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Detection of celiac disease in adult patients with type I diabetes mellitus

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Abstract

Celiac disease (CD) is a chronic, immune-determined disorder that affects the small intestine in individuals with a genetic predisposition. Identifying silent CD is crucial, as a gluten-free diet in asymptomatic type 1 diabetes mellitus (T1DM) patients can improve glycemic control and growth. This study aimed to determine the prevalence of CD in adult T1DM patients by using serological immune-enzymatic tests. The study included 90 patients divided into two groups: Group 1 included 45 adults with T1DM (aged 20-40 years) exhibiting gastrointestinal symptoms of CD. Group 2 consisted of 45 asymptomatic adults with T1DM (aged 20-40 years). Celiac serology markers were positive in 3 patients (6.7%) from Group 1 and in 1 patient (2.2%) from Group 2. In Conclusion, there is a significant association between CD and T1DM. Celiac serology should be conducted in T1DM patients presenting with gastrointestinal and/or extraintestinal symptoms.

Keywords: Celiac disease, Type 1 diabetes mellitus (T1DM), Silent, Serology, Endoscopy.

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Introduction

Type 1 diabetes mellitus (T1DM) is an immune mediated disease that leads to the destruction of insulin-producing β cells in the pancreatic islets of Langerhans cells, resulting in insulin deficiency. The incidence of T1DM, especially in childhood, surged during the 20th and early 21st centuries, with a prevalence estimated at around 2-3% of the general population.[1] According to the international diabetes federation, the prevalence of DM among Egyptian adults was 15.2% in 2022.[2]

Celiac disease (CD) is an inflammatory condition of the small intestine triggered by gluten intolerance. In adults, CD commonly presents with abdominal cramps, distention, and chronic diarrhea or constipation.[3] Children more than 3 years may exhibit non-gastrointestinal symptoms such as short stature, delayed puberty, fatigue, and iron deficiency anemia. Gastrointestinal symptoms are less common in T1DM patients, with many having silent or mild CD. CD is frequently associated with other autoimmune disorders, such as autoimmune thyroid disease and Addison's disease. These conditions are often presented with organ-

specific autoantibodies, which can sometimes be detected before the clinical onset, aiding in the prevention of significant health issues. The prevalence of CD in T1DM patients ranges from 4.4 to 11.1% compared to 0.5% in the general population. This is due to a shared genetic predisposition: human leucocyte antigens (HLA) genotypes DR3-DQ2 and DR4-DQ8 are strongly associated with T1DM, whereas DR3-DQ2 is specifically linked to CD.[4]

Identifying silent CD is crucial because a gluten-free diet can enhance glycemic control and growth in asymptomatic T1DM patients, and also mitigate risks including osteoporosis, infertility, malabsorption, poor nutrition, and long-term cancer risks.[4,5] The aim of the study was to detect the presence of CD in adults with T1DM using serological immune-enzymatic tests.

Patients and Methods

This comparative descriptive study involved 90 patients with T1DM, aged between 20 to 40 years. Participants were selected from the Hepatology, Gastroenterology, and Infectious Diseases Department, and the Endocrinology Department at Al-Zahraa University Hospital, Faculty of Medicine for Girls, Al-Azhar University, between April 2022 and March 2023. They were divided into two groups

-Exclusion criteria: Patients previously diagnosed with or treated for Celiac disease.

-Group 1 included 45 adults with T1DM, aged 20-40, and exhibited gastrointestinal complaints such as abdominal pain, distention, diarrhea, vomiting, or flatulence. While Group 2 included 45 asymptomatic adults with T1DM as controls, aged 20-40, without gastrointestinal symptoms suggestive of CD.

All participants underwent comprehensive medical history taken, including history of autoimmune diseases, medication use, and dietary habits (all patients were on a gluten-rich diet). Demographic information including age at presentation, gender, diabetes duration, and family history of diabetes mellitus and CD were collected. Symptoms suggestive of gastrointestinal disturbance, such as abdominal pain, flatulence, diarrhea, constipation, and cramps, were also recorded.

The general condition of the patients, intellectual functions, Kussmaul respiration, and signs of dehydration were assessed. Vital signs, including blood pressure, pulse, respiratory rate (RR), oxygen saturation, random blood sugar (RBS) and body temperature were measured. Upper limbs were examined for oedema, skin pigmentation, pulsation, and neuro-muscular examination. Lower limbs were examined for oedema, skin pigmentation, peripheral pulsation, ulceration and neuro-muscular examination. Clinical examination of thyroid, abdomen, chest and heart were performed to exclude other causes of GIT disturbance.

