Microb Health Dis 2021; 3: e535

REVIEW – *HELICOBACTER PYLORI* & NON-MALIGNANT UPPER GI DISEASES

V. Ivanova[1], R. Jaensch[2], A. Link[2], D.S. Bordin[1,3,4]

[1]A.S. Loginov Moscow Clinical Scientific Center, Moscow, Russia
[2]Section of Molecular Gastroenterology and Microbiota-associated Diseases, Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University Magdeburg, Magdeburg, Germany
[3]Department of Outpatient Therapy and Family Medicine, Tver State Medical University, Tver, Russia
[4]Department of Propaedeutic of Internal Diseases and Gastroenterology A.I. Yevdokimov Moscow State University of Medicine and Dentistry, Moscow, Russia

Corresponding Author: Dmitry S. Bordin, MD; email: dmitrybordin@gmail.com

Abstract: *Helicobacter pylori* remains a crucial factor in the development of gastrointestinal (GI) diseases including chronic gastritis, peptic ulcer disease (PUD) and gastric cancer, even decades after its discovery. This review summarizes the advances in the field of *H. pylori* and non-malignant diseases of the upper GI tract and includes the most relevant studies on this topic published between April 2020 and March 2021. Here we include the published data on associations between *H. pylori* infection and diseases, such as gastroesophageal reflux disease (GERD), Barrett's esophagus, eosinophilic esophagitis (EoE), PUD, gastritis, gastric polyps and celiac disease. Observations over the past 25 years highlight the trends in decreasing prevalence of gastric and duodenal ulcer while the rate of reflux esophagitis increased. A meta-analysis links the prevalence of GERD with *H. pylori* eradication. Other studies support the inverse correlation of *H. pylori* infection with Barrett's esophagus. Large cohort studies highlight the negative association between *H. pylori* infection and the prevalence of fundic gland polyps. On the contrary, successful eradication of *H. pylori* resulted in a significant increase in the clearance rate of hyperplastic polyps. Novel data on *H. pylori* infection, microbiome, and immune-triggered diseases highlight the potential role of the microbiome in disease development, its impact on mucosal injury in patients with *H. pylori* infection and even its potential value in *H. pylori* management. An inverse association of *H. pylori* infection and several immune diseases, including asthma and EoE remains a scientific focus.

Keywords: Polyps, Eosinophilic esophagitis, Gastroesophageal reflux disease, Peptic ulcer disease, Barrett's esophagus, Celiac disease.

INTRODUCTION

Helicobacter pylori is an infectious disease that is linked with a broad variety of diseases, including peptic ulcer disease (PUD), preneoplastic changes of gastric mucosa, gastric cancer etc. Over the past years, *H. pylori* has been shown to have a negative association with several immune-triggered diseases or gastroesophageal reflux disease (GERD). Therefore, it is crucial

to review the published clinically relevant knowledge and recent advances in the field of *H. pylori*. This review summarizes selected articles published during the period of April 2020 and March 2021 with a focus on non-malignant upper gastrointestinal (GI) diseases.

EOSINOPHILIC ESOPHAGITIS

H. pylori infection has been associated with a lower risk of several immune diseases, including asthma, GERD and eosinophilic esophagitis (EoE). In a recent study from Japan the authors aimed to assess the frequency of EoE and clinical features associated with the disease[1]. For this purpose, they evaluated the endoscopic data from 9 institutes, in total 130,013 examinations. The overall incidence was 0.051% (66 cases) with a mean age of 45.2 (range 7-79 years). As expected, the EoE patients had more symptoms and more allergies compared to controls, while the prevalence of atrophic gastritis was found in the EoE group in 20.0% cases compared to 33.3% in the control group. *H. pylori* infection was evaluated by serology, urea breath test, or histologically and was found in seven of the 66 EoE cases (10.6%). Twelve percent of the EoE subjects had a history of *H. pylori*-eradication[2].

