

HISTOLOGICAL EVALUATION OF GASTRIC AND DUODENAL BIOPSY FROM PATIENTS PRESENTING WITH DYSPEPSIA

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ABSTRACT

Background: The aim of endoscopy of the upper digestive tract as a routine diagnostic procedure has increased the number of gastric and duodenal biopsy specimens. In gastric biopsy to evaluate inflammatory processes including Helicobacter pylori related gastritis and alterations of the mucosa secondary to mucosal injury, generally referred to as reactive gastropathy. The aim of study is to histopathological evaluation of gastric and duodenal biopsy in cases of patient presented with dyspepsia and to study the correlation between some histopathological measures and causes of dyspepsia (age, sex, diagnosis). **Method:** This is a retrospective cross-sectional study, included a total of 150 cases obtained from gastric and duodenal biopsy, conducted from archived material (Gastroenterology and hepatology teaching hospital). covering the period from (June 2019 to November 2021). It included Endoscopic (Gastric and Duodenal biopsies), tissue paraffin block. Each block was sectioned into one slide and stained with H&E stain. **Results:** No statistically significant association was found between sociodemographic characteristics (age and gender) and either gastric or duodenal biopsies. A statistically significant association was found between both gastric and duodenal biopsies. **Conclusion:** No association was found between gastric histopathological findings and either age or gender. No association was found between duodenal histopathological findings and either age or gender. A significant association was found between gastric and duodenal histopathological findings, which when taken in consideration with the high prevalence of H. pylori infection, can explain the very high percentage of abnormal duodenal biopsies.

KEYWORDS: Histological, evaluation, gastric, duodenal, biopsy, dyspepsia.

INTRODUCTION

The word dyspepsia (Greek “dys” bad, “pepsis” digestion) refers to a set of symptoms that the patient has localized to the epigastric area. Feeling bloated after a meal (80%), epigastric discomfort and burning (60–70%), early satiation (60–70%), distension in the epigastric area (80%), nausea (60%), and vomiting (40%). The symptoms of dyspepsia may be acute in gastroenteritis, or chronic. In the latter condition, an underlying organic disease (e.g. reflex, ulcer, heart and muscle disease, pancreatic disease) may be the reason.^[1,2,3] Dyspepsia can be divided into 2 main types: “organic” when an organic disease is identified. Functional dyspepsia: It is diagnosed when there is no organic abnormality. Diagnostic overlap with IBS and GERD is common, but it does not rule out FD. The pathophysiology is unknown, but it is likely related to disrupted brain-gut communication, resulting in motility disturbances, visceral hypersensitivity, and changes in

the gastrointestinal microbiota⁽⁴⁾. Risk factors include; Female sex, NSAIDs, H- pylori infection, Acute gastroenteritis, other.^[4] Inflammation of the stomach is divided into.

1. Acute gastritis, associated with the use of NSAIDs (especially aspirin).
2. Chronic Gastritis; can be divided into subtypes:
 - A. Chronic infection: *usually caused by H. pylori*.
 - B. Chronic chemical gastritis (*reactive or reflux gastritis*) It is related to alkaline or bile duodenal secretions refluxing into the stomach.
 - C. Chronic autoimmune gastritis is linked to autoantibodies against parietal cells of the stomach, as well as pernicious anemia.^[5]

Helicobacter pylori is a gram-negative microaerophilic bacterium that infects around 50% of the world's population. The mechanism of transmission is not fully clear. However, person-to-person transmission appears to be the most likely mechanism of transmission. H. pylori's

pathogenicity stems from the bacterium's ability to adapt to the gastric environment and infiltrate the gastric mucosa while inducing an immune response that adds to pathological alterations in the host. *H. pylori* infection can cause a slew of dyspeptic symptoms as well as an elevated risk of gastric adenocarcinoma, making *H. pylori* diagnosis and treatment critical.^[6] *H. pylori* eradicated remains a matter of debate, strongly recommended for patients with peptic ulcer, or patients with low-grade mucosa associated lymphoid tissue; atrophic gastritis; and functional dyspepsia, gastroesophageal reflux. eradication include PPI, Clarithromycin, Amoxicillin.^[7] A series of precancerous lesions precede invasive gastric carcinoma, recognized by active chronic inflammation, non-atrophic chronic gastritis, atrophic gastritis, intestinal metaplasia; dysplasia. This steps could be associated with degradation of the intercellular matrix.^[8] Duodenal biopsy is of the utmost importance in the evaluation of malabsorption, a constellation of signs and symptoms that can result from a large variety of disorders, of which celiac disease (CD) is the most commonly encountered.^[2] Duodenal biopsy is mainly indicated in the following: to investigate patients with iron deficiency anemia, to evaluate patients with malabsorption or diarrhea, to diagnose and monitor celiac disease, to diagnose neoplasia, to assess for NSAIDs-induced ulceration.^[9] The aim of study is to histopathological evaluation of gastric and duodenal biopsy in cases of patient presented with dyspepsia and to study the correlation between some histopathological measures and causes of dyspepsia (age, sex, diagnosis).

