Original Research

Histomorphological evaluation of Esophagus in Cases Of Gastroesophageal reflux Disease and its association with Gastric H. Pylori Infection

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ABSTRACT

BACKGROUND: Helicobacter pylori is a gram-negative, microaerophilic bacterium that inhabits various areas of the stomach and duodenum. Recently, it has been observed that gastric colonization with H.pylori may also have beneficial effects for the human host. In this respect, the interest is in particular going to the potential preventive effect of H.pylori colonization on the development of gastro-esophageal reflux disease (GERD) and its complications. This interesting note made us think to evaluate the various histomorphological changes seen in esophagus in cases of GERD and to correlate the findings with the status of gastric H pylori colonization in those cases.

METHODOLOGY: In our study 150 cases of patients presenting with symptoms of GERD were included. The patients were evaluated clinically and subjected to upper Gastrointestinal (GI) endoscopy the findings in the upper gastrointestinal (UG) endoscopy were recorded and biopsy were taken from the esophageal lesions. Subsequent gastric antral biopsies were also done in these cases. The histopathological changes of esophagus were recorded. The findings were correlated with the H. Pylori status of the gastric antral biopsies.

RESULTS: In our study population of 150 cases of GERD esophageal biopsy was done in all 150 cases and gastric antral biopsy was done in 138 patients. In our study population 88 patients had chronic reflux esophagitis, 46 had Barrett's esophagus, vascular ecstasia was seen in 4 and malignancy was present in 12 cases. Among 12 malignant cases adenocarcinoma was present in 3 patients and squamous cell carcinoma was present in 9 patients. Among total 138 gastric antral biopsies we did H.Pylori positivity was seen in 50 (32.6%) of patients.

CONCLUSION: In our study, 39% of cases with chronic esophagitis had H.pylori positivity, 34% of cases with Barrett's oesophagus had H.Pylori positivity and none of the malignancy cases had H.pylori positivity. So it is observed that patients with H.pylori positivity has low incidence of Barrett's oesophagus and adenocarcinoma. Henceforth whether the presence of H.Pylori infection in GERD patient's decrease the incidence of malignancy needs to be further studied.

KEYWORDS: H.Pylori, GERD, Histomorphology

INTRODUCTION

Gastro-esophageal reflux disease [GERD] emerged as the most common upper gastrointestinal disease of the western world. This disease is a major contributor to the rise in the war of endoscopy and acid suppression therapy. Epidemiologic studies suggest a 3% to 4% prevalence of GERD in the general population with the preponderance of individuals having mild or moderate disease. Reflux esophagitis results from the action of peptic juice on the esophageal mucosa. Reflux esophagitis can occur in any age group but is most common in the middle aged persons. Risk factors include hiatal -hernia, excessive vomiting and peptic ulcer disease. The use of Non - steroidal anti-inflammatory agents, alcohol abuse, cigarette smoking, diabetes, systemic sclerosis and pemphigus are also associated with gastro -esophageal reflux.[1]Barrett's esophagus, defined as the presence of the columnar metaplastic epithelium in the distal esophagus over a length of more than 2 to 3cm is usually considered to be a complication of long standing gastro-esophageal reflux disease [GERD] and is one of the major manifestations of GERD.[2]Helicobacter pylori are a gram-negative, microaerophilic bacterium that inhabits various areas of the stomach and duodenum. It causes a chronic low-level inflammation of the stomach lining and is strongly linked to the development of duodenal and gastric ulcers and stomach cancer.

Over 80% of individuals infected with the bacterium are asymptomatic.

Helicobacter pylori have acquired great importance during the last two decades, after being recognized as an important pathogen that infects a great portion of the human population. Helicobacter pylori is of major concern today because of its causal relationship with gastroduodenal diseases. The bacteria are prevalent worldwide andmore than half of the world's population is infected with H. pylori.[3]Recently, it has been observed that gastric colonization with H.pylori may also have beneficial effects for the human host. In this respect, the interest is in particular going to the potential preventive effect of H.pylori colonization on the development of gastro-esophageal reflux disease (GERD) and its complications such as Barrett's esophagus and adenocarcinoma of the distal esophagus. If so, this will have a major impact on issues such as screening and treatment of H. pylori infections.[4]By now, the potential role of H. Pylori in the development of GERD is a key issue in the treatment of patients with upper gastrointestinal disorders. GERD patients with concomitant H.pylori infection showed more severe gastritis in the antrum than in other parts of the stomach, such as corpus, fundus and cardia. Apart from a lower prevalence of GERD among H.pylori-positives, some also reported that if GERD is present in H.pylori-positive subjects, it may be less severe. This interesting note made us think to evaluate the various histomorphological changes seen in esophagus in cases of GERD and to correlate the findings with the status of gastric H pylori colonization in those cases. Based on this aim of our study is to analyze study the histomorphological changes of esophagus in cases of GERD and its association with gastric H.pylori infection.

