coefficient. All statistical actions were performed using SPSS version 22 software. All data were presented as mean ± SD. Statistical differences between 2 independent groups were assessed using the independent sample Student's *t*-test. The significance level was set at $p < 0.05$. The prognostic value was expressed as the risk ratio (RR) and corresponding 95% confidence interval (CI).

Results

In this cross-sectional study, 224 patients were enrolled including 124 patients with CD and 100 patients with negative results regarding celiac disease. Of these patients, 138 (61.6%) were female, and the mean age of the patients was 6.91 (±4.26) years. The youngest and oldest patients were aged one and 17 years, respectively. The prevalence of patients with MARSH I, II, and III lesions were 11 (13.7%), 10 (8.1%), and 97 (78.2%), respectively. Among children in the Marsh III group, 38 (39.1%) had mild villus atrophy (subgroup a), 27 (27.8%) showed marked villus atrophy (subgroup b), and 32 (33.1%) had developed complete villus atrophy (subgroup c).

The rate of lymphocyte infiltration in the antral epithelial tissue of children with CD compared to the non-celiac group showed a statistically significant difference ($p \leq 0.001$) (Fig. 1). Also, a significant difference was observed in the rate of lymphocyte infiltration in the lamina propria of the antrum of children with CD compared to the non-celiac children ($p < 0.001$) (Fig. 2). However, no significant difference was observed in the size of antrum epithelial crypts between the celiac and non-celiac groups.

As illustrated in Figure 3 and Table I, the AUC of the pathological tests varied from 0.615 ($p = 0.003$) for lymphocyte infiltration in lamina propria to 0.887 ($p < 0.001$) for the gland size in the antrum tissue. The AUC for the mean of all pathological tests was estimated to be 0.90 ($p < 0.001$). The pooled AUC for combination of 3 findings with the highest AUCs (epithelial cell, crypt, and gland size) was estimated to be 0.89 ($p < 0.001$).

The optimal cut-off values for gland size, epithelial cell size, and epithelial crypt size were 434.25, 16.50, and 4.65, respectively. The best cut-off values for screening of CD by these 3 tests were 318.55, 14.30, and 3.40, respectively. Sensitivity, specificity, and the best diagnostic cut-off values for each of these tests are shown in Table II. Considering the 3 pathologic measurements with the largest AUCs (glands, epithelial cells, and crypts of the antrum), sensitivity, specificity, and positive and negative predictive values of having all 3 positive tests were 44.4%, 100%, 100%, and 59.2%, respectively (Fig. 5–7).

Table I. The area under the ROC curve for different pathological measurements of the antrum

Pathological measurements	AUC	*p*-value	95% Confidence interval	
			Lower bound	Upper bound
Lymphocyte infiltration in epithelial tissue	0.625	0.001	0.553	0.698
Lymphocyte infiltration in lamina propria	0.615	0.003	0.542	0.688
Epithelial cell size	0.854	0.000	0.805	0.904
Crypt size	0.768	0.000	0.705	0.830
Gland size	0.887	0.000	0.846	0.929
Mean of cell, crypt, and gland size	0.893	0.000	0.853	0.933
Mean of all parameters	0.900	0.000	0.861	0.940

Table II. Cut-off values and diagnostic utility of different pathological tests for identifying patients with celiac disease

Pathological measurements	Purpose	Cut-off value	Sensitivity	Specificity
Gland size	Screening	318.55	0.99	0.25
	Optimal	434.25	0.85	0.79
	Diagnostic	568.85	0.54	0.97
Epithelial cell size	Screening	14.30	0.98	0.48
	Optimal	16.50	0.77	0.76
	Diagnostic	19.70	0.28	0.98
Crypt size	Screening	3.40	0.99	0.08
	Optimal	4.65	0.65	0.77
	Diagnostic	5.50	0.18	0.97

We also considered MARSH III as a gold standard measure for detecting patients with and without CD. The AUCs for diagnosis of MARSH III celiac disease varied between 0.64 ($p<0.001$) for lymphocyte infiltration in lamina propria and 0.90 ($p<0.001$) for gland size (Table III, Fig. 4). Considering the MARSH III as the gold standard for detecting celiac patients, the optimal cut-off values for gland, epithelial cell, and crypt sizes were estimated to be 434.25, 16, and 4.50, respectively (Table IV). The sensitivity, specificity, and positive and negative predictive values of having all 3 positive pathological measurements (glands, epithelial cells, and crypts of the antrum) were calculated to be 55.7%, 99%, 98.2%, and 69.7%, respectively.