METHOD

This is a retrospective cross-sectional study, included a total of 150 cases obtained from gastric and duodenal biopsy of patient complain from dyspepsia. was conduct from gastroenterology and hepatology teaching hospital in Baghdad Iraq. (covering the period from June 2019 to November 2021). Include parameters such as age, gender, type of biopsy was obtained and statically analyzed.

Inclusion criteria for cases collection

A total number of 150 cases were included in the study, inclusion criteria was as the following:

1. Undiagnosed patient who is recently presenting with dyspeptic symptoms (ie, postprandial epigastric pain or fullness).
2. Patients with both gastric and duodenal biopsies.

exclusion criteria for cases collection

1. Patients presenting with either continuous vomiting, weight loss, or hematemesis.
2. Patients with recent use of antibiotics, H2 receptor blockers, or PPIs.
3. Patients who did not have both duodenal and gastric biopsies.

Histopathological analysis

Formalin fixed, paraffin embedded tissue blocks represent 150 cases of endoscopic biopsies from patient suffering dyspepsia. these blocks were collected from archived material from gastroenterology and hepatology teaching hospital. sections include (gastric and duodenal endoscopic biopsies from the same patient. one section of 5mm thickness was taken from each block and stain with hematoxylin and eosin stain (H & E), with Modified Giemsa stain was used for gastric biopsies to diagnose *H. pylori* infection for histopathological revision. Statistical analysis data entry was done using Microsoft Excel 2019. Analysis was done using statistical package for social sciences (SPSS version 26). Pearson's chi-squared test was used to test for statistical significance. P value of less than or equal to 0.05 was assigned as a criterion for declaring statistical significance.

RESULTS

Cross sectional study of 150 patients, mean age of patients 35 ± 17 years. (58.7%) are females and (41.3%) are males, (62>7%) of patients at age group ≤ 40 years old, (37.3%) of incidence and new record cases are record in year 2019, (84%) of duodenal biopsy are abnormal while (88%) of Gastric biopsy finding are abnormal. As show in table 1.

Table 1: distribution of gender, year, age of patients, Duodenal biopsy finding and Gastric biopsy finding.

| variables | | frequency | percentage |
|-------------------------|-----------------|-----------|------------|
| gender | <i>female</i> | 88 | 58.7 |
| | <i>male</i> | 62 | 41.3 |
| Age (years) | ≤ 40 | 94 | 62.7 |
| | >40 | 56 | 37.3 |
| year | 2019 | 56 | 37.3 |
| | 2020 | 47 | 31.3 |
| | 2021 | 47 | 31.3 |
| Duodenal biopsy finding | <i>abnormal</i> | 126 | 84.0 |
| | <i>normal</i> | 24 | 16.0 |
| Gastric biopsy finding | <i>abnormal</i> | 132 | 88.0 |
| | <i>normal</i> | 18 | 12.0 |

As show in table 2 and fig1; (24.7%) of Duodenal biopsy finding are (V.D-IEL), (20%) are (V.A-IEL), while (16%) are normal. And so on.

Table 2: Distribution of Du. Biopsy finding.

| variables | frequency | percentage |
|------------------------------------|-----------|------------|
| <i>V.D-IEL</i> | 37 | 24.7 |
| <i>V.A-IEL</i> | 30 | 20.0 |
| <i>NORMAL</i> | 24 | 16.0 |
| Du. biopsy <i>V.D-N.S.D</i> | 21 | 14.0 |
| <i>V.D</i> | 15 | 10.0 |
| <i>V.A-IEL-N.S.D</i> | 13 | 8.7 |
| <i>IEL</i> | 4 | 2.7 |
| <i>C.H-IEL</i> | 2 | 1.3 |
| <i>V.A</i> | 2 | 1.3 |
| <i>Giardial</i> | 1 | 0.7 |
| <i>low grade dysplasia</i> | 1 | 0.7 |