A venous blood sample (7-10 ml) was collected from each patient under aseptic conditions. Two milliliters were used for complete blood picture (CBC) and erythrocyte sedimentation rate (ESR), while the rest was clotted and centrifuged. The serum was divided: one aliquot for iron, HbA1c, liver, and kidney function tests; the other stored at -20°C for later antibody tests.

Laboratory analysis included CBC which was done on an automated hematology analyzer (Sysmex Xb, Sysmex Egypt), ESR was measured by using the Westergern tube method, and immunoglobulin levels which was done on a biochemistry analyzer (Integra, Roche-Cobas, Roche Diagnostics, USA) to rule out IgA deficiency. Serum iron levels, glycosylated hemoglobin (HbA1c), and complete liver function tests (serum transaminases, albumin, bilirubin, and prothrombin time and concentration) were also assessed using a clinical chemistry analyzer (Cobas C 3 11, Roche Diagnostics, USA). Additionally, serum urea and creatinine levels were measured by using the same chemistry analyzer.

Anti-tissue transglutaminase antibodies (IgA) were measured with commercial ELISA kits (Catalog No: ORG 540S, Orgentec Diagnostika GmbH, Germany), according to the manufacturer' instructions. The test was done through a complete set of ELISA washer and reader (BioTek instruments, Italy). The final product was measured at 450 nm.

Anti-endomysium (EMA) antibodies (IgA) were measured with commercial ELISA kits (Catalog No:SG-00215, Sinogeneclon Co., Ltd, China), according to the manufacturer' instructions. The final product was measured at 450 nm. The test was done through the same complete set of ELISA reader and washer.

Upper Esophagogastroduodenoscopy (EGD)

This was performed using diagnostic endoscopic procedure (EG-2990i, Pentax) for duodenal biopsy for patients positive for anti-endomysium and/or anti-transglutaminase (anti-TTG) antibodies.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), IBM version 23. Quantitative data are presented as mean ± SD, median with IQR, or range. Qualitative data are reported as counts and percentages. Chi-square or Fisher's exact tests were used for group comparisons. Spearman correlation evaluated relationships between quantitative variables. A 95% confidence interval and a 5% margin of error were used, a value < 0.05 was considered significant.

Results

Table 1 showed that there was no statistically significant difference in IgA, serum level of anti-TTG and anti-endomysium Ab between both groups ($p > 0.05$)

Table 1. Comparison of Celiac panel results between the two studied groups.

	With GIT symptoms (N = 45)		Without GIT symptoms (N = 45)		*p value
	Median	Range	Median	Range	
IgA (g/l)	2.70	0.80-4.40	2.90	0.80-6.00	NS
Anti-TTG Ab Reference range (0-10) U/ml	5.25	0.30-36	4.17	0.06-18	NS
Anti-endomysium Ab Cut off: 0.2 AU/ml	0.09	0.02-2.45	0.10	0.05-2.34	NS

*Mann Whitney U test. $p > 0.05$ is not significant (NS).

Table 2 showed that there was a statistically insignificant difference in CD frequency in patients with GIT symptoms than in those without GIT symptoms ($p > 0.05$). As shown in Table 2, there were four CD patients, three with GIT symptoms and one without GIT symptoms.

Table 2. Comparison of Celiac disease frequency between the studied groups.

		With GIT symptoms (N = 45)		Without GIT symptoms (N = 45)		*p value
		N	%	N	%	
Celiac disease	No	42	93.3%	44	97.8%	NS
	Yes	3	6.7%	1	2.2%	

*Chi- Square test. $p > 0.05$ is not significant (NS).

Data in Table 3 indicated a significant positive correlation between anti-TTG antibody levels and the duration of diabetes, hemoglobin A1c (HbA1c), liver enzymes, serum creatinine, and erythrocyte sedimentation rate (ESR). It also showed a significant negative correlation with Hb levels and a significant negative correlation with red blood cell (RBC) count, mean corpuscular volume (MCV), and serum iron levels.

Table 3. Correlation between anti-tissue transglutaminase (anti-TTG) antibodies, clinical and laboratory data of the two studied groups.