The correlation of coefficients between the TTG test and all pathological measures were estimated among all celiac patients as well as among those with MARSH III. TTG was directly correlated only with epithelial cell size (r = 0.304, p = 0.047) among all celiac patients. There was no significant correlation between TTG and other pathological measurements (Table V).

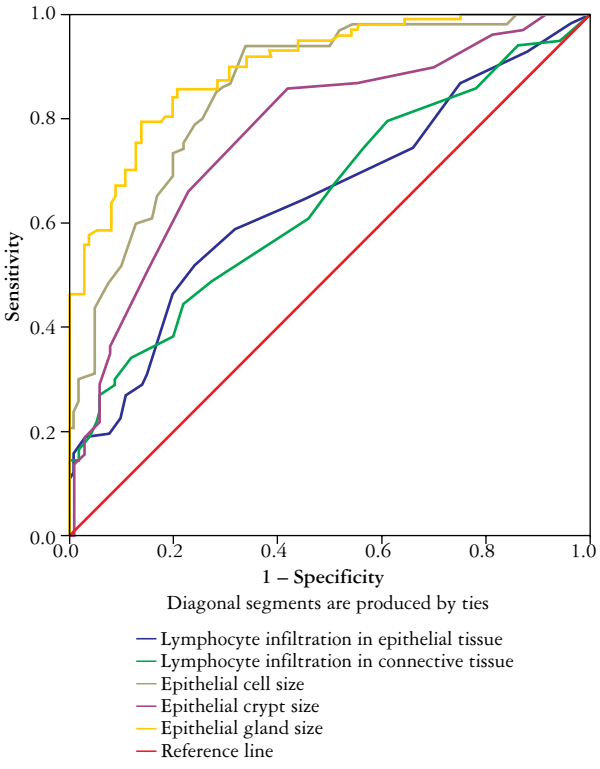

Fig. 4. ROC curves for different pathological measurements of the antrum for diagnosis of MARSH III celiac patients