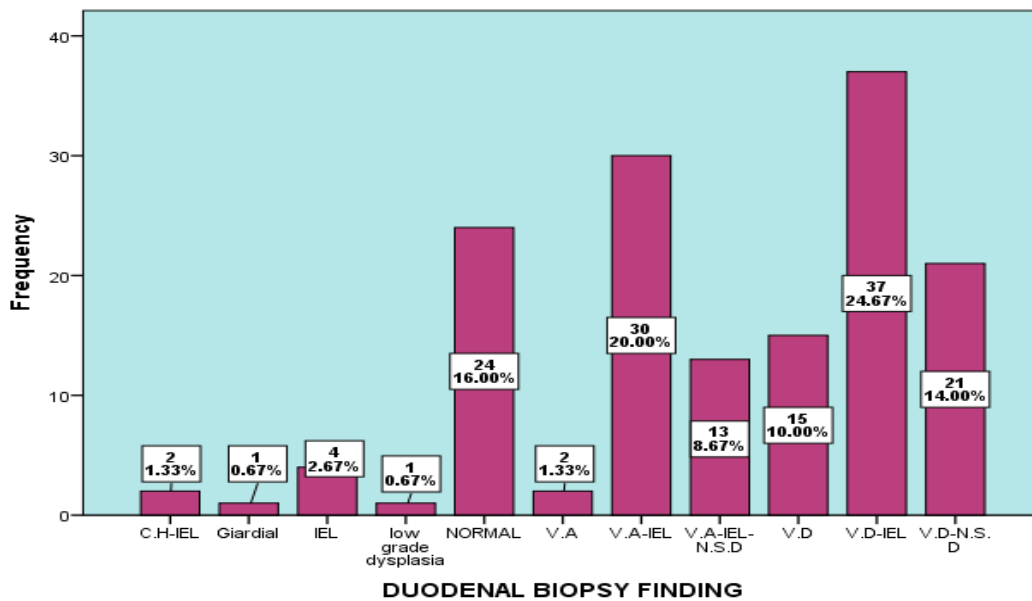


Fig (1): distribution of Du. Biopsy finding.

As show in table 4 and fig 2; (69.3%) of Gastric Biopsy finding are (C.G -H.P), (12%) are (*normal*), while (10%) of Gastric Biopsy finding are (*N.S.G*). And so on.

Table 4: Distribution of Gastric Biopsy finding.

| variables | frequency | percentage | |
|-----------------------|-------------------|------------|------|
| gastric biopsy | <i>C.G -H.P</i> | 104 | 69.3 |
| | <i>NORMAL</i> | 18 | 12.0 |
| | <i>N.S.G</i> | 15 | 10.0 |
| | <i>C.G-H.P-IM</i> | 13 | 8.7 |

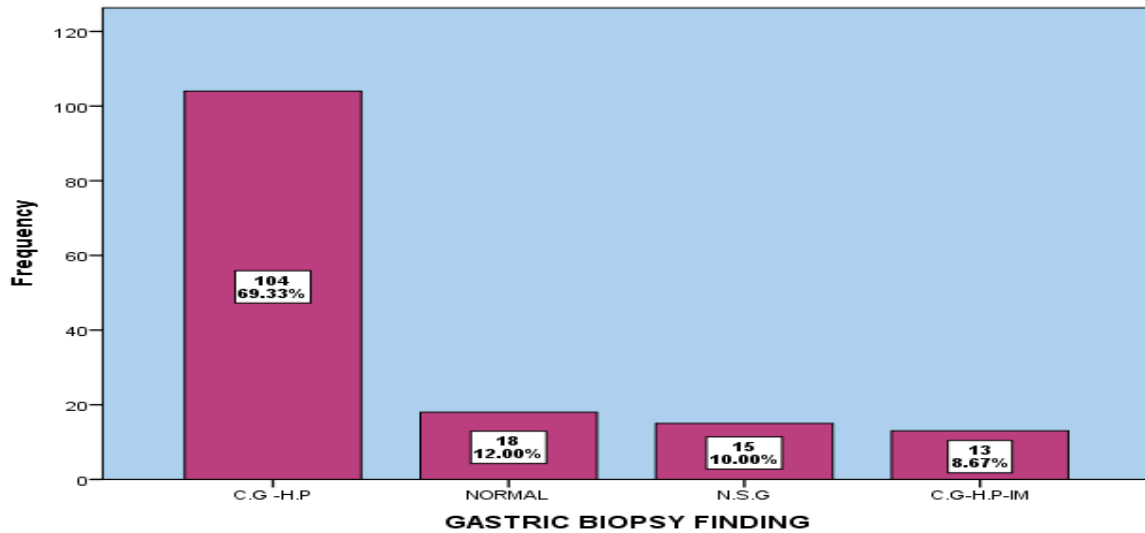


Fig 2: Distribution of Gastric Biopsy finding.