Knowing that EoE is a disease triggered by environmental factors, it is likely that the interaction between *H. pylori* and the disease may be more complex and is likely to involve the entire microbial community. In one study[3] the authors compared the oral and esophageal microbiome of 20 patients undergoing upper GI endoscopy. There was a high similarity in the microbiome of oral and esophageal specimens within individuals, suggesting that the oral microbiome may be co-involved in the pathogenesis of esophageal disease. Interestingly, the data from two other clinical studies provided discordant results. First, a microbiome analysis of the esophagus in 24 EoE patients in comparison to 25 controls revealed no significant differences[4]. In the second study, the authors demonstrated that microbiome alterations were linked to EoE and concomitant therapy with differential abundance of *Filifactor*, *Parvimonas* and *Porphyromans* genera[5]. Interestingly, all studies did not report on *H. pylori* infection in studied specimens.

Nevetheless, the hypothesis of a "protective" role of *H. pylori* in EoE remains mainly supported by data of association. An in-depth view will be necessary to delineate the interplay between GI mucosa, potential allergens and immune response in the background of *H. pylori* infection. Although several potential molecular mechanisms have been proposed such as an immune shift from Th1 (*H. pylori* triggered response) to Th2 (EoE-like response), this view is most likely an oversimplification, with the need for longitudinal observational and mechanistic models[6].

Over the past years, EoE has been increasingly recognized, while little is still known concerning another group of diseases, such as eosinophilic gastritis, duodenitis and colitis. Using a large database of histopathologic records, Sonnenberg et al[7] aimed to examine the prevalence and occurrence of GI eosinophilia. The highest prevalence rate (PR) was observed for EoE (PR 9.96), while gastric eosinophilia (1.21), duodenal eosinophilia (0.03) and colonic eosinophilia (0.41) were relatively rare. EoE was associated with gastric eosinophilia and was more common in the pediatric population. The *H. pylori* prevalence in those analyses was low, with 3.9% in patients with EoE and up to 12.9% in colonic eosinophilia patients.

GASTROESOPHAGAL REFLUX DISEASE

The role of *H. pylori* infection in esophageal diseases is controversial. *H. pylori* infection has been suggested to exert a protective effect against GERD, Barrett's esophagus (BE), and esophageal adenocarcinoma (EAC). *H. pylori* associated gastritis can lead to both an increase or a decrease in acidic secretion, depending on the disease phenotype. *H. pylori*-associated antral gastritis is associated with hyperacidity, which may aggravate GERD, while corpus gastritis may be associated with hypoacidity and plays a protective role against that disease. Epidemiologic data demonstrate that erosive reflux esophagitis (ERD), BE, and EAC are inversely related to *H. pylori* infection. Eradication therapy is considered to increase the risk of GERD and reflux esophagitis (RE) and the development of reflux-related symptoms.

Over the past years, 3 meta-analyses were published on the topic[8-10]. The first[8] was a large meta-analysis including 27 studies, in which the authors analyzed an association between reflux esophagitis and *H. pylori* eradication therapy. The incidence rate of endoscopic RE after eradica-

tion was 16.8% compared to 6.6% in controls and *de novo* esophagitis was 15.3% compared to 6.2%, respectively. The significant effect was demonstrated for the development of endoscopic reflux esophagitis (RR: 1.46, 95%CI: 1.16-1.840) and *de novo* esophagitis (RR: 1.42, 95%CI: 1.01-2.00), while no significant difference in reflux-related symptoms was observed between the case and control groups[8]. In a successful *vs.* failed eradication model, however, the effect of eradication on RE development or *de novo* RE did not reach statistical significance, suggesting that more original studies with an assessment of covariates will be needed in the future.

The second meta-analysis[9] including 19 studies reported the data of 3,221 patients in the *H. pylori* eradication group and 3,970 in the control group with regard to the prevalence of GERD. The prevalence of gastroesophageal reflux was significantly higher in patients with *H. pylori* eradication compared with patients without eradication (RR: 1.54, 95%CI: 1.06-2.24; $p=0.02$). The analysis did not identify any significant difference related to geographic regions specifically outside of China (RR: 1.62, 95%CI: 0.98-2.68) *vs.* in China (RR: 1.30, 95%CI: 0.76-2.22). Researchers concluded that eradication of *H. pylori* infection may be associated with gastroesophageal reflux; however, regional differences in the prevalence may occur.