MATERIALS AND METHODS

In our study 150 cases of patients presenting with symptoms of GERD attending outpatient department of Government Tiruvannamalai Medical College Hospital from July 2018 - July 2020 were included. The patients were evaluated clinically and subjected to upper Gastrointestinal (GI) endoscopy the findings in the upper gastrointestinal (UG) endoscopy were recorded and biopsy were taken from the esophageal lesions. Subsequent gastric antral biopsies was also done in these cases during the same sitting The samples were fixed in 10% neutral buffered formalin and processed in routine manner. 4 µ (micron) sections were cut from both the tissues and stained with Hematoxylin and eosin. Gastric biopsy was also stained with Warthin's starry stain to evaluate the presence of H. Pylori. The demographic data were recorded in a Proforma. The histopathological changes of esophagus were recorded. The findings were correlated with the H. Pylori status of the gastric antral biopsies. The gastric antral biopsies were stained with hematoxylin and eosin and graded according to the modified Sydney system of classification. Statistical analysis was done using SPSS version 24.0 and was described in percentages where ever needed.

RESULTS

In our study population of 150 cases of GERD esophageal biopsy was done in all 150 cases and gastric antral biopsy was done in 138 patients.102 patients were male (68%) and rest 32% of patients were female in our study. Most common age group being 31-40 years age group (n=46) followed by 21-30 and 41-50 years age group (n=25).As age increase incidence of GERD is high .In our study population 88 patients had chronic reflux esophagitis, 46 had Barrett's esophagus, vascular ecstasia was seen in 4 and malignancy was present in 12 cases. Among 12 malignant cases adenocarcinoma was present in 3 patients and squamous cell carcinoma was present in 9 patients.

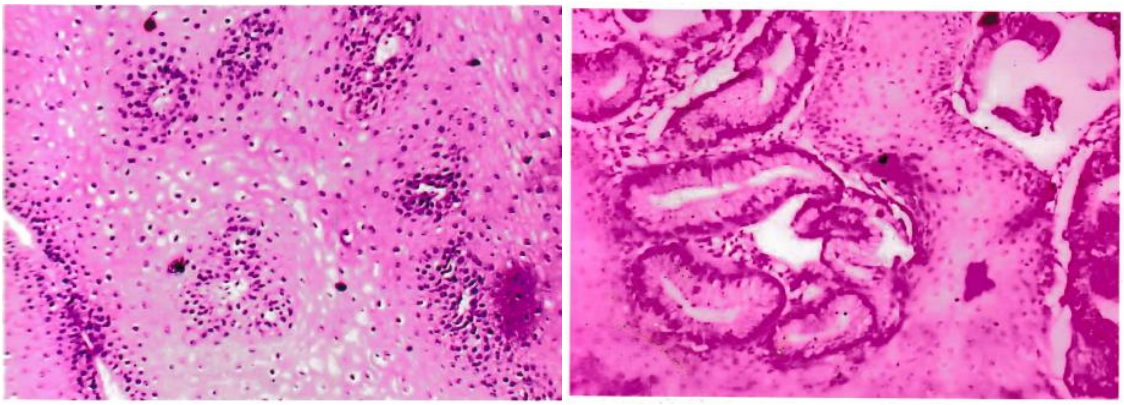

Figure 1: Photomicrograph of Chronic reflux esophagitis, Barrett's esophagus.

Table 1: Different types of esophageal lesions

Sl.No.	Type of Lesion	Number of cases
1	Chronic reflux esophagitis	88
2	Barrett's esophagus	46
3	Vascular Ectasia	4
4	Malignancy	12

Barrett's esophagus was present in 46 cases and they were histologically classified – classic Barrett's was present in 39 patients, Low grade dysplasia in 4 patients and high grade dysplasia in rest 3 cases.