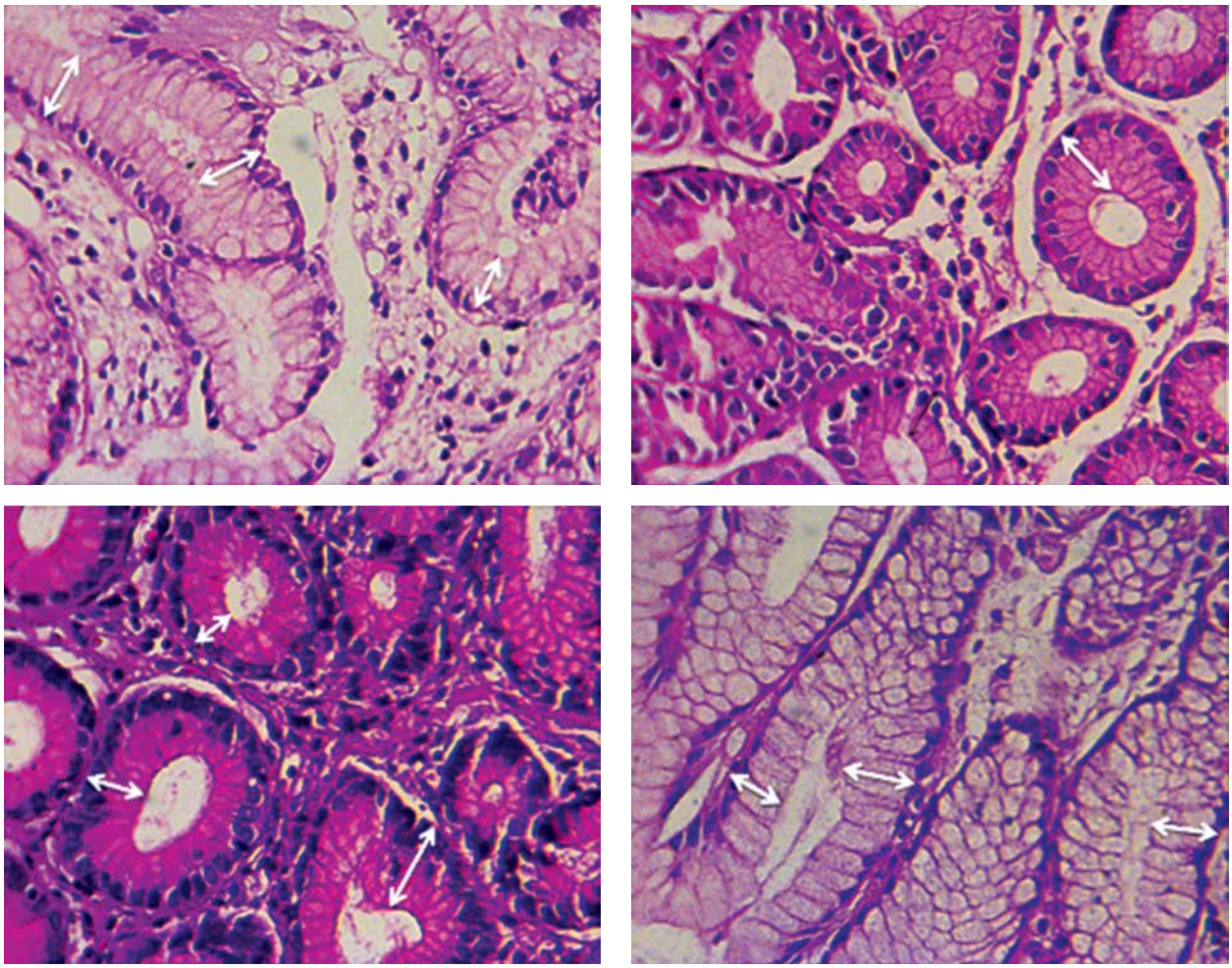

Fig. 5. Antral cell size in patients with celiac disease (400×)

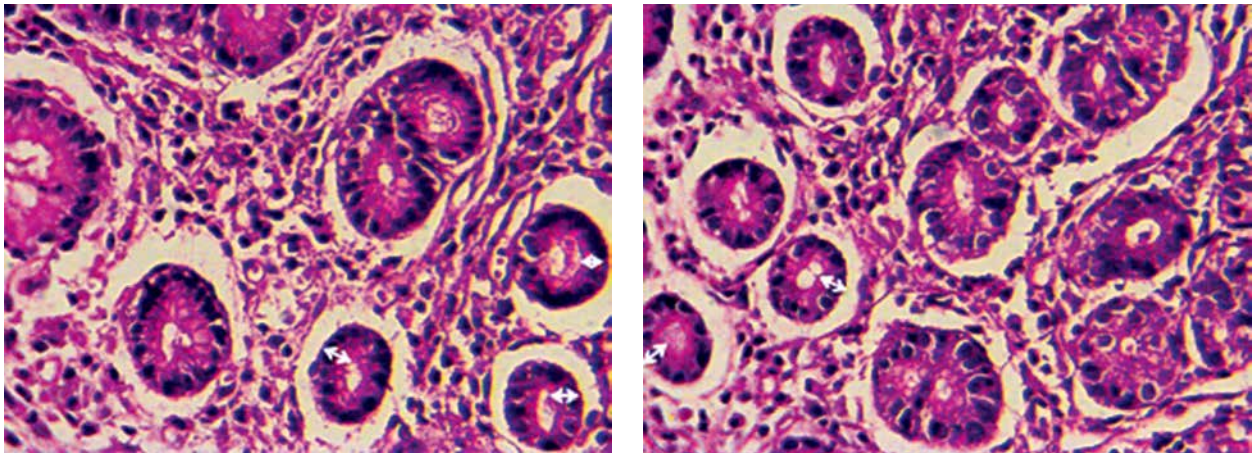

Fig. 6. Antral cell size in non-celiac patients (400×)