	Anti-TTG Ab	
	r	*p* value
Age	0.112	NS
Duration of DM	0.376	<0.00
WBCs (thousand/mm^3)	-0.096	NS
RBCs (million /mm^3)	-0.303	0.004
HB (g/dl)	-0.208	0.049
MCV (FL)	-0.455	<0.00
Platelets (thousand/mm^3)	0.048	NS
ESR (mm)	0.295	0.005
PC%	-0.005	NS
PT (sec)	0.172	NS
ALT (U/L)	0.316	0.002
AST (U/L)	0.414	<0.00
Albumin (g/dl)	-0.044	NS
Bilirubin (mg/dl)	-0.197	NS
Urea (mg/dl)	0.035	NS
Creatinine (mg/dl)	0.318	0.002
Iron (mcg/dl)	-0.431	<0.00
HB A1C %	0.383	<0.00
IgA level (g/L)	-0.072	NS
BMI	-0.119	NS

p > 0.05 is not significant (NS).

Data in Table 4 showed a significant positive correlation between anti-endomysium antibody levels and the duration of diabetes, HbA1c, and liver enzymes. Also, there was a significant positive correlation between serum creatinine and ESR. Conversely, anti-endomysium antibody levels had a significant negative correlation with RBC count, MCV, and serum iron levels, and a significant negative correlation with Hb levels.

Table 4. Correlation between Anti-endomysium antibodies, clinical and laboratory data of the studied groups.

	Anti-endomysium	
	r	*p* value
Age	-0.025	NS
Duration of DM	0.376	<0.00
WBCs (thousand/mm^3)	-0.004	NS
RBCs (million /mm^3)	-0.433	<0.00
HB (g/dl)	-0.222	0.035
MCV(FL)	-0.596	<0.00
Platelets (thousand/mm^3)	-0.015	NS
ESR (mm)	0.235	0.026
PC%	0.052	NS
PT (sec)	0.03	NS
ALT (U/L)	0.385	<0.00

Table 4. Continued.

	Anti-endomysium	
	r	*p* value
AST (U/L)	0.487	<0.00
Albumin (g/dl)	-0.06	NS
Bilirubin (mg/dl)	-0.042	NS
Urea (mg/dl)	-0.007	NS
Creatinine (mg/dl)	0.251	0.018
Iron (mcg/dl)	-0.465	<0.00
HB A1C %	0.503	<0.00
IgA level (g/L)	0.064	NS
BMI	-0.154	NS

p > 0.05 is not significant (NS).

Description of the four seropositive patients found in our study

The first was a female patient 36 y, she was diabetic for 21 years back with a positive family history of diabetes. Her Hb was 10.5 gm/dl and HbA1C reached 11.5%. Her serological results: Anti TTG=36 U/ml and Anti-endomysium=2.45 AU/ml. She was complaining of chronic abdominal pain, diarrhea, and flatulence. Also, complained of recurrent oral lesions. She had undergone an upper endoscopy, and the results showed that esophagus had normal mucosa, no hiatus hernia or distal esophagitis. The stomach showed normal gastric mucosa with no ulcers or polyps or diverticulum or masses, and duodenal fissuring with absence of villous architecture, (Figure 1 & 2).

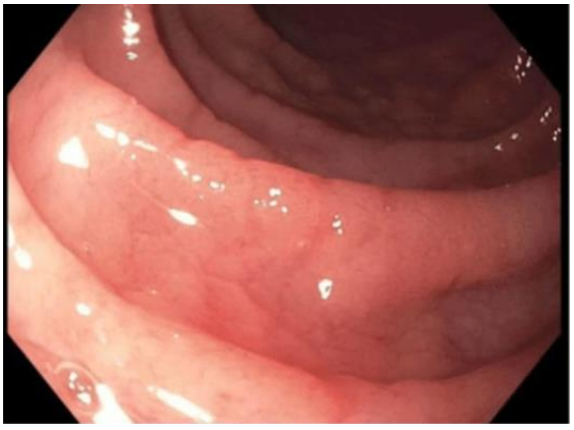

Figure 1. Upper endoscopic finding in case 1. Her histopathological results show partial villous atrophy (Marsh III A).