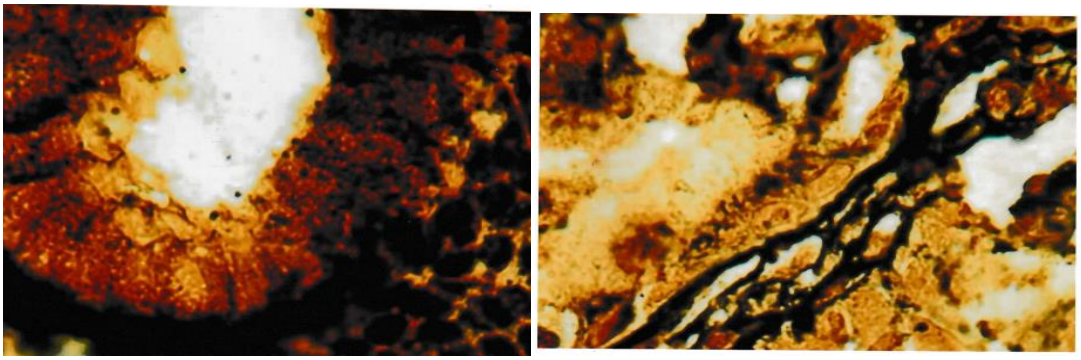

Figure 2: photomicrograph of helicobacter pylori

Table 2: Correlation between esophageal lesion and H.Pylori status

Sl. No.	Type of Esophageal lesion	Number of cases	Number of cases Positive for H.Pylori
1	Chronic reflux esophagitis	88	34 (39%)
2	Barrett's esophagus	46	16 (34%)
3	Malignancy	12	0
4	Vascular Ectasia	4	0

We correlated the type of lesion with H.pylori positivity and 39% of patients having chronic reflux esophagitis were positive for H.Pylori. Among Barrett's 34% of patients were positive for H.Pylori. P value was significant with 0.027. Similarly we also correlated H.Pylori with grading of Barrett's esophagus and among that in 39 classic cases 14 were positive for H.pylori and 1 case was positive each in low and high grade dysplasia. Here p vale was not significant with 0.908.

Table 3: Correlation between different grades of Barrett's esophagus and H.Pylori positivity

Sl.no.	Histological grade of Barrett's esophagus	Number of cases	H.Pylori Positive
1	Classical Barrett's	39	14
2	Low – Grade Dysplasia	4	1
3	High – Grade Dysplasia	3	1

Among total 138 gastric antral biopsies we did H.Pylori positivity was seen in 50 (32.6%) patients. We analyzed the severity of inflammation in our study, among these 50 patients, mild inflammation was present in 37(74%) of cases, moderate inflammation was present in 10 (20%) cases and rest 3(6%) of cases had severe inflammation based on Sydney system of classification.

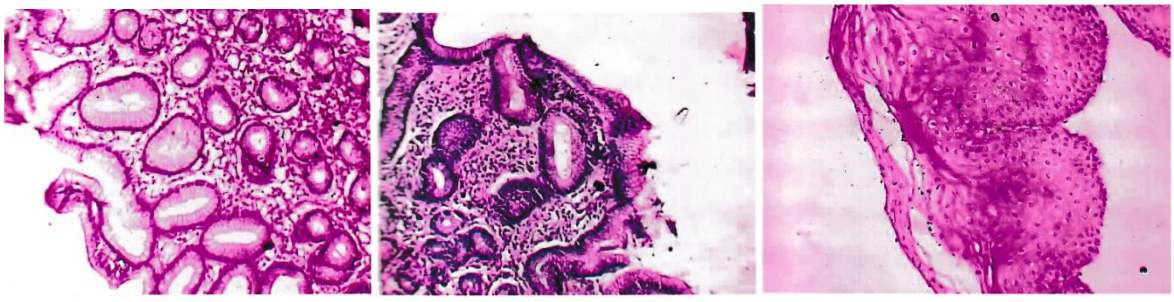

Figure 3: Chronic superficial antral gastritis- mild, moderate and severe

DISCUSSION

In our study we have analyzed the histomorphology of esophagus in 150 patients, who presented with symptoms of gastroesophageal reflux disease. The study population included both children and adults, however adults were predominant.