Discussion

In this study, gastric antrum biopsies from children with CD and non-celiac children were used, and the histological changes of antrum in the 2 groups were compared. For this comparison, 5 pathological criteria were used, including lymphocyte infiltration in epithelial and lamina propria, gland size, epithelial cell size, and epithelial crypt size. In addition, all biopsy specimens were evaluated according to MARSH criteria, and MARSH III lesions were considered as confirmation of CD definite diagnosis. The present study showed that the same CD group that had the most histological changes in the duodenum had the highest sensitivity and specificity observed in their gastric antrum histological changes. Use of the above 5 patho-

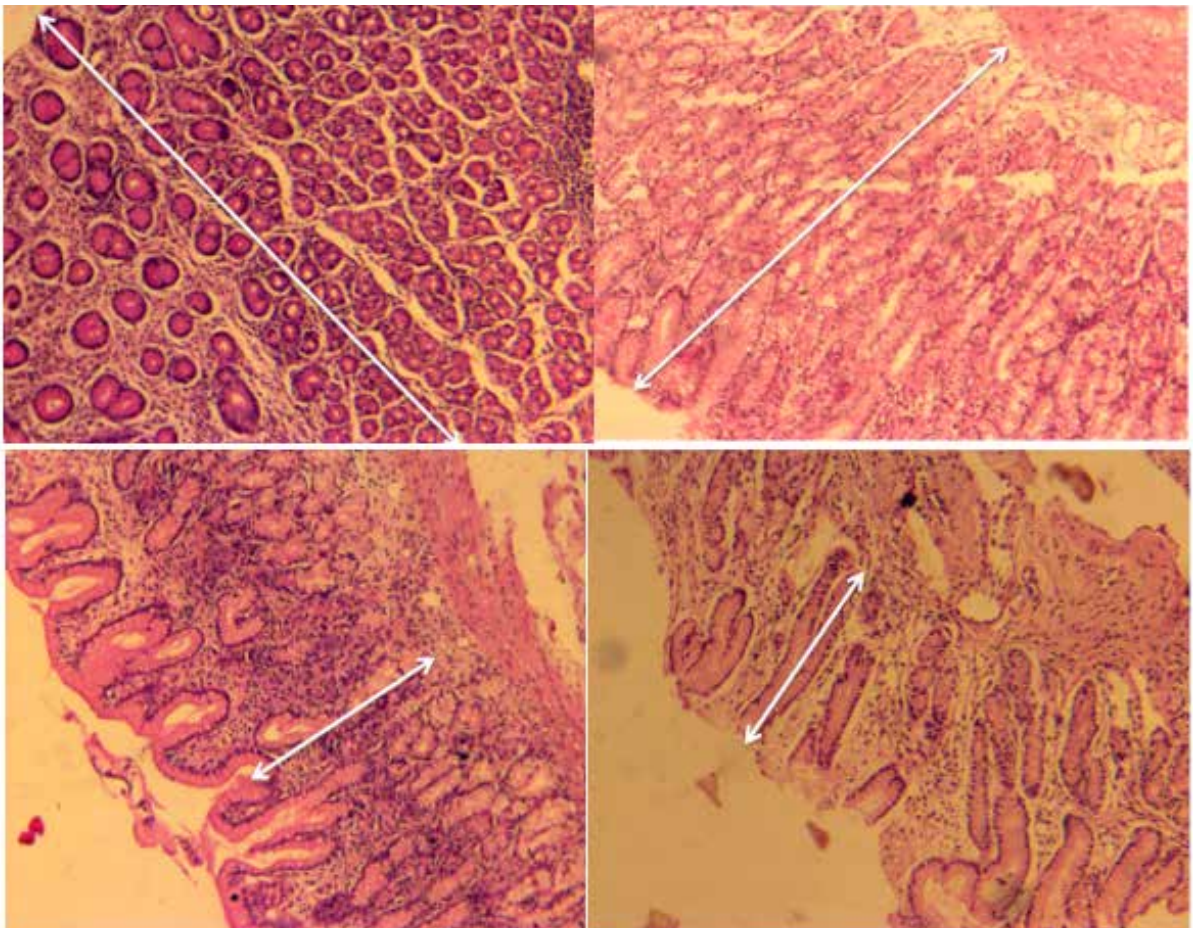

Fig. 7. Comparison of gland sizes in patients with celiac (upper figures) and healthy controls (lower figures) (100×)

Table III. Area under the curve for pathological parameters for diagnosis of MARSH III celiac patients

Pathological measurements	AUC	*p*-value	95% Confidence interval	
			Lower bound	Upper bound
Lymphocyte infiltration in epithelial tissue	0.646	0.000	0.568	0.723
Lymphocyte infiltration in lamina propria	0.644	0.000	0.567	0.721