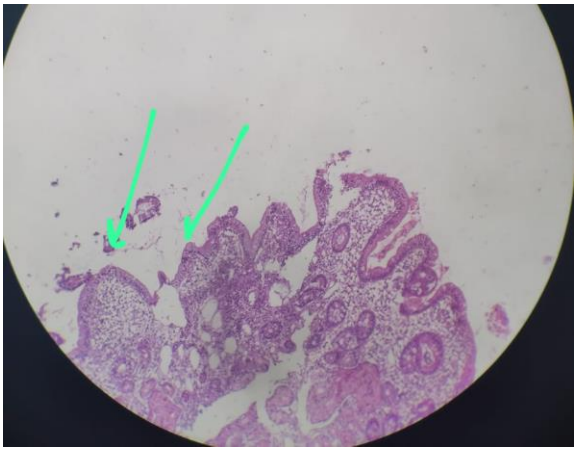

Figure 2. Histopathological results of the duodenal biopsy showed partial villous atrophy with broadening and shortening of the villi.

The second patient was a female with 38 y, diabetic for 28 years back with positive family history of diabetes. Her Hb was 9.5 gm/dl and HbA1C reached 10%. Her serological results were: Anti TTG=15.5 U/ml and Anti-endomysium=2.18 AU/ml. She was complaining of chronic abdominal pain, diarrhea, flatulence, fatigue, and weight loss. Also, she was complaining about hair loss, skin lesions, and anxiety. She had undergone an upper endoscopy, and indicated that esophagus showed normal mucosa, no hiatus hernia or distal esophagitis. The stomach had mild erythema with no ulcers or polyps or diverticulum or masses, and the duodenal fissuring and scalloping, (Figure 3 & 4).

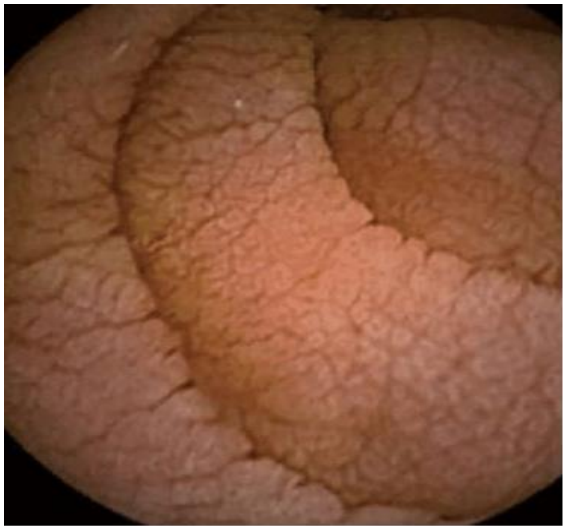

Figure 3. Upper endoscopic finding in case 2. Her histopathological results show total villous atrophy (Marsh III C).

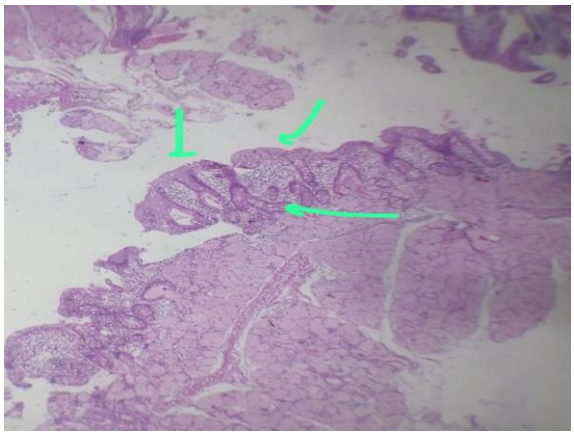

Figure 4. Histopathological results of the duodenal biopsy showing total villous atrophy associated with crypt hyperplasia and intra-epithelial lymphocytosis.

The third patient was a female patient 26 y, diabetic for 20 years back with positive family history of diabetes. Her Hb was 10 gm/dl and HbA1C reached 11%. Her serological results were: Anti TTG=11.7 U/ml and Anti-endomysium=2.05 AU/ml. She was complaining of chronic abdominal pain and flatulence with no extra-intestinal symptoms. She had undergone an upper endoscopy and results indicated that the esophagus showed normal mucosa, no hiatus hernia or distal esophagitis. The stomach had normal mucosa, no ulcers or polyps or diverticulum or masses and the duodenum was unremarkable, with no fissuring or scalloping, (Figure 5 & 6).