We had four children (2.6%) and one hundred forty six (97.4%) adults. This correlates with the study of Sonnenberg HB et al[5], who found a significant rise in the number of children with symptoms of Gastroesophageal reflux Disease. In most of the children in our study, the esophageal changes were thatof reflux esophagitis and we did not have even a single case of Barrett's. This observation differs from that of Robbins 7th Edition, who found out that reflux esophagitis is occasionally seen in infants and children.[6]

The peak age groups of patients implicated with symptoms of Gastroesophageal reflux disease were between 31-40 years of age. This is in coherence with the observation of Johnson DA and Fennerty MB et al[7] who found out that increasing age is an important factor in the prevalence of Gastroesophageal reflux disease complications and they attributed this to the cumulative acid induced injury to the esophagus overtime.

We had 102, (68%) number of male patients and 48 female patients (32%). This is similar to observation made by various authors, who found that gastroesophageal reflux disease is almost equally seen in both gender, however the esophageal lesions of the gastroesophageal reflux disease were more common in men than in women. We found out that the men had a higher number of reflux esophagitis and Barrett's esophagus than women (68%). This is similar to the observation made by Cecilia M. F who found that there is an unequivocal male predominance of reflux esophagitis and Barrett's esophagus.[8]

Regarding the common associated symptoms, most of our cases included in the study presented with heartburn which resembles the observation made by Nebel et al[9] who opined that heartburn is the most common and classical symptoms of Gastroesophageal reflux disease. In our study, we found that most of the patients expressed heartburn postprandially especially after intake of spicy, fatty food. Few of our cases had thissymptom following intake of certain medications for headache and body ache.

Analysis of the esophageal lesions reveal that the most common histomorpholgical changes encountered was that of chronic reflux esophagitis (58.6%) followed, by Barrett's (29.3%) malignancies (8%) and few cases of miscellaneous changes like vascular ecstasias (2.6%) This correlates well with similar observation made by other authors.

Chronic reflux esophagitis

Epithelial hyperplasia with expansion of the basal zone and elongation of the vascular papillae of the lamina propria was found in most of our cases of chronic reflux esophagitis. This correlates well with the observation made by Collins BJ et al[10] who was of the opinion that epithelial hyperplasia indicated a rapid epithelial turnover and proliferation, was a very significant histological change seen in patients with chronic reflux esophagitis. They called this change as a marker of reflux.

We also had many cases, showing balloon degeneration of the squamous epithelium. 42 cases of the total 88 cases Chronic reflux esophagitis showed the presence of balloon cells. This correlates well with the observation of Sternberg et al[11] who found that two thirds of the patients with Chronic reflux esophagitis showed presence of balloon cells in the epithelium.

In this present study, only few of our cases with Chronic reflux esophagitis showed presence of eosinophils within the epithelium. In our study 18 cases of total 88 cases showed significant presence of intra epithelial eosinophils. Presence of intra epithelial eosinophils is an additional indicator of Gastroesophageal reflux disease as per study done by Tummala V et al.[12]

Barrett's Esophagus

In Barrett's esophagus the squamous cell epithelium has undergone metaplastic change to columnar epithelium, presumably as a result of long standing gastro-esophageal reflux. Spechler SJ and Goyal RK[13]. In our study, we had 46 patients presenting with Barrett's Esophagus. In most of them, the metaplastic epithelium was made up of columnar cells, resembling the gastric mucous cells.

Inflammation was not very significant in the cases of Barrett's Esophagus. We had noticed non-specific inflammation in 7(15%) of our cases and ulceration was seenonly in 2 cases 4(%). This is in coherence with the observation made by Petras REet al[14], who found that ulceration and inflammation are non-specific changes seen in association with Barrett's esophagus.

In our present study we had 7 cases of dysplasia seen out of 46 cases of Barrett's esophagus. Of these 4 were typed as low grade dysplasia and 3 as high grade dysplasia. Dysplasia in Barrett's esophagus is classified into low or high grade in a fashion comparable to the dysplasia in inflammatory bowel disease, Riddell RH et al[15]. This implies that the grade of dysplasia should be determined by the features of the most dysplastic region, either surface or base.

Weston AP et al[16] found that about 53% of the patients with high grade dysplasia progressed to multifocal high grade dysplasia or an invasive carcinoma. In contrast, a large study of patients

with Barrett – related high – grade dysplasia suggested that surveillance endoscopy with biopsy is a valid and safe follow – up strategy for patients with high – grade dyplasia without concurrent cancer since only 16% of patients subsequently developed carcinoma during a mean surveillance period of 7.3 years (Schnell TG et al[17]). Burke et al[18] was of the opinion that low grade dysplasia is rather indolent and a not a reliable hall mark for malignancy.