There is no significant association between Du biopsy and (gender, year, age of patients).

Table 5: Association between Du biopsy and (gender, year, age of patients).

| variables | | Du Biopsy | | P-value |
|-----------|--------------------|---------------|--------------|---------|
| | | abnormal | normal | |
| Gender | <i>female</i> % | 74 58.7% | 14 58.3% | 1.000 |
| | <i>male</i> % | 52 41.3% | 10 41.7% | |
| | Total % | 126 100.0% | 24 100.0% | |
| Year | 2019 % | 44 34.9% | 12 50.0% | 0.37 |
| | 2020 % | 41 32.5% | 6 25.0% | |
| | 2021 % | 41 32.5% | 6 25.0% | |
| | Total % | 126 100.0% | 24 100.0% | |
| Age | ≤ 40 % | 79 59.8% | 15 83.3% | 0.07 |
| | >40 % | 53 40.2% | 3 16.7% | |
| | Total % | 132 100.0% | 18 100.0% | |

P-value ≤ 0.05 (significant).

There is no significant Gastric biopsy and (gender, year, age of patients).

Table 6: Association between Gastric biopsy and (gender, year, age of patients).

| variables | | Gastric Biopsy | | P-value |
|-----------|---------------|----------------|--------|---------|
| | | abnormal | normal | |
| Gender | <i>female</i> | 79 | 9 | 0.45 |
| | % | 59.8% | 50.0% | |
| | <i>male</i> | 53 | 9 | |
| | % | 40.2% | 50.0% | |
| | Total | 132 | 18 | |
| | % | 100.0% | 100.0% | |
| Year | 2019 | 45 | 11 | 0.08 |
| | % | 34.1% | 61.1% | |
| | 2020 | 44 | 3 | |
| | % | 33.3% | 16.7% | |
| | 2021 | 43 | 4 | |
| | % | 32.6% | 22.2% | |
| | Total | 132 | 18 | |
| | % | 100.0% | 100.0% | |
| Age | ≤ 40 | 82 | 12 | 0.174 |
| | % | 65.1% | 50.0% | |
| | >40 | 44 | 12 | |
| | % | 34.9% | 50.0% | |
| | Total | 126 | 24 | |
| | % | 100.0% | 100.0% | |

P-value ≤ 0.05 (significant).

There is significant association between Gastric Biopsy and Du. Biopsy, (25%) of patients with C.G -H.P biopsy have V.A-IEL, 27.9% of patients with C.G -H.P biopsy have V.D-IEL, (30%) of patients with C.G-H.P-IM biopsy have V.D-IEL, (33.3%) of patients with N.S.G

biopsy have V.D- N.S.D, while (26.7%) of patients with N.S.G biopsy have V.D-IEL, (72.2%) of patients with normal biopsy have V.A-IEL- N.S.D. As show in table 7.

Table 7: Association between Gastric Biopsy and Du. Biopsy.

| variables | | Gastric Biopsy | | | | P-value |
|-----------------------|----------------------------|----------------|------------|--------|--------|---------|
| | | C.G -H.P | C.G-H.P-IM | N.S.G | NORMAL | |
| Du. Biopsy | <i>C.H-IEL</i> | 1 | 0 | 1 | 0 | 0.0001 |
| | | 1.0% | 0.0% | 6.7% | 0.0% | |
| | <i>Giardial</i> | 1 | 0 | 0 | 0 | |
| | | 1.0% | 0.0% | 0.0% | 0.0% | |
| | <i>IEL</i> | 3 | 1 | 0 | 0 | |
| | | 2.9% | 7.7% | 0.0% | 0.0% | |
| | <i>low grade dysplasia</i> | 0 | 1 | 0 | 0 | |
| | | 0.0% | 7.7% | 0.0% | 0.0% | |
| | <i>NORMAL</i> | 19 | 2 | 0 | 3 | |
| | | 18.3% | 15.4% | 0.0% | 16.7% | |
| | <i>V.A</i> | 1 | 0 | 1 | 0 | |
| | | 1.0% | 0.0% | 6.7% | 0.0% | |
| <i>V.A-IEL</i> | 26 | 2 | 2 | 0 | | |
| | 25.0% | 15.4% | 13.3% | 0.0% | | |
| <i>V.A-IEL- N.S.D</i> | 0 | 0 | 0 | 13 | | |
| | 0.0% | 0.0% | 0.0% | 72.2% | | |
| <i>V.D</i> | 11 | 2 | 2 | 0 | | |
| | 10.6% | 15.4% | 13.3% | 0.0% | | |
| <i>V.D-IEL</i> | 29 | 4 | 4 | 0 | | |
| | 27.9% | 30.8% | 26.7% | 0.0% | | |
| <i>V.D- N.S.D</i> | 13 | 1 | 5 | 2 | | |
| | 12.5% | 7.7% | 33.3% | 11.1% | | |
| Total | 104 | 13 | 15 | 18 | | |
| | 100.0% | 100.0% | 100.0% | 100.0% | | |

P-value ≤ 0.05 (significant).