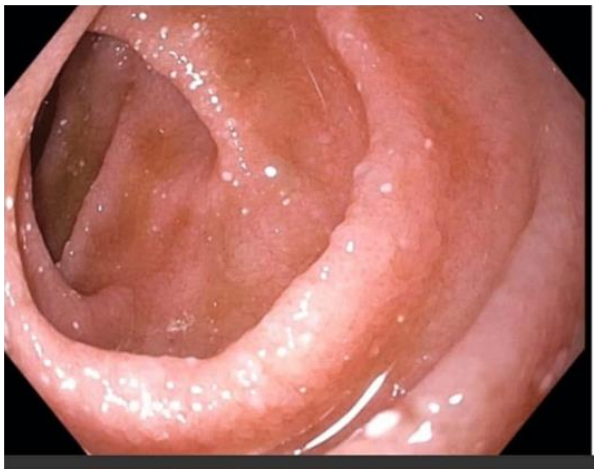

Figure 5. Upper endoscopic finding in case 3. Her histopathological results show lymphocytic enteritis (Marsh I).

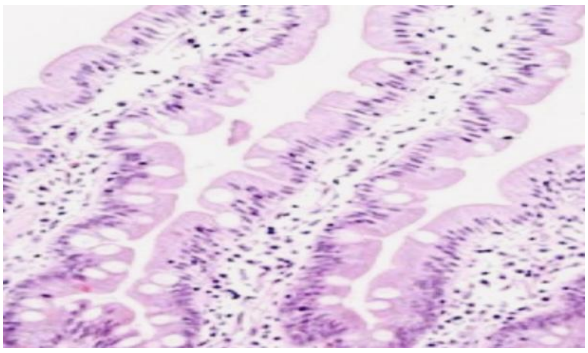

Figure 6. Histopathological result of the duodenal biopsy showing normal villi with pathological increase of intra-epithelial lymphocytosis.

The fourth was a male patient 20 y, diabetic for 4 years back with negative family history of diabetes. His Hb was 10.7gm/dl and his HbA1C =9.5%. His serological results indicated: Anti TTG=18 U/ml and Anti-endomysium=2.3 AU/ml. He had neither GIT symptoms nor extra-intestinal symptoms. He had undergone an upper endoscopy, and the results indicated that the esophagus had normal mucosa, with no hiatus hernia or distal esophagitis. The stomach showed normal gastric mucosa with no ulcers or polyps diverticulum or masses. The duodenum showed fissuring with the absence of villous architecture, (Figure 7 & 8).

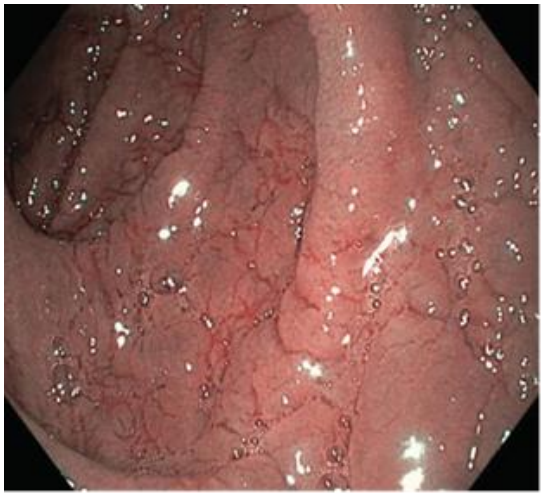

Figure 7. Upper endoscopic finding in case 4. His histopathological results showed partial villous atrophy (Marsh III A).

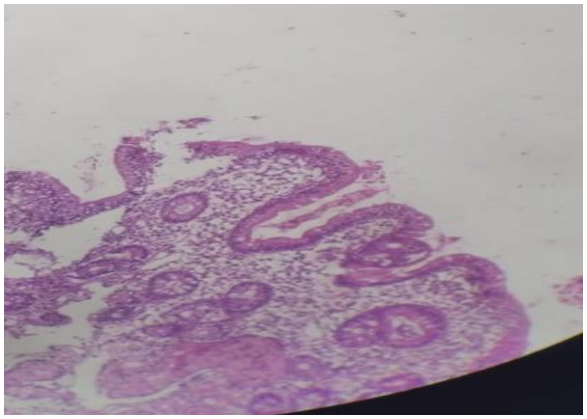

Figure 8. Histopathological results of the duodenal biopsy showing partial villous atrophy.