The third meta-analysis[10] showed that *H. pylori* eradication may lead to the development of new erosive GERD (OR 1.67, 95%CI: 1.12-2.48; $p=0.01$); but not to the development of GERD-related symptoms compared with control group without GERD at baseline (OR 1.04, 95%CI 0.84-1.29; $p=0.71$).

BARRETT'S ESOPHAGUS

The suggestion that RE in subjects without *H. pylori* infection (non-*H. pylori*) is associated with the progression of Barrett's esophagus (BE) has been previously made. In a study in Japan, 11,493 asymptomatic subjects underwent a check-up and were diagnosed with short-segment BE (SSBE)[11]. According to their analysis, subjects with RE and negative for *H. pylori* infection (current or past) had a higher risk of progression from SSBE to long-segment BE (LSBE) (Hazard Ratio (HR)R: 7.17, 95%CI: 2.48-20.73) compared to RE with *H. pylori* infection. Irrespective of RE, subjects with *H. pylori* had a lower rate of progression to LSBE (HR: 0.48, 95%CI: 0.22-1.07) compared to the *H. pylori* negative group. Interestingly, the *H. pylori*-related protection was detectable even a few years after *H. pylori* eradication suggesting that these factors may need to be considered in the future for the risk assessment[11].

The same group investigated the link between *H. pylori*, SSBE and LSBE using a medical survey of 41,065 asymptomatic Japanese individuals[12]. *H. pylori* status was evaluated using serological analysis. *H. pylori*-positivity was significantly associated with a lower rate of LSBE (OR: 0.42; 95%CI: 0.16-0.91) and a higher rate of SSBE (OR: 1.66; 95%CI: 1.56-1.78). However, the *H. pylori*-related association with SSBE was only found in subjects without RE. In the subgroup analysis, *H. pylori*-positivity was significantly associated with a high rate of SSBE in subjects without RE (OR: 1.73; 95%CI: 1.61-1.85). Based on these analyses, an *H. pylori* positivity status may be considered as a potential risk of SSBE without RE, while it is protective against LSBE, as reported in the study above[12]. Nevertheless, the associative evidence from the above-mentioned studies from Japan need validation in Western cohorts, and molecular plausibility of *H. pylori*-related protection to LSBE needs to be determined.

With the introduction of the next generation of chromoendoscopy, it is likely that the prevalence of SSBE and its association with *H. pylori* infection may need to be re-evaluated. In particular, the delineation of BE using palisade vessels may be consistently implemented with the help of linked color imaging (LCI)[13].

GASTRITIS AND PEPTIC ULCER DISEASE

A study investigated[14] the risk of upper GI bleeding after a failed *H. pylori* eradication. The authors performed a large retrospective analysis of 70,518 patients who received a clarithromycin-based triple therapy in Hong Kong and required retreatment for *H. pylori* infection. Patients who required a second treatment had an increased risk of upper GI bleeding (HR: 1.5), which increased progressively with the time to retreatment, in comparison to the reference groups.

The time trends of PUD and RE are associated with *H. pylori* infection. A recent study[15] from Japan focused on the epidemiology of gastroduodenal ulcer and GERD using the records of 211,347 subjects from the general population. Over a 25-year period the author observed a gradual decrease in prevalence of gastric (3.0% to 0.3%) and duodenal ulcer (2.0% to 0.3%), while the rate of RE increased (2.0% to 22%). The multivariable logistic regression analysis revealed a significant positive association between *H. pylori* and ulcers and a negative association with RE. Interestingly, despite the decreasing *H. pylori* infection in the United States, the incidence of PUD showed a subsequent flattening of the decline over the past years[16].

Multiple factors contribute to the development of GI pathologies, including host genetics, environmental factors and *H. pylori* with its virulence factors. Genetic factors are considered to play an important role in the susceptibility to develop GI pathologies, in particular, PUD in relation to *H. pylori*. Wu et al[17] performed a genome-wide association study (GWAS) analysis using data from the UK Biobank of 456,327 individuals. The authors identified 8 loci (MUC1, MUC6, FUT2, PSCA, ABO, CDX2, GAST and CCKBR) that are implicated in the development of GI pathologies. Among those, only two SNPs (PSCA rs2294008 and ABO rs505922) had been previously reported as associated with PUD[18], while the 6 others were not linked with susceptibility to PUD but were known to be related to a major function in the stomach. MUC1, MUC6, and FUT2 have been linked to *H. pylori* susceptibility. PSCA, ABO have been associated with the response after *H. pylori* infection. CCKBR and GAST are involved in stomach physiology with stimulation of hydrochloric acid secretion or gastric motility.