Malignancy

Out of the 150 cases included in our study we found out malignant lesion in 12 cases (8%). The endoscopic picture was classical in 8 of the cases with ulcerated, ulceroproliferative lesion, whereas in the other 4 the endoscopic picture was not classical. Multiple biopsies were taken in suspicion to exclude a malignancy. Histological analysis of cases of malignancies showed 9 cases (75%) of squamous cell carcinoma and 3 cases (25%) of adenocarcinoma. This is comparable to the observation made by Souza R.F et al[19], who found that occurrence of squamous cell carcinoma was the most common type of carcinoma followed by adenocarcinoma. All of them presented with ulcerative type of lesion. This goes hand in hand with the observation made by several workers that majority of adenocarcinoma arise from pre-existing Barrett's Esophagus. (Blot W et al) [20].

H-pylori and GERD

The main aim of our study was to determine the prevalence of gastricH.pylori infections in patients with esophageal lesions of GERD. The gastric antral biopsy was analyzed for the type of inflammatory reaction according to modified Sydney system of classification and was broadly grouped into mild, moderate and severe. Warthin starry silver stain was used to detect the presence of H.pylori and it was noted as positive or negative.

Out of the total 138 antral biopsies, H.pylori was detected in 50 cases (32.6%). H.pylori was not detected in 88(63.7%) number of cases. The presence of H.pylori status was then compared with that of the esophageal histomorphology.

Chronic reflux esophagitis was the most common esophageal lesion studied, and we had 88 cases of the total 150 cases. H.pylori was detected in 34 of the total 88 cases with chronic reflux esophagitis (39%). This correlates very well with similar observation made by Abbas Z et al[21] who found 38% of positivity in their studyof 29 cases.

Barrett's esophagus was the second common lesion observed in our study. The prevalence of gastric H.pylori was analyzed for the patients presenting with Barrett'sesophagus. In our study we found 34% of the patients presenting with Barrett's esophagus had gastric H.pylori infection. This observation matches well with that s Weston AP et al[16]. He was able to demonstrate the presence of H.pylori in 95 of the total 289 cases (32.9%).

The incidence of Helicobacter pylori infection in the patients with Gastroesophageal reflux disease varies widely in literature from 30% to 90% and approximately of 35% in most series. Our study showed that 30% of the gastroesophageal reflux disease patients were infected with H. Pylori. This correlateswell with the various other studies done by others in various parts of the world. GERD patients with concomitant H.Pylori infection showed more severe gastritis in the antrum than in other parts of the stomach, such as corpus, fundus andcardia.

Reflux disease results from interaction between acid production, lower esophageal sphincter pressure, esophageal clearance and gastric emptying. H. Pylori may affect several of these factors. Few individuals respond to H. Pylori colonization with and exaggerated gastric response leading to increased acid production. These individuals are at the risk of developing duodenal ulcer disease and reflux disease.

Schenk et al[22] observed in a prospective endoscopic study that H. Pylori negative patients had a higher incidence of Barrett's esophagus than H. Pylori positive GERD patients. We also had a similar observation in our study in which the H. Pylori positivity was lower in Barrett's and it was absent in cases of adenocarcinoma. Kiltz U et al[23] in his study concluded that the presence of H. Pylori might delay the development of Barrett's esophagus, which could explain the lower positivity rate of H. Pylori positivity in cases of Barrett's esophagus.

CONCLUSION

In our study, 39% of cases with chronic esophagitis had H.pylori positivity, 34% of cases with Barrett's oesophagus had H.Pylori positivity and none of the malignancy cases had H.pylori positivity. So it is observed that patients with H.pylori positivity has low incidence of Barrett's oesophagus and adenocarcinoma. Henceforth whether the presence of H.Pylori infection in GERD patient's decrease the incidence of malignancy needs to be further studied.