Discussion

The present study aimed to detect the presence of CD in adults with T1DM using serological immuno-enzymatic tests. In our study, all patients had normal IgA levels, with no significant difference in CD frequency between those with and without gastrointestinal symptoms. Group 1 (T1DM with GIT symptoms) had 6.7% positive for Celiac serology markers, while 2.2% of Group 2 (T1DM without GIT symptoms) were positive for these markers.

These results align with those of Bakker et al., 2016,[6] who reported a 0.8% to 16.4% prevalence of CD in T1DM patients, averaging 6%. The study by *Camarca et al.,* 2012[4] found a prevalence of 4.4% to 11.1% in T1DM, compared to 0.5% in the general population. The study by *Dogan et al*., 2015[7] identified CD in 1-8% of T1DM, with some being asymptomatic. Silent CD is often detected through serological screening or endoscopy and may present with atypical symptoms such as iron deficiency anemia or neurological disorders. The study by *Nowier et al.,* 2009[8] found that 5.48% of T1DM children were seropositive for anti-TTG antibodies, with symptoms like chronic diarrhea and short stature. The study by Monar et al., 2022,[9] reported a 5% global prevalence of CD in T1DM type 1 diabetes patients. The study by Schuppan and Dieterich 2018[10] noted that 2.6% to 7.8% of adults with T1DM had IgA autoantibodies to endomysium or tissue transglutaminase.

The study by Obaid et al., 2012[11] reported a higher prevalence of IgA anti-tissue transglutaminase antibodies (11.66%) in asymptomatic T1DM patients, potentially due to their larger sample size and younger age. The study by *Sari et al., 2010, [12]* found 30.8% CD seropositivity in Turkish patients, possibly due to genetic and environmental factors. The study by Elfström et al., 2014,[13] observed varying CD prevalence in T1DM patients across regions, with notably high rates in Algeria, India, and Saudi Arabia, likely due to genetic and dietary factors.

Our study found that anti-TTG and anti-endomysium antibody levels were positively correlated with diabetes duration, HbA1c, liver enzymes, serum creatinine, and ESR. This is consistent with findings of the study by Mollazadegan et al., 2014,[14] and *Monar et al.,* 2022,[9] who observed higher HbA1c in T1DM patients with concurrent CD. The study by Schuppan and Dieterich 2018[10] reported elevated serum aminotransferases in CD patients, which were normalized on a gluten-free diet. The study by Sainsbury et al., 2011,[15] found abnormal serum transaminases in 27% of newly diagnosed CD patients, which improved with diet.

Additionally, our study showed a significant negative correlation between anti-TTG and anti-endomysium antibody levels with RBC count, hemoglobin, MCV, and serum iron. Such findings, aligned with those of the study by Schuppan and Dieterich[10] who linked CD to iron deficiency anemia. The study by Mant et al.,

2006,[16] suggested that occult gastrointestinal bleeding in CD patients might cause positive colorimetric test results due to intestinal cell loss or malabsorption rather than direct blood loss.

In summary, there were three T1DM patients (6.7%) with GIT symptoms with positive Celiac serology markers and one patient (2.2 %) in T1DM patients without GIT symptoms also with positive Celiac serology markers. Histopathological results for two diabetic patients with GIT symptoms and positive serological markers came with partial villus atrophy and total villus atrophy and they were diagnosed with Celiac disease. However, the third patient result came with lymphocytic enteritis (Marsh 1) and was diagnosed as a case of potential CD versus enteritis. Histopathological results for diabetic patients without GIT symptoms came with partial villous atrophy. He was diagnosed as a case of silent Celiac disease.

Author Contributions

NMB, study conception and design. NAE, performed upper endoscopy for assigned patients, made statistical analysis and interpretation of results. NMB, examined the patients. HEA, performed the histopathological work. ASH, ARM, performed the laboratory work. ARM, collected samples, made statistical analysis. All authors participated in writing, reviewed the results and approved the final version of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The study was reviewed and approved by the Research Ethics committees of the Faculty of Medicine for Girls, Al-Azhar University (Approval no: 201909162, dated September 2019).

Informed consent

A written consent was obtained from each participant after explaining the study's objectives and benefits.

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