Development of GI pathologies may be triggered by molecular alterations in an *H. pylori*-dependent and independent manner. MicroRNA (miRNAs) are thought to be involved in the pathogenesis of gastritis. In a prospective interventional study, *H. pylori*-infection was associated with increased expression of miR-223, which is enriched in neutrophil granulocytes, and miR-155, which is highly expressed in lymphocytes[19]. *H. pylori* eradication led to a normalization of miR-223, while miR-155 only partially decreased. In correlation to histological PMN-infiltration, PPI therapy revealed an association with lower miR-155 expression in the independent case-control study, suggesting the functional and biomarker role of miRNA in gastric inflammation[19]. To identify a potential biomarker, the trefoil-factor 3 (TFF3) has been studied in *H. pylori*-associated gastric ulcer patients[20]. In the cohort of 40 patients each, with and without gastric ulcer, the level of TFF3 which is involved in gastric mucosa repair was lower in *H. pylori* positive patients and patients with gastric ulcer compared to *H. pylori* negative individuals. However, the receiver operating curve only showed a sensitivity of 67.5% and a specificity of 42.5%, questioning the diagnostic value of TFF3 as potential biomarker.

El Khadir et al[21] evaluated the predictive value of several *H. pylori* virulence factors to predict GI pathology. An analysis of *H. pylori* strains from 823 patients with gastritis, PUD, and gastric cancer revealed that *cag*A+/*cag*E+ strains had up to a 1.97-fold higher risk of PUD while *cag*E+/2EPIYA-C had up to 5.19-fold higher risk of gastric cancer, suggesting that bacterial virulence factors may be used for prediction of *H. pylori*-associated diseases.

With an increasing awareness of the role of gastric microbiota in addition to *H. pylori* infection, more knowledge is necessary to understand the role of gastric microbiota in PUD. At present, no specific species have been identified to contribute to PUD. Devi et al[22] studied the gut microbiome of 375 residents from Trivandrum (Southwestern India), and the subjects were characterized according to *H. pylori* genotype. In comparison to *H. pylori* negative subjects, *H. pylori* positivity was associated with a lower abundance of the genera *Bifidobacterium* and *Bacteroides*, while *Dialister* and *Prevotella* were detected in higher abundance. Most interestingly, patients with a severe form of *H. pylori* gastritis had a very low relative abundance of *Bifidobacterium* species (*Bifidobacterium adolescentis. Bifidobacterium longum*). Although this association does not provide a causality and various factors could have contributed to the alterations, further studies will be needed to define the functional role of *Bifidobacterium* in upper GI pathologies.

GASTRIC POLYPS

The most frequent type of polyps found in the stomach are the fundic gland polyps (FGP). The prevalence of FGP has been linked to various factors and specifically a negative correla-

tion has been observed with *H. pylori* infection. It has been suggested that patients with FGP may have a natural lysozyme present in the gastric juice, which could inhibit the growth of *H. pylori* to a certain extent. In a similar fashion, *H. pylori* infection has been suggested as a protective factor for FGP.

To evaluate the relationship between FGP prevalence and *H. pylori* infection, Notsu et al[23] analyzed 3,400 patients including *H. pylori* positive (n=239), *H. pylori* negative (n=1,617) and patients who underwent *H. pylori* eradication therapy (n=1544). The highest prevalence of FGP was found in *H. pylori* negative patients (51.9%) while only 1.7% of *H. pylori* positive patients had FGP. In comparison, 12% of those with previous *H. pylori* eradication had FGP, and the duration following eradication correlated with the risk of FGP development. The risk of FGP occurrence in individuals who had undergone *H. pylori* eradication treatment remained lower compared to those who were never infected.