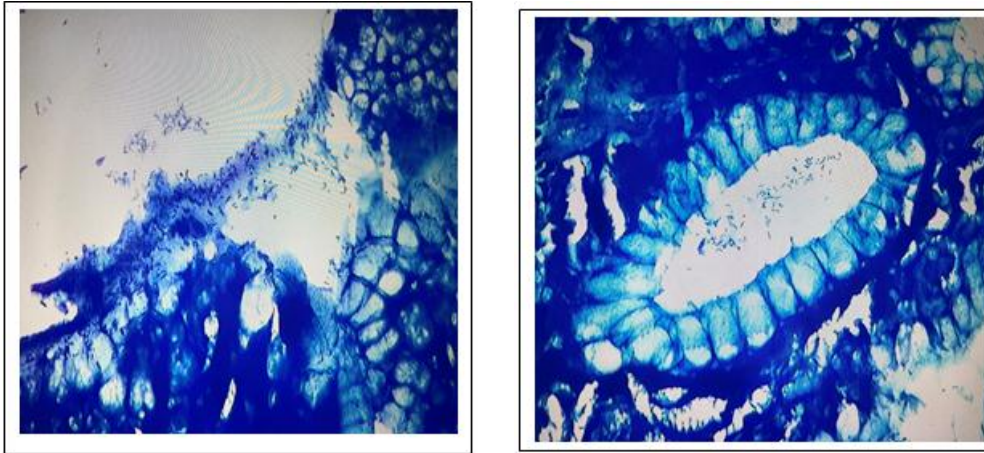


Fig 3): Microphotograph; showing a microscope section of gastric mucosa with chronic superficial gastritis with *H. pylori*.

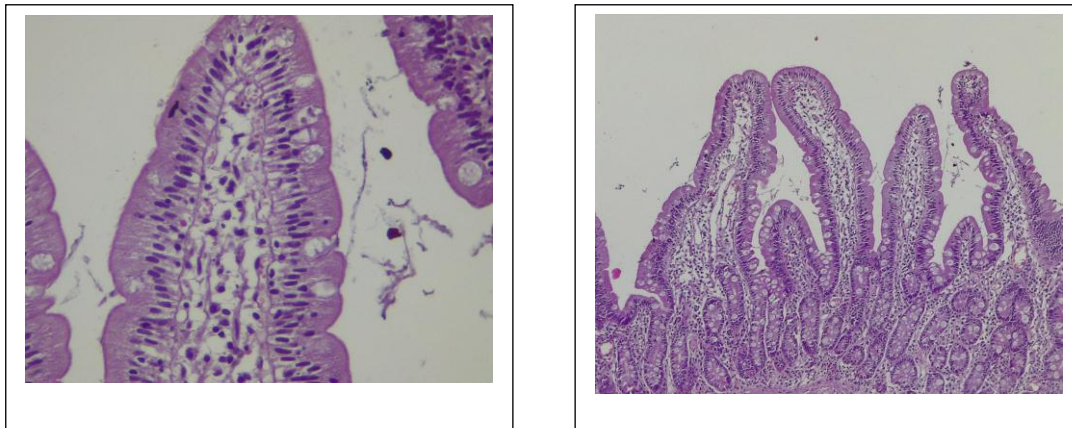


Fig (4): Microscopic sections showing duodenal Villi with increase Intraepithelial lymphocyte and crypt hyperplasia (high and medium power).