Epithelial cell size	0.856	0.000	0.805	0.908
Crypt size	0.769	0.000	0.703	0.836
Gland size	0.898	0.000	0.856	0.939

Table IV. Cut-off values and diagnostic utility of different pathological tests for identifying patients with MARSH III celiac disease

Pathological measurements	Purpose	Cut-off value	Sensitivity	Specificity
Gland size	Screening	318.55	0.99	0.25
	Optimal	434.25	0.85	0.79
	Diagnostic	568.85	0.54	0.97
Epithelial cell size	Screening	14	0.98	0.46
	Optimal	16	0.84	0.72
	Diagnostic	19.70	0.30	0.98
Crypt size	Screening	3.60	0.97	0.13
	Optimal	4.50	0.77	0.66
	Diagnostic	5.50	0.19	0.97

Table V. Correlation coefficients between anti-transglutaminase 2 and pathological measurements

TTG		Lymphocyte infiltration in epithelial tissue	Lymphocyte infiltration in lamina propria	Epithelial cell size	Crypt size	Gland size
All celiac patients	*r**	–0.028	–0.112	0.304*	0.043	0.027
	p-value	0.861	0.475	0.047	0.785	0.863
MARSH III celiac patients	*r*	–0.071	–0.053	0.287	–0.015	0.036
	p-value	0.681	0.758	0.090	0.932	0.833

**Correlation coefficient (Spearman)*
TTG – anti-transglutaminase 2

logical criteria had the highest AUC subtype for the diagnosis of CD (AUC = 900, $p \leq 0.000$).