Contrary to FGP, hyperplastic polyps have been positively correlated with *H. pylori* infection. To study the direct effect of eradication on hyperplastic polyps, Nam *et al.* performed an open-labeled, single-center, randomized controlled trial[24]. Among 32 patients, 27 completed the study including 14 in the eradication group and 13 in non-eradication group. All patients in the eradication group showed polyp regression, and persistence of *H. pylori* infection was related to progression of the hyperplastic polyps.

IMMUNE THROMBOCYTOPENIA

H. pylori infection has been previously linked to secondary immune thrombocytopenia (ITP). Nevertheless, there is no consensus on a standardized procedure for *H. pylori* testing in patients with ITP. An international survey was performed to evaluate the patterns of practice with respect to screening and treatment of *H. pylori*[25]. The result from 186 responders representing 39 countries showed that only 29% of the responders routinely tested for *H. pylori* in ITP patients while 53% did it inconsistently. Patients in Asia and those with GI symptoms were more likely to be tested. The testing was more common overall in Asia, highlighting the variation in ITP management across different geographic regions.

The long-term effect of *H. pylori* in ITP subjects was studied in South Korea[26]. *H. pylori* prevalence was 54.3% in this cohort. Patients with successful eradication using a first-line treatment had a 2.78-fold increase in platelet count compared to the baseline, while a 1.36-fold and 1.33-fold increase was documented in a group with failed eradication and an *H. pylori* negative group, respectively. These results clearly suggest that all *H. pylori* positive patients may benefit from eradication.

CELIAC DISEASE

The mechanistic data on possible interfering between *H. pylori* and celiac disease (CD) remains lacking and existing evidence is largely supported by the association observed in cohort studies. Bayrak et al[27] compared a cohort of 482 CD patients (mean 9.71 years) with 2,060 controls. The rate of *H. pylori* infection was high in this cohort from Turkey. Consistent with previous reports, the positivity was significantly lower in the CD group (26.3%) compared to the controls (50.1%). No correlation was observed between *H. pylori* infection and the modified Marsh scores in CD.

The results of a meta-analysis on 26 studies with a total of 6,001 cases and 135,512 controls demonstrated the negative association between *H. pylori* colonization and CD (pooled OR: 0.56; 95%CI: 0.45-0.70; $p<0.001$)[28]. Gungor et al[29] to evaluated the effect of *H. pylori* eradication on serology and mucosal changes in children with CD. They analyzed anti-tissue transglutaminase and endomysium antibody levels, histology before and after *H. pylori* eradication in subjects with potential CD and histologically confirmed CD. The authors show that the anti-tissue transglutaminase and endomysium antibody levels decreased significantly after *H. pylori* eradication therapy in *H. pylori* positive potential CD but the change in the *H. pylori* negative potential CD group was less prominent (n=8 in each group). Furthermore, more severe mucosal injury including Marsh 2, 3 was present in *H. pylori* infected subjects.

Based on those results the authors conclude that *H. pylori* eradication may be an important primary step prior to further CD management, especially before the initiation of the gluten-free diet. However, the last point has not been studied in cases of confirmed CD and it remains rather speculative whether the *H. pylori* eradication might provide any additional benefit with the focus on small bowel mucosa in histologically confirmed CD.

Acknowledgements

A.L. is supported by funds from the European Commission, as part of the "European funds for regional development" (EFRE), as well as by the regional Ministry of Economy, Science and Digitalization as part of the "Autonomie im Alter" research group for "LiLife"-Project.

Conflict of interest

The authors have no potential conflicts to declare.