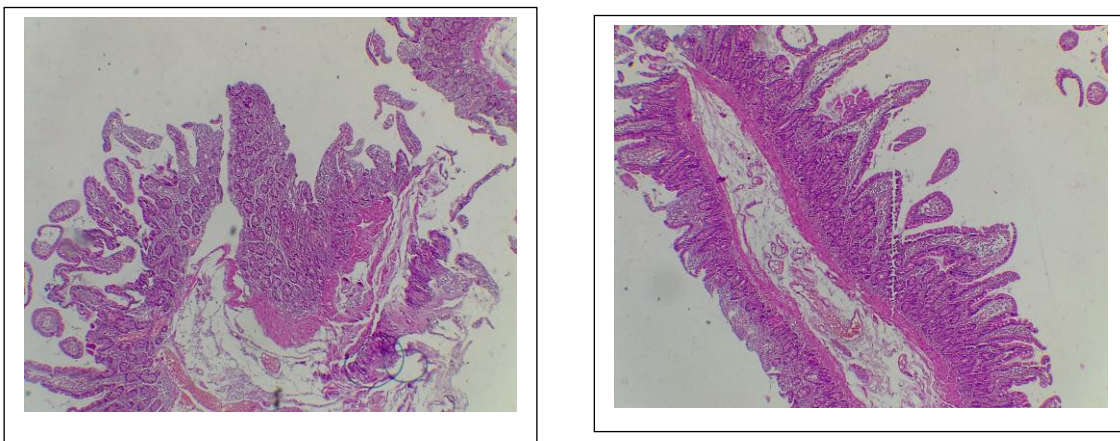


Fig 5: Microscopic description of duodenal mucosa on (low power) showing villous atrophy with crypts hyperplasia.

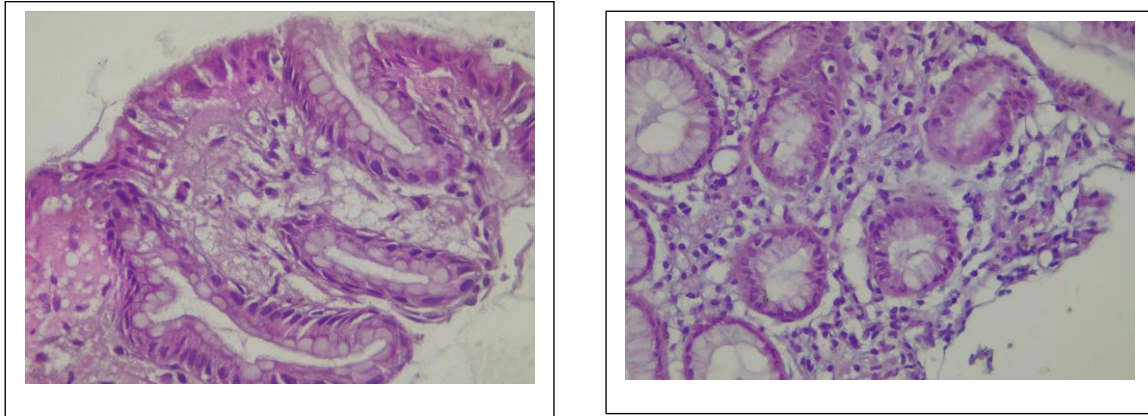


Fig 6: Microscopic description of gastric mucosa on (high power) showing intestinal metaplasia.

DISCUSSION

It is estimated that in USA, Canada, and UK; dyspepsia affects 30% of the general population with the majority (70%) being functional dyspepsia.^[10] The Canadian Association of Gastroenterology (CAG) and the American College of Gastroenterology (ACG) define functional dyspepsia as epigastric discomfort of at least one month without evidence of any organic disease on endoscopy.^[11] According to the Rome IV diagnostic criteria, functional dyspepsia is defined as the presence of one or more of the following: (3 days/week postprandial fullness), (3 days/week early satiety), (1 day/week epigastric pain), or (1 day/week epigastric burning) without evidence of structural disease.^[12] In the present study, *H. pylori* was diagnosed in 117 (78%) cases. (Hussein *et al.*, 2021) in Iraq found that the prevalence of *H. pylori* infection ranged from 47.8 to 70.4%^[13] (Ghosn *et al.*, 2019) in Lebanon found a prevalence of 37%^[14] (Eusebi *et al.*, 2014) concluded that low socioeconomic status in childhood is confirmed to be the most important risk factor for *H. pylori* infection.^[15] In the present study, Chronic gastritis was found in 132 (88%) cases either alone in 119 (79.3%) or associated with intestinal metaplasia in 13 (8.7%). About (88.6%) of cases of chronic gastritis were associated with *H. pylori* infection. This is understandable given that *H. pylori* is responsible for approximately 90% of cases of chronic gastritis.^[16] Regarding 13 (8.7%) cases of intestinal metaplasia, (Aziz *et al.*, 2020) in Mosul found a percentage of (3.0%).^[17] A meta-analysis by (Chen *et al.*, 2016) found that it represents a point of no return in the precancerous cascade as *H. pylori* eradication didn't reduce the risk of gastric carcinoma in such patients; while the risk was significantly reduced in patients with non-atrophic and atrophic gastritis after successful *H. pylori* eradication.^[18] No statistically significant association was found between age and gastric biopsy findings. (Ghosn *et al.*, 2019) found a that older age increased the likelihood of abnormal finding. This discordance can be explained by the smaller sample size of the present study when compared to the sample obtained by (Ghosn *et al.*, 2019).^[14] Furthermore, both studies found no association between gender and

