

HISTOPATHOLOGICAL CHANGES OF GASTRIC MUCOSA AND *H. PYLORI* INFECTION IN PATIENTS WITH CELIAC DISEASE

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ABSTRACT

*The study initially included 66 patients with clinical suspicion of celiac disease (CD). Forty-four (17 males and 27 females) fulfilled the diagnostic criteria of CD. The study revealed that the common histopathological finding of duodenal mucosa in CD was subtotal villous atrophy 22(50%), while total villous atrophy was found only in 6(13.6%) of patients. Also, 88.6% of patients had changes of gastric mucosa ranging from superficial gastritis to intestinal metaplasia. Gastric intraepithelial lymphocytosis (IEL) was found in 12(27.3%) of patients, and was significantly associated with both, the degree of duodenal changes and with *H. pylori* infection ($P < 0.05$). On the other hand, *H. pylori* documented by histopathology was found in 30(68.2%) patients and by urease test in 33(75.4%) patients. We conclude that *H. pylori* infection is not uncommon in patients with CD, & Gastric IEL is an important histopathological finding, correlating with duodenal changes as well as *H. pylori* infection.*

INTRODUCTION

Celiac disease (CD) is a syndrome characterized by intestinal mucosal damage resulting from immunological intolerance to gluten in persons genetically predisposed to this condition.^[1] CD is not uncommon cause of malabsorption of one or more nutrients in Caucasians. It has had several names including non tropical sprue, celiac sprue and gluten sensitive enteropathy.^[2] The clinical manifestations of CD are protean in nature and vary markedly with age of patients, with the onset of symptoms occurring at ages ranging from first year of life through the eighth decade.^[3] The symptoms of CD may appear with introduction of cereals in an infant's diet, although there is frequently spontaneous remission during the second decade of life may be either permanent or followed by recurrence of the symptoms over several years, alternatively the symptom of CD may first become evident at almost any age through adulthood.^[2] Clinical manifestations of CD vary markedly with age of patients, duration and extent of disease and the presence of extra-intestinal manifestations.^[3-12] Diagnosis of CD may be accomplished by small intestinal biopsy.^[2] However, patients with CD can have a normal or minimally alternate endoscopic pattern of 2nd part of duodenum.^[13] A serological diagnosis by auto antibodies have great diagnostic value and also have great value in screening for CD. Auto antibodies have different sensitivity and specificity.^[3,14,15] A variety of histological changes of gastric mucosa occur in CD, notably lymphocytic

gastritis which may progress to intestinal metaplasia.^[16,17] In addition, several studies were carried out worldwide to evaluate the association between *Helicobacter pylori* (*H. pylori*) infection and CD with controversial results.^[18,19] This study was carried out to determine the histopathological changes of gastric mucosa in patients with CD and to study the frequency of *H. pylori* infection in patients with CD.

PATIENTS AND METHODS

This cross-sectional study was conducted on 66 patients, 33 females and 33 males, who consulted the gastro-enterology centre in Basrah Teaching Hospital during the period from August 2001 throughout September 2002. Those patients had clinical features of CD. All patients were subjected to a detailed history, clinical examination, laboratory investigations including complete blood picture and blood film, general stool examination, blood sugar, HbA variant if needed. Barium follow through examination was done in some patients. Upper gastrointestinal endoscopy was done for the studied patients, two biopsies were taken from second part of duodenum for histopathological examination for diagnosis of CD, and at the same time four biopsies were taken from antral part of stomach. Diagnosis of CD was based on the clinical features of the disease together with histopathological changes of duodenal mucosa of malabsorption with significant clinical response to gluten free diet (GFD) indicated by resolution of symptoms and improvement of

anaemia. Out of 66 patients, 44 patients fulfilled the criteria for the diagnosis of CD, 17 males and 27 females. The duodenal biopsies were stained by hematoxylin and eosin stain and examined by the same pathologist. Histopathological changes were classified into total villous atrophy (TVA), subtotal villous atrophy (SVA), partial villous atrophy grade II (G.II PVA), and grade III (G.III PVA). Grade I PVA was excluded. One gastric biopsy stained by giemsa stain for detection of *H. pylori*, other biopsies were stained by H and E stain and examined by the same pathologist for histopathological changes and classified into chronic superficial gastritis, chronic atrophic gastritis, intestinal metaplasia, & normal gastric mucosa. Gastric biopsies were examined also for intraepithelial lymphocytosis (IEL) and considered to be positive if IEL were 25 or more/ 100 gastric columnar cells. Finally, one gastric biopsy for each patient was immediately immersed in tube containing urease solution, for the detection of *H. pylori* infection, and watched after one hour, & after 6 hours. Positive result was considered when the colour of the solution changed from colourless to purple colour.