REFERENCES

1. Gravina AG, Priadko K, Ciamarra P, Granata L, Facchiano A, Miranda A, Dallio M, Federico A, Romano M. Extra-Gastric Manifestations of *Helicobacter pylori* Infection. J Clin Med 2020; 9: 3887.
2. Imamura K, Haruma K, Matsumoto H, Maruyama Y, Ayaki M, Tazaki S, Hisamoto N, Manabe N, Kamada T, Kawamoto H. Clinical and endoscopic characteristics of eosinophilic esophagitis in Japan: a case-control study. Asia Pac Allergy 2020; 10: e16.
3. Annavajhala MK, May M, Compres G, Freedberg DE, Graham R, Stump S, Que J, Korem T, Uhlemann AC, Abrams JA. Relationship of the Esophageal Microbiome and Tissue Gene Expression and Links to the Oral Microbiome: A Randomized Clinical Trial. Clin Transl Gastroenterol 2020; 11: e00235.
4. Johnson J, Dellon ES, McCoy AN, Sun S, Jensen ET, Fodor AA, Keku TO. Lack of association of the esophageal microbiome in adults with eosinophilic esophagitis compared with non-EoE controls. J Gastrointestin Liver Dis 2021; 30: 17-24.
5. Laserna-Mendieta EJ, FitzGerald JA, Arias-Gonzalez L, Ollala JM, Bernardo D, Claesson MJ, Lucendo AJ. Esophageal microbiome in active eosinophilic esophagitis and changes induced by different therapies. Sci Rep 2021; 11: 7113.
6. Doulberis M, Kountouras J, Rogler G. Reconsidering the "protective" hypothesis of *Helicobacter pylori* infection in eosinophilic esophagitis. Ann N Y Acad Sci 2020; 1481: 59-71.
7. Sonnenberg A, Turner KO, Singhal A, Genta RM. Prevalence and concordant occurrence of esophageal, gastric, duodenal, and colonic eosinophilia. Dis Esophagus 2020; 33: doaa064.
8. Sugimoto M, Murata M, Mizuno H, Iwata E, Nagata N, Itoi T, Kawai T. Endoscopic Reflux Esophagitis and Reflux-Related Symptoms after *Helicobacter pylori* Eradication Therapy: Meta-Analysis. J Clin Med 2020; 9: 3007.
9. Mou WL, Feng MY, Hu LH. Eradication of *Helicobacter Pylori* Infections and GERD: A systematic review and meta-analysis. Turk J Gastroenterol 2020; 31: 853-859.
10. Zhao Y, Li Y, Hu J, Wang X, Ren M, Lu G, Lu X, Zhang D, He S. The Effect of *Helicobacter pylori* Eradication in Patients with Gastroesophageal Reflux Disease: A Meta-Analysis of Randomized Controlled Studies. Dig Dis 2020; 38: 261-268.
11. Usui G, Shinozaki T, Jinno T, Fujibayashi K, Morikawa T, Gunji T, Matsuhashi N. Relationship between time-varying status of reflux esophagitis and *Helicobacter pylori* and progression to long-segment Barrett's esophagus: time-dependent Cox proportional-hazards analysis. BMC Gastroenterol 2020; 20: 270.
12. Usui G, Sato H, Shinozaki T, Jinno T, Fujibayashi K, Ishii K, Horiuchi H, Morikawa T, Gunji T, Matsuhashi N. Association Between *Helicobacter pylori* Infection and Short-segment/Long-segment Barrett's Esophagus in a Japanese Population: A Large Cross-Sectional Study. J Clin Gastroenterol. 2020; 54: 439-444.
13. Adachi K, Ishimura N, Kishi K, Notsu T, Mishiro T, Sota K, Ishihara S. Prevalence of Barrett's Epithelium Shown by Endoscopic Observations with Linked Color Imaging in Subjects with Different H. pylori Infection Statuses. Intern Med 2021; 60: 667-674.
14. Guo CG, Cheung KS, Zhang F, Chan EW, Chen L, Wong ICK, Leung WK. Delay in Retreatment of *Helicobacter pylori* Infection Increases Risk of Upper Gastrointestinal Bleeding. Clin Gastroenterol Hepatol 2021; 19: 314-322.e2.
15. Yamamichi N, Yamaji Y, Shimamoto T, Takahashi Y, Majima K, Wada R, Mitsushima T, Koike K. Inverse time trends of peptic ulcer and reflux esophagitis show significant association with reduced prevalence of *Helicobacter pylori* infection. Ann Med 2020; 52: 506-514.
16. Guo H, Lam AY, Shaheen AA, Forbes N, Kaplan GG, Andrews CN, Laffin M, Singh S, Jairath V, Teriaky A, Lee JK, Ma C. Urban-Rural Disparities and Temporal Trends in Peptic Ulcer Disease Epidemiology, Treatment, and Outcomes in the United States. Am J Gastroenterol 2021; 116: 296-305.
17. Wu Y, Murray GK, Byrne EM, Sidorenko J, Visscher PM, Wray NR. GWAS of peptic ulcer disease implicates *Helicobacter pylori* infection, other gastrointestinal disorders and depression. Nat Commun 2021; 12. doi:10.1038/s41467-021-21280-7