abnormal gastric biopsy finding. It is worth mentioning that a meta-analysis by (Ibrahim *et al.*, 2017) found a higher incidence of *H. pylori* infection in male gender which was attributed to certain male habits like alcohol and smoking.^[19] In the present study, 126 (84.0%) cases showed abnormal duodenal biopsy findings. This is very high when compared to the studies by (Ghosn *et al.*, 2019), (Brada *et al.*, 2014) and (Lebwohl *et al.*, 2013) who found rates of 4%, 1.8%, and 0.6% respectively.^[14,20,21] Furthermore, a statistically significant association has been found between gastric biopsy findings and duodenal biopsy findings as the majority of patients with abnormal duodenal biopsy were infected with *H. pylori*. This is also in discordance with (Ghosn *et al.*, 2019)^[14] who found no association between *H. pylori* infection and positive duodenal biopsy. This contrast can be explained by the much higher prevalence of *H. pylori* in the present study, (Sahin *et al.*, 2014) found that in high prevalence regions, there was a significant association between *H. pylori* infection and duodenitis and obtained a rate of 36.9% of abnormal duodenal biopsy.^[22] Moreover, patients with celiac disease were not excluded in the present study. Celiac disease is considered an important confounding factor as it is considered the main cause of villous abnormalities.^[23] In the present study, no significant association was found between duodenal biopsy findings and either gender or age; which is in agreement to (Ghosn *et al.*, 2019).^[14] As to abnormal duodenal biopsies, (2.7%) had increased IEL corresponding to Marsh-Oberhuber grade 1, (1.3%) showed both increased IEL and crypt hyperplasia which corresponds to Marsh-Oberhuber grade 2, (30%) had villous atrophy corresponding to Marsh-Oberhuber grades 3a and 3b, and (48.7%) showed villous distortion corresponding to grade 3c.^[23]

CONCLUSION

No association was found between gastric histopathological findings and either age or gender. No association was found between duodenal histopathological findings and either age or gender. A significant association was found between gastric and

duodenal histopathological findings, which when taken in consideration with the high prevalence of *H. pylori* infection, can explain the very high percentage of abnormal duodenal biopsies.

List of abbreviations

V.A = villous atrophy
 C.H= crypt hyperplasia
 IEL= increase intraepithelial lymphocytes
 V.D= villous distortion
 N.S.D= nonspecific duodenitis
 N.S.G=nonspecific gastritis
 I.M= intestinal metaplasia
 H.P= *h.pylori*
 C.G= chronic gastritis