The results of this study showed that the rate of lymphocyte infiltration in epithelial tissue and also in lamina propria was increased significantly in celiac patients compared to non-celiac cases ($p \leq 0.000$). These findings were similar to those in the study by Bhatti, which examined 304 patients with CD for gastric mucosal involvement and identified lymphocytic gastritis associated with CD [11]. Lebwohl *et al.* [8] also found a strong association between CD and lymphocytic gastritis, especially in association with more severe signs of villi atrophy. In fact, lymphocytic gastritis reflects host immunity in response to dietary gluten, similarly to that seen in the small intestine of patients with CD [18]. The pattern of gastric mucosal involvement in lymphocytic gastritis is closely related to duodenal pathology [19]. Numerous studies have shown that lymphocytic gastritis is a part of diffuse lymphocytic gastroenteropathy that is more common in the gastric antrum due to its extension to the duodenum [11, 20, 21]. Hayat *et al*. [19] also confirmed this, and they found lymphocytic gastritis lesions mostly in the gastric antrum of celiac patients. Involvement of the gastric mucosa is common in CD because mucosal involvement is prevalent in other parts of the gastrointestinal tract such as the mouth [22] and colon [23]. In fact, in addition to the small intestine, gluten intolerance also affects other parts of the gastrointestinal tract. Numerous studies have shown the effect of gastric epithelial cells on inflammatory and autoimmune diseases of the gastrointestinal tract. Louise [24] examined the effects of autoimmune gastritis on gastric cells in animal specimens and showed that inflammatory cell infiltration alters gastric mucosa, which indicates the importance of the role of CD4+ T cells in the pathology of gastritis. In inflammatory diseases of the gastrointestinal tract, the proliferation of inflammatory cells is stimulated by various factors [25]. Many studies have considered the role of TTG antibodies in the high proliferation rate observed in crypts of the antrum of celiac patients [26]. TTG autoantibodies, in interaction with membrane-bound TTG, activate cellular responses, stimulate cell cycle progression, and play an important role in epithelial cell proliferation in CD [27]. Tissue transglutaminase 2 (TG2) has the highest expression in the family of transglutaminase proteins. The biological role of TG2 is affected by the presence of antibodies against it [28, 29]. Because TG2 is involved in the differentiation of epithelial cells via TGF-β, its antibodies can reduce the differentiation of epithelial cells, increase the permeability of intestinal cells, and cause intestinal damage (especially villous atrophy and crypt hyperplasia). TG2 is present in almost all cell types, so the morphology of antral epithelial cells can also be affected by CD due to its location along with the duodenum. Therefore, the dimensions of antral epithelial cells were compared between celiac and non-celiac cases, and it was found that the dimensions of the epithelial cells of celiac children are significantly increased compared to the size of these cells in healthy children ($p \leq 0.000$). Epithelial cell size alone or in combination with other criteria can be considered as one of the most efficient pathological criteria of antrum for the diagnosis of CD. The epithelial cell size was 98% specific for the diagnosis of MARSH III as the gold standard for the CD diagnosis, which was the highest specificity among other criteria.

Also, because one of the pathological changes and symptoms that lead to the CD diagnosis is epithelial tissue hyperplasia and changes in the sizes of the glands of the duodenum, in the present study we compared the size of the glands between the 2 groups. The results showed that the size of the glands of the antrum of children with CD were significantly increased compared to the antrum of non-celiac children. Considering MARSH III as the gold standard criterion for CD diagnosis, the size of the antrum glands had the highest AUC for the diagnosis of MARSH III celiac disease. Also, among other pathological criteria, the size of the glands had the highest sensitivity and specificity for the CD diagnosis using optimal cut-off values. Hyperplasia of epithelial crypts of the duodenum is another pathological change considered in the MARSH classification of CD. In fact, crypt hyperplasia refers to an increase in the size of Lieberkuhn crypts, a process that occurs before villous atrophy and is followed by increased production