RESULTS

Forty-four patients; 27 females and 17 males aged from 5 years-60 years fulfilled the criteria for diagnosis of CD. The commonest age group in females was 21-30 years (44%), while the commonest age group in males was 31-40 years (47%), (Table-1).

Table 1. *Age and sex distribution of patients with Celiac disease.*

Sex Age (yrs)	Female	Male	Total
	No. (%)	No. (%)	No. (%)
0-10	0 (0)	1 (5.9)	1 (2.3)
11-20	9 (33.3)	4 (23.5)	13 (29.5)
21-30	12 (44.5)	4 (23.5)	16 (36.4)
31-40	3 (11.1)	8 (47.1)	11 (25)
41 and above	3 (11.1)	0 (0)	3 (6.8)
Total	27 (61.4)	17 (38.6)	44(100)

AS shown in (Table-2), the common presentation was recurrent diarrhoea (93.2%),

abdominal pain (86.4%), abdominal distension (81.8%) and weight loss (54.5%). Microcytic anaemia was the commonest type of anaemia (45.5%).

Table 2. *Patient's Clinical and haematological features.*

Features	Patients number	%
Diarrhea	41	93.2
Abdominal pain	38	86.4
Abdominal distension	36	81.8
Weigh loss	24	54.5
Anaemia	34	77.3
Microcytic	20	45.5
Normocytic	13	29.5
Macrocytic	1	2.3

As shown in (Table-3), the most common findings at endoscopy were gastritis, oesophagitis and billiary reflux. Flat doudenal-mucosa was found in 31(70.5%) patients.

Table 3. *Gross endoscopic findings of CD patients.*

Finding	NO.	%
Duodenal ulcer	2	4.5
Gastric ulcer	1	2.3
Gastritis	23	52.3
Gastric polyp	1	2.3
Oesophagitis	10	22.7
Billiary reflux	10	22.7
Oesophageal varices	1	2.3
Flat duodenal mucosa	31	70.5

(Table-4), shows that the common histological finding of duodenal mucosa in CD was SVA (50%) followed by G.III PVA (27.3%), while TVA was detected in 13.6% of patients only. On the other hand, the commonest histopathological changes of gastric mucosa were chronic superficial gastritis (45.5%), atrophic gastritis (36.4%) and IEL (27.3%).On the other hand, *H. pylori* documented by histopathology was found in 30 patients (68.2%), while urease test demonstrated *H. pylori* in 33(75.4%) patients.

Table 4. *Histopathological finding of gastric and duodenal mucosa.*

	Histopathological finding	No.	%
Duod.	TVA	6	13.6
	SVA	22	50.0
	G. III PVA	12	27.3
	G. II PVA	4	9.1
Stomach	Intraepithelial lymphocyte	12	27.3
	Chronic superficial gastritis	20	45.5
	Atrophic gastritis	16	36.4
	Intestinal metaplasia	3	6.8
	Normal gastric mucosa	5	11.4
	H. pylori by histopathology	30	68.2

The relation between gastric changes and the severity of duodenal changes are shown in (Table-5). Forty percent of patients with chronic superficial gastritis had SVA and G.III PVA respectively, while 75% of patients with chronic atrophic gastritis had SVA.

Table 5. *Relation between gastric changes and severity of duodenal changes.*

	TVA No. %	SVA No. %	GIII PVA No. %	GII PVA No. %	Total
Ch. Sup. Gastritis	2(10)	8(40)	8(40)	2(10)	20
Atrophic	2(12.5)	12(75)	2(12.5)	0	16
Intestinal metaplasia	2(66.7)	1(33.3)	0	0	3
Normal	0	1(20)	2(40)	2(40)	5
Total	6(13.6)	22(50)	12(27.3)	4(9.1)	44

As presented in (Table-6), the histopathological changes were correlated with the degree of anaemia. The more the villous atrophy, the more severe was the anaemia.

Table 6. *Relation between histopathological finding of duodenum and severity of anaemia.*

Histopathologic Finding	Hb (gm/dl)			
	< 11	11-13	> 13	Total
TVA	4 (66.8%)	1 (16.6%)	1(16.6%)	6
SVA	10(45.4%)	10(45.4%)	2 (9.0%)	22
G. III PVA	2 (16.6%)	5(41.6%)	5(41.6%)	12
G.II PVA	0 (0.0%)	2(50.0%)	2(50.0%)	4
Total	16(36.4%)	18(40.9%)	10(22.7%)	44

(Table-7) shows, that there was no significant difference in anaemia severity with respect to *H. pylori* infection positivity ($P > 0.05$).