REFERENCES

- Molavi D. The Practice of Surgical Pathology. Cham: Springer, 2018.
- Rosai J, Ackerman L. Ackerman's surgical pathology. 11th ed. St. Louis: Mosby, 2018; 3.
- Madisch A, Andresen V, Enck P, Labenz J, Frieling T, Schemann M. The Diagnosis and Treatment of Functional Dyspepsia. *Dtsch Arztebl Int*, 2018 Mar 30; 115(13): 222-232. doi: 10.3238/arztebl.2018.0222. PMID: 29669681; PMCID: PMC5938438.
- Ford AC, Mahadeva S, Carbone MF, Lacy BE, Talley NJ. Functional dyspepsia. *Lancet*, 2020 Nov 21; 396(10263): 1689-1702. doi: 10.1016/S0140-6736(20)30469-4. Epub 2020 Oct 10. PMID: 33049222.5. Geraldine, O'Dowd, Sarah Bell, Sylvia Wright, WHEATER'S PATHOLOGY, 6th edition, 2015.
- Young B, Stewart W, O'Dowd G, Wheeler P. Wheeler's Basic pathology. Edinburgh: Churchill Livingstone, 2015.
- Ghosn Y, Hussein Kamareddine M, Tawk A, Bou-Ayash N, Bou-Ayash H, Mokamer N, Yared R, Aoun M, Khoury S, Cortas G, Jabbour G, Bedran K, Farhat S. Analysis of gastric and duodenal biopsy results in patients presenting with dyspepsia: a cross-sectional study in a middle eastern population. *BMJ Open Gastroenterol*, 2019.
- Romano M, Cuomo A. Eradication of *Helicobacter pylori*: a clinical update. *MedGenMed*, 2004; 6(1): 19.
- Bettington ML, Walker NI, Rosty C, et al. A clinicopathological and molecular analysis of 200 traditional serrated adenomas. *Mod Pathol*, 2015; 28(3): 414-427.
- Serra S, Jani PA. An approach to duodenal biopsies. *J Clin Pathol*, 2006 Nov; 59(11): 1133-50.
- Aziz I, Palsson OS, Törnblom H, et al. Epidemiology, clinical characteristics, and associations for symptom-based Rome IV functional dyspepsia in adults in the USA, Canada, and the UK: a cross-sectional population-based study. *Lancet Gastroenterol Hepatol*, 2018; 3(4): 252-262.
- Moayyedi P, Lacy BE, Andrews CN, et al. ACG and CAG clinical guideline: management of dyspepsia. *Am J Gastroenterol*, 2017; 112(7): 988-1013.
- Stanghellini V, Chan FK, Hasler WL, et al. Gastrointestinal disorders. *Gastroenterology*, 2016; 150(6): 1380-1392.
- Hussein RA, Al-Ouqaili MTS, Majeed YH. Detection of *Helicobacter Pylori* infection by invasive and non-invasive techniques in patients with gastrointestinal diseases from Iraq: A validation study. *PLoS One*, 2021 Aug 23; 16(8): e0256393. doi: 10.1371/journal.pone.0256393. PMID: 34424925; PMCID: PMC8382163.
- Ghosn Y, Hussein Kamareddine M, Tawk A, Bou-Ayash N, Bou-Ayash H, Mokamer N, Yared R, Aoun M, Khoury S, Cortas G, Jabbour G, Bedran K, Farhat S. Analysis of gastric and duodenal biopsy results in patients presenting with dyspepsia: a cross-sectional study in a middle eastern population. *BMJ Open Gastroenterol*, 2019 Sep 9; 6(1): e000330. doi: 10.1136/bmjgast-2019-000330. PMID: 31645989; PMCID: PMC6781958.
- Eusebi LH, Zagari RM, Bazzoli F. Epidemiology of *Helicobacter pylori* infection. *Helicobacter*, 2014 Sep; 19 Suppl 1: 1-5. doi: 10.1111/hel.12165. PMID: 25167938.
- The Sydney System. Histological division. *J gastroenterology and Hepatology*, 1991; 6: 209-222.
- Aziz Z, Saleem S, Al-Nuaimy H. *Helicobacter pylori* in Gastric biopsy: A Histochemical and Immunohistochemical Assessment. *Annals of the College of Medicine, Mosul*, 2020; 41(2): 139-147.
- Chen HN, Wang Z, Li X, Zhou ZG. *Helicobacter pylori* eradication cannot reduce the risk of gastric cancer in patients with intestinal metaplasia and dysplasia: evidence from a meta-analysis. *Gastric Cancer*, 2016 Jan; 19(1): 166-75. doi: 10.1007/s10120-015-0462-7. Epub 2015 Jan 22. PMID: 25609452.
- Ibrahim A, Morais S, Ferro A, Lunet N, Peleteiro B. Sex-differences in the prevalence of *Helicobacter pylori* infection in pediatric and adult populations: Systematic review and meta-analysis of 244 studies. *Dig Liver Dis*, 2017 Jul; 49(7): 742-749. doi: 10.1016/j.dld.2017.03.019. Epub 2017 Apr 4. PMID: 28495503.
- Barada K, Habib R, Malli A, et al. Prediction of celiac disease at endoscopy. *Endoscopy*, 2014; 46: 110-9.
- Lebwohl B, Blaser MJ, Ludvigsson JF, et al. Decreased risk of celiac disease in patients with *Helicobacter pylori* colonization. *Am J Epidemiol*, 2013; 178: 1721-30.
- Sahin A, Cihangiroglu G, Bilgic Y, Calhan T, Cengiz M. Is duodenal biopsy appropriate in areas endemic for *Helicobacter pylori*? *North Clin Istanbul*, 2017 May 10; 4(1): 13-21. doi: 10.14744/nci.2017.85520. PMID: 28752138; PMCID: PMC5530152.

23. Martins C, Teixeira C, Ribeiro S, Trabulo D, Cardoso C, Mangualde J, Freire R, Alves AL, Gamito É, Cremers I, Oliveira AP. Seronegative Intestinal Villous Atrophy: A Diagnostic Challenge. *Case Rep Gastrointest Med*, 2016; 2016: 6392028. doi: 10.1155/2016/6392028. Epub 2016 Oct 10. PMID: 27803820; PMCID: PMC5075602.