of immature epithelial cells and an influx of inflammatory cells [30]. In the present study, the sizes of antrum epithelial crypts of the 2 groups were compared. However, we found no significant difference between the size of epithelial crypts of antrum in celiac and non-celiac patients. Meanwhile, epithelial crypt size along with other pathological criteria showed high sensitivity and specificity for diagnosis and screening of CD. The pathologic measurements of gland size and epithelial cell size detected the celiac patients more accurately than the other pathologic criteria. Of these, epithelial cell size was the most accurate because the area under its ROC curve was the largest. However, the overlapped confidence intervals between these 2 tests suggests that both of them are useful diagnostic tests for CD. Although combining the results of the pathological measurements as new diagnostic criteria for CD provided larger AUCs, overlapping the confidence intervals suggested no difference between these 2 combined criteria and the primary pathological criteria (epithelial cell size and gland size). The highest sensitivity and specificity for diagnosis of CD by the optimal cut-off values was observed for the optimal cut-off values of gland size. Our results showed that for diagnostic purposes, the best cut-off values for gland size, epithelial cell size, and epithelial crypt size were 568.55, 19.70, and 5.50, respectively, which can detect celiac patients with the lowest false positive rates. While, for screening of the celiac patients within the community, it is recommended that 318.55, 14.30, and 3.40 be considered as the best cut-off values. Such cut-off points distinguish patients with and without celiac disease with the lowest false negative rate. It should be noted that considering MARSH III as the gold standard criterion for detecting patients with and without celiac, gastric antrum gland size and epithelial cell size were found to have the highest accuracy, which was similar to the results obtained when all grades of celiac were considered as the gold standard. In addition, we found that combining the results of the 3 measurements provides the best specificity and positive predictive value for detecting CD. It means that positive results of all 3 measurements (gland, epithelial cell, and crypt of the antrum) can be the best criteria for the diagnosis of celiac disease with the lowest false positive rate, which was similar to the findings in which MARSH III criteria were applied for detecting celiac patients. We observed that out of all pathological measurements, only epithelial cell size had a weak positive correlation with TTG. Therefore, it seems that TTG cannot be a strong predictor for CD.

Conclusions

We observed that the histological changes that we found in the gastric antrum were identical to those found in the duodenum of paediatric CD patients. The pathological criteria of gland size and epithelial cell size in gastric antrum biopsy were the most accurate in CD diagnosis, with the fewest false positive or false negative results. Since providing a biopsy from the gastric antrum is easier than obtaining multiple biopsies from the duodenum, we suggest using the criteria mentioned in this study in studies with larger sample sizes.

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Ethical approval

The study was conducted in accordance with the Declaration of Helsinki for conducting research involving humans, and all sample collections and experiments were approved by the Ethics Committee of Zahedan University (IR. ZAUMS. REC.1397.23).

The authors declare no conflict of interest.

References

1. Noori NM, Khalili M, Shahramian I, Teimouri A. Evaluation of aortic elasticity in children with celiac disease compared with controls. Int J Pediatr 2020; 9: 13817-13832.
2. Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018; 16: 823-36.e2.
3. Graczyk J, Makowska O, Łężyk-Ciemniak E, Szaflarska-Popławska A, Krogulska A. Celiac disease and ulcerative colitis as comorbid diseases – the diagnostic challenge. Pediatr Pol 2022; 97: 356-361.
4. Myléus A, Ivarsson A, Webb C, et al. Celiac disease revealed in 3% of Swedish 12-year-olds born during an epidemic. J Pediatr Gastroenterol Nutr 2009; 49: 170-176.
5. Ensari A. Gluten-sensitive enteropathy (celiac disease): controversies in diagnosis and classification. Arch Pathol Lab Med 2010; 134: 826-836.
6. Kelly CP, Bai JC, Liu E, Leffler DA. Advances in diagnosis and management of celiac disease. Gastroenterology 2015; 148: 1175-1186.
7. Popp A, Kivelä L, Fuchs V, Kurppa K. Diagnosing celiac disease: towards wide-scale screening and serology-based criteria? Gastroenterol Res Pract 2019; 2019: 2916024.
8. Lebwohl B, Kapel RC, Neugut AI, Green PH, Genta RM. Adherence to biopsy guidelines increases celiac disease diagnosis. Gastrointestinal Endoscopy 2011; 74: 103-109.