REFERENCES

1. Cecilia m. Fenoglio – preiser Gastro Intestinal pathology an Atlas and text. Third edition Lippincott, Williams, Wilkins.
2. Chen YY:Antonioli DA:Spechler SJ:Zeroogian JM:Goyal RK:Wang HH.Gastroesophageal reflux disease versus Hellcobacter pylori infection as the cause of gastric carditis. Mod Pathol 1998; 11:950-6.
3. Clark GWB:Smyrk TC:Burdiles P:Hoeft SF:Peters JH:Kiyabu M:Hinder RA:Bremner CG:DeMeester TR. Is Barrett's metaplasia the source of adenocarcinomas of the cardia? Arch Surg 1994:129:609-14.
4. Collins BJ, Elliott. H, Sloan JM, et al. Oesophageal Histology in reflux esophagitis J. Clin Pathol 1985.
5. Sonnenberg A, EL serag HB: clinical epidemiology and natural history of gastroesophageal reflux disease

– Yale J Biol Med 1999 ; 12;81
6. Robbins and Cotran 7th edition Elsevier.
7. Johnston DA, Fennerty MB Heart burn Severity under estimates erosive esophagitis severity in elderly patients with gastro esophageal reflux disease. Gastroenterology 126: 660, 2004.
8. Cecilia m. Fenoglio – preiser Gastro Intestinal pathology an Atlas and text. Third edition Lippincott, Williams, Wilkins.
9. Nebel OT, Fornes MF, and Castell DO: symptomatic gastroesophageal reflux incidence and precipitating factors. Dig Dis Sci 1976; 21: 953.
10. Collins BJ, Elliott. H, Sloan JM, et al. Oesophageal Histology in reflux esophagitis J. Clin Pathol 1985.
11. Sternberg's Diagnostic Surgical pathology volume 2. Jaypee, Litincott, Williamsand Wilkins.
12. Tummala V, Barwick KW, sontag SJetal. The significance of intra epithelial eosniophils in the hisologic diagnosis of gastroesophageal reflux. Am J clin Pathol 1987.
13. Spechler SJ, Goyal RK, Barrett's esophagus N.Engl J Med 1986
14. Petra M. Trastek VF, Pairolero PC, Cardesa A, Allen MS, Deschamps C. Barrett's Disease: Pathophysiology of metaplasia and adenocarcinoma. Ann Thorac Surg 1993; 56:1191-7.
15. Riddell RH:Goldman H.Ransohoff DF:Appelman HD:Fenoglio CM:Haggitt RC:Ahren C.Correa P:Hamilton SR:Morson BC:Sommers SC:Yardley JH.Dysplasia in inflammatory bowel disease: Standardized classification with provisional clinical application. Hum pathol 1983; 14:931-66.
16. Weston AP, Badr AS, Topalovski M, cherian R, Dixon A, Hassanein RS. Prospective evaluation of the prevalence of gastric Helicobacter pylori infectionin patients with GERD, Barrett's esophagus, Barrett's dysplasia, and Barrett's adenocarcinoma. AM J Gastroenterol, 2000
17. Schhell TG, Sontag SJ, Chief fec G, etal Longterm non-surgical management of Barrett's esophagus with high – grade dysplasia – Gastroenterology 2001; 120: 1607.
18. Burke AP, Sobin LH:Shekitka KM:Helwig EB. Dysplasia of the stomach and Barrett esophagus: A follow-up study. Mod pathol 1991;4:336-41
19. Souza RC, Lima JH. Helicobacter pylori and gastroesophageal reflux disease: a review of this intriguing relationship. Dis Esophagus. 2009;22(3):256-63. doi: 10.1111/j.1442-2050.2008.00911.x. PMID: 19425207.
20. Blot WJ: Devesa SS:Kneller RW: Fraumeni JF. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991; 265:1287-9.
21. Miftahussurur M, Doohan D, Nusi IA, Adi P, Rezkitha YAA, Waskito LA, Fauzia KA, Bramantoro T, Maimunah U, Thamrin H, Masithah SI, Sukadiono S, Uchida T, Lusida MI, Yamaoka Y. Gastroesophageal reflux disease in an area with low Helicobacter pylori infection prevalence. PLoS One. 2018 Nov 14;13(11):e0205644.
22. Schenk BE, Kurpers EJ, Klinkenberg-knol EC, Eskes SA, Meuwissen SGM. Helicobacter Pylori and the efficacy of omeprazole for gastroesophageal reflux disease. AMJ Gastroenterol 1999.
23. Kiltz U, Baier J, Schmidt WE, Adamek RJ. Barrett's metaplasia and *Helicobacter pylori infection* (letter) Am J Gastroenterol. 1999; 94:1985–6.