Table 7. *Relation between H. Pylori infection and severity of anaemia.*

H. pylori Infection	Hb (gm/dl)			
	< 11	11-13	> 13	Total
Positive	10	12	8	30
Negative	6	6	2	14
Total	16	18	10	44

Gastric IEL showed significant correlation with histopathological changes in duodenum and also significantly correlated to *H. pylori* infection ($P < 0.05$), (Table-8).

Table 8. *Relation between H. Pylori infection and severity of duodenal damage in patients with IEL.*

H. pylori Infection	TVA	SVA	G. II PVA	G. III PVA	Total
Positive	2	7	1	0	10
Negative	0	0	1	1	2
Total	2	7	2	1	12

DISCUSSION

It is clear that CD is common in young adult age group of both sexes which is examined by occurring of an infection that destructed tight junction which triggers immune system.^[2] Gliadin induces zonulin release (intestinal protein facilitate permeability) and occluding down regulation and tight junctions assembly leading to increase permeability.^[20] No association between *H. pylori* infection and CD, but immune disorders promoting *H. Pylori* colonization.^[21] Significant association was found between *H. pylori* infection and CD, which indicates that diagnosis and treatment of this worldwide infection is needed.^[22] Although TVA is more specific of celiac disease, it was seen only in 6 patients (13.6%), while SVA was seen in 22 patients (50%) which is not diagnostic of celiac disease while PVA was found in 16 patients (36.4%). This indicates that we should rely on combination of history, physical examination, & endoscopy, together with histopathological examination to reach a diagnosis of CD in the absence of serological marker and response to GFD. The study revealed that gastric IEL was found in 27.3% of patients. Several studies reported an association between gastric IEL and CD.^[17,23,24] Feeley et al^[23] found a frequency of IEL of 10% in CD. Jevon et al^[17] also found significant difference of IEL in patients with CD from control group, also showed a decrease of it's incidence after treatment with GFD. Unfortunately We couldn't repeat the endoscopy after treatment with GFD to evaluate the changes in IEL. In this study we found a significant correlation between gastric IEL and *H. pylori* infection in patients with CD. Hayat et al^[24] found a significant relationship between *H. pylori* infection and IEL in non-CD patients and also observed significant reduction in IEL following treatment of the infection. Feeley et al^[23] found no significant difference observed between *H. pylori* positive and negative patients. This can be explained by the possibility that *H. pylori* infection may be a triggering factor to produce symptomatic CD.^[3,25] Lymphocytic gastritis defined as 25 or more intraepithelial lymphocyte/ 100 gastric columnar epithelial cells. The persistence of lymphocytic gastritis with time, the association with increased duodenal IELs, and abnormal small intestine permeability suggest

lymphocytic gastritis may be a manifestation of diffuse lymphocytic gastroenteropathy related to sensitivity to gluten or some other agents.^[26] Niemda et al^[27] found that patients with *H. pylori* infection associated with an increase in IEL which may progress to intestinal metaplasia. Basso et al^[28] found that *H. pylori* infection was associated with persistent antral chronic gastritis and intestinal metaplasia. As expected, anaemia increased in severity corresponding with duodenal histopathological changes, and it was dependent on the degree of the immune response to gluten.^[29] The present study revealed no significant association between *H. pylori* infection and anaemia. In contrast, several workers reported strong association between *H. pylori* infection in CD and iron deficiency anaemia.^[18,30,31] In this study, we found significant changes of gastric mucosa in 88.6% of patients with CD, there was strong correlation between atrophic gastritis and chronic superficial gastritis with STVA. Further studies with control group are needed for comparison. Diamante et al^[32] found that there were changes in gastric mucosa in patients with CD, but with no difference in the prevalence of chronic superficial gastritis, atrophic gastritis and intestinal metaplasia, but IEL was common in patient with CD. *H. pylori* infection was detected in 68.2% of patients. It is well known that *H. pylori* infection increases with age and reaching to 80-85% in persons older than 60 years and 60-70% in 40 years. This finding may be explained by the fact that the main age group in the study was between 20-40 years. In conclusion, *H. pylori* infection is relatively common among CD patients; CD is associated with an increase in gastric IEL which in turn increased with *H. pylori* positivity.

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