9. Drut R, Drut RM. Lymphocytic gastritis in pediatric celiac disease–immunohistochemical study of the intraepithelial lymphocytic component. Med Sci Monitor 2004; 10: CR38-CR42.
10. Gabrieli D, Ciccone F, Capannolo A, et al. Subtypes of chronic gastritis in patients with celiac disease before and after gluten-free diet. United European Gastroenterol J 2017; 5: 805-810.
11. Bhatti TR, Jatla M, Verma R, Bierly P, Russo PA, Ruchelli ED. Lymphocytic gastritis in pediatric celiac disease. Pediatr Develop Pathol 2011; 14: 280-283.
12. Lebwohl B, Green PH, Genta RM. The coeliac stomach: gastritis in patients with coeliac disease. Aliment Pharmacol Ther 2015; 42: 180-187.
13. Marsh MN. Gluten, major histocompatibility complex, and the small intestine: a molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). Gastroenterology 1992; 102: 330-354.
14. Marsh MN, Johnson MW, Rostami K. Mucosal histopathology in celiac disease: a rebuttal of Oberhuber's sub-division of Marsh III. Gastroenterol Hepatol Bed Bench 2015; 8: 99-109.
15. Heidari Z, Mahmoudzadeh-Sagheb H, Moudi B. A quantitative study of sodium tungstate protective effect on pancreatic beta cells in streptozotocin-induced diabetic rats. Micron 2008; 39: 1300-1305.
16. Heidari Z, Mahmoudzadeh-Sagheb H, Sheibak N, Nourzaei N. Quantitative changes of extravillous trophoblast cells in placentas of systemic lupus erythematosus patients. J Obstet Gynaecol 2017; 37: 746-751.
17. Heidari Z, Sakhavar N, Mahmoudzadeh-Sagheb H, Ezazi-Bojnourdi T. Stereological analysis of human placenta in cases of placenta previa in comparison with normally implanted controls. J Reprod Infertil 2015; 16: 90-95.
18. Alsaigh N, Odze R, Goldman H, Antonioli D, Ott MJ, Leichtner A. Gastric and esophageal intraepithelial lymphocytes in pediatric celiac disease. Am J Surg Pathol 1996; 20: 865-870.
19. Hayat M, Arora D, Wyatt J, O'mahony S, Dixon M. The pattern of involvement of the gastric mucosa in lymphocytic gastritis is predictive of the presence of duodenal pathology. J Clin Pathol 1999; 52: 815-819.
20. Prasad KK, Thapa BR, Lal S, Sharma AK, Nain CK, Singh K. Lymphocytic gastritis and celiac disease in Indian children: evidence of a positive relation. J Pediatr Gastroenterol Nutr 2008; 47: 568-572.
21. Marsilio I, Maddalo G, Ghisa M, Savarino EV, Farinati F, Zingone F. The coeliac stomach: a review of the literature. Digest Liver Dis 2020; 52: 615-624.
22. Pastore L, Carroccio A, Compilato D, Panzarella V, Serpico R, Muzio LL. Oral manifestations of celiac disease. J Clin Gastroenterol 2008; 42: 224-232.
23. Casella G, Villanacci V, Di-Bella C, et al. Colonoscopic findings in coeliac disease on a gluten-free diet. Rev Esp Enferm Dig 2010; 102: 538-541.
24. Judd LM, Gleeson PA, Toh BH, van Driel IR. Autoimmune gastritis results in disruption of gastric epithelial cell development. Am J Physiol 1999; 277: G209-G218.
25. MacDonald TT. Epithelial proliferation in response to gastrointestinal inflammation. Ann N Y Acad Sci 1992; 664: 202-209.
26. Savidge T, Walker-Smith J, Phillips A, Savidge T. Intestinal proliferation in coeliac disease: looking into the crypt. Gut 1995; 36: 321-323.
27. Barone MV, Caputo I, Ribecco MT, et al. Humoral immune response to tissue transglutaminase is related to epithelial cell proliferation in celiac disease. Gastroenterology 2007; 132: 1245-1253.
28. Gundemir S, Colak G, Tucholski J, Johnson GV. Transglutaminase 2: a molecular Swiss army knife. Biochim Biophys Acta 2012; 1823: 406-419.
29. Yu XB, Uhde M, Green PH, Alaedini A. Autoantibodies in the extraintestinal manifestations of celiac disease. Nutrients 2018; 10: 1123.
30. Odze RD, Goldblum JR. Surgical Pathology of the GI Tract, Liver, Biliary Tract and Pancreas. 2nd ed. Philadelphia, PA: Saunders Elsevier; 2009.

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