18. Wu Y, Murray GK, Byrne EM, Sidorenko J, Visscher PM, Wray NR. GWAS of peptic ulcer disease implicates *Helicobacter pylori* infection, other gastrointestinal disorders and depression. Nat Commun 2021; 12: 1146.
19. Vasapolli R, Venerito M, Schirrmeister W, Thon C, Weigt J, Wex T, Malfertheiner P, Link A. Inflammatory microRNAs in gastric mucosa are modulated by *Helicobacter pylori* infection and proton-pump inhibitors but not by aspirin or NSAIDs. PLoS One 2021; 16: e0249282.
20. Ramadan RA, Zaki MA, Ooda SA, Abo Khalifa HM, Ragab WS. Comparison of Serum Trefoil Factor-3 to Endoscopy in Diagnosing *Helicobacter Pylori* Associated Gastric Ulcer. Asian Pac J Cancer Prev 2020; 21: 2149-2153.
21. El Khadir M, Boukhris SA, Zahir SO, Benajah DA, Ibrahimi SA, Chbani L, El Abkari M, Bennani B. CagE, cagA and cagA 3' region polymorphism of *Helicobacter pylori* and their association with the intra-gastric diseases in Moroccan population. Diagn Microbiol Infect Dis 2021; 100: 115372.
22. Devi TB, Devadas K, George M, Gandhimathi A, Chouhan D, Retnakumar RJ, Alexander SM, Varghese J, Dharmaseelan S, Chandrika SK, Jissa VT, Das B, Nair GB, Chattopadhyay S. Low Bifidobacterium Abundance in the Lower Gut Microbiota Is Associated With *Helicobacter pylori*-Related Gastric Ulcer and Gastric Cancer. Front Microbiol 2021; 12: 631140.
23. Notsu T, Adachi K, Mishiro T, Ishimura N, Ishihara S. Fundic gland polyp prevalence according to *Helicobacter pylori* infection status. J Gastroenterol Hepatol 2020; 35: 1158-1162.
24. Nam SY, Lee SW, Jeon SW, Kwon YH, Lee HS. *Helicobacter pylori* Eradication Regressed Gastric Hyperplastic Polyp: A Randomized Controlled Trial. Dig Dis Sci 2020; 65: 3652-3659.
25. Vishnu P, Duncan J, Connell N, Cooper N, Lim W, Rodeghiero F, Tomiyama Y, Grace RF, Bakchoul T, Arnold DM; Platelet Immunology Scientific, Standardization Committee. International survey on *Helicobacter pylori* testing in patients with immune thrombocytopenia: Communication of the platelet immunology scientific and standardization committee. J Thromb Haemost 2021; 19: 287-296.
26. Lee A, Hong J, Chung H, Koh Y, Cho SJ, Byun JM, Kim SG, Kim I. *Helicobacter pylori* eradication affects platelet count recovery in immune thrombocytopenia. Sci Rep 2020; 10: 9370.
27. Bayrak NA, Tutar E, Volkan B, Sahin Akkelle B, Polat E, Kutluk G, Ertem D. *Helicobacter pylori* infection in children with celiac disease: Multi-center, cross-sectional study. Helicobacter 2020; 25: e12691.
28. Amlashi FI, Norouzi Z, Sohrabi A, Shirzad-Aski H, Norouzi A, Ashkbari A, Gilani N, Fatemi SA, Besharat S. A systematic review and meta-analysis for association of *Helicobacter pylori* colonization and celiac disease. PLoS One 2021; 16: e0241156.
29. Gungor S, Köylü AA. Effects of *Helicobacter Pylori* Infection on Serology and Intestinal Mucosal Changes in Pediatric Patients With Celiac Disease: A Retrospective Cohort Study. Cureus 2020; 12: e11134.