Judishapur Journal of Oncology (JJO)

Original Article

The Association Between *H. pylori* Antibodies as a Risk of Gastric Cancer and Vitamin D Levels

Mehrdad Haghighi[1], Amir Mohammad Alborzi[2], Reza Ghanbari[3*]

1. Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Cancer Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
3. Digestive Oncology Research Center, Digestive Diseases Research Institute, Tehran University of Medical Science, Tehran, Iran.

Use your device to scan and read the article online

Citation Haghighi M, Alborzi AM, Ghanbari R. The Association Between H. pylori Antibodies as a Risk of Gastric Cancer and Vitamin D Levels. Judishapur Journal of Oncology. 2016; 2(2):38-44. http://dx.doi.org/10.32598/jjo.20.2.3

http://dx.doi.org/10.32598/jjo.20.2.3

ABSTRACT

Objectives: *Helicobacter pylori* (*H. pylori*) infection is a significant cause of chronic gastritis. Various studies have reported a link between *H. pylori* and vitamin D levels. Most showed the effect of serum levels of 25 hydroxy vitamin D (25[OH]D) on the eradication of *H. pylori* infection. In the present study, we aimed to assess the association between vitamin D serum levels and various types of antibodies against *H. pylori* infection. It is well recognized that *H. pylori* infection is the most important risk factor for gastric adenocarcinoma. Furthermore, vitamin D deficiency may be associated with a poor prognosis in gastric cancer.

Methods: In the present laboratory-based retrospective study, the medical records of random individuals referred for screening to the Negaresh Pathobiology Laboratory in Tehran, Iran, from 2019 to 2021 were retrospectively reviewed. A total of 196 subjects were eligible for evaluation and were enrolled. The serum concentration of Vitamin D was determined quantitatively via a fully automated enzyme-linked immunosorbent assay (ELISA), and *H. pylori* IgG, IgM, and IgA antibodies were analyzed quantitatively by using the ELISA microplate reader.

Results: According to our results, the serum levels of 25(OH)D did not change significantly in different groups of patients with different levels of *H. pylori* IgG, IgM, and IgA antibodies.

Discussion: The relationship between vitamin D and *H. pylori* remains to be determined. In conclusion, no significant relationship was identified between the level of vitamin D and the amount of different anti-H pylori antibodies, including IgG, IgM, and IgA.

Keywords: Anti-*Helicobacter pylori* antibody, *Helicobacter pylori*, Vitamin D

Article info:
Received: 13 Sep 2016
Accepted: 11 Oct 2016
Available Online: 01 Dec 2016

*** Corresponding Author:**
Reza Ghanbari, PhD.
Address: *Digestive Oncology Research Center, Digestive Diseases Research Institute, Tehran University of Medical Science, Tehran, Iran.*
Tel: *+98 (21) 82415225*
E-mail: *r.ghanbari98@gmail.com*

1. Background

Gastric cancer is the second leading cause of cancer-related mortality worldwide, accounting for 10% of all cancer-related deaths [1]. The risk of gastric cancer is three to six times higher in people with *H. pylori* infection than in non-infected population [2]. *H. pylori* has been revealed to play a prominent role in gastric inflammation and carcinogenesis via producing various virulence factors and dysregulating intracellular signaling pathways such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) in hosts [3].

Helicobacter pylori (*H. pylori*) infection is a significant cause of chronic gastritis [4]. This gram-negative bacterium affects 50% of the world's population. If not treated effectively, it can continue to live throughout the host's life, leading to several diseases, including gastric and gastroduodenal ulcers, dysplasia, and gastric cancer [5]. Many factors can affect *H. pylori* infection. Previous studies have shown that *H. pylori* infection can be related to the geographical situation and the average daily sun, and it is speculated that the leading cause is vitamin D deficiency [6]. Vitamin D is the main regulator of the immune system and is widely known for bone metabolism. It also plays an essential role in target tissues [7]. Several studies have shown an association between vitamin D and *H. pylori* infection, as well as an association between the eradication of this infection and vitamin D levels [8].

As mentioned before, *H. pylori* is an important pathogen in the development of gastric malignancies, and it is suggested that the eradication of this pathogen from the human stomach can be considered a possible prophylactic factor against the formation of gastric cancer [9]. Studies have shown that adequate vitamin D levels are associated with a reduction in *H. pylori* infection, and its high concentrations can also be linked to a reduced risk of gastric cancer [10]. Furthermore, Vyas et al. in a retrospective study revealed that patients with reduced vitamin D have a further chance of developing gastric adenocarcinoma [11].

The easiest and cheapest way to make a non-invasive diagnosis of *H. pylori* infection is by identifying the various types of antibodies (IgM, IgG, and IgA) against this infectious agent. The most commonly used serological test is the Enzyme-Linked Immunosorbent Assay (ELISA) method, which is also used for large population screening [12]. Many studies have been conducted to identify the association between the anti-*H. pylori* antibodies level and severity of histological gastritis or *H. pylori* density, but the results have not always been the same and sometimes conflicting [13-16]. To get a more convincing result, in the present study, we aimed to conduct a retrospective analysis to identify any association between the serum levels of vitamin D with different amounts of various types of antibodies (IgM, IgG, and IgA) against *H. pylori* infection.

2. Materials and Methods

Study population

In the present laboratory-based retrospective study, the medical records of individuals referred to Negaresh Pathobiology Laboratory in Tehran for screening tests from February 2019 to April 2021 were retrospectively reviewed. A total of 500 medical records were evaluated for the present study. After removing records with missing data, additional information, or other exclusion criteria, 196 cases were finally eligible for evaluation and were enrolled in the study. Then, all data related to the levels of different types of antibodies (IgM, IgG, and IgA) against *H. pylori* infection in these cases were collected so that the relationship between vitamin D levels and antibody levels could be evaluated as well.

Serum concentration of vitamin D3

The serum 25(OH)D concentration was measured using an ELISA test. All the steps were performed according to the instructions of the EUROIMMUN-ELISA kit (Medizinische Labordiagnostika AG, Germany) at the Negaresh Pathobiology Laboratory (Tehran, Iran). The EUROIMMUN 25-OH Vitamin D ELISA assay is an optimized and reliable method for detecting 25-OH vitamin D3 and consists of an ELISA microwell plate coated with monoclonal anti-25(OH)D antibodies. This method has been designed for in vitro analysis of 25(OH)D in human serum or plasma samples.

Anti-*H. pylori* antibodies

Blood samples of all participants were taken, and then the serum was used to measure levels of anti-*Helicobacter pylori* IgG and IgA and IgM using an indirect ELISA kit (Diagnostic kit, Pishtaz Teb Company, Tehran, Iran), according to the manufacturer's instructions. Reference standards have been applied to make a standard curve to quantitate *H. pylori* antibody levels in individuals' serum specimens.

Statistical analysis

The data obtained from the history, clinical examination, and investigations were statistically analyzed using the STATA 12. Mean, and Standard Deviation (SD) were used to identify the data related to the continuous variables. The comparison of the variables (without normal distribution) was performed with the Mann-Whitney U test. We categorized all three *H. pylori* antibodies into two main positive and negative categories using 12 AU/mL as the cut-off value. The Vitamin D variable was also categorized into deficient (less than 25 nmol/mL) and normal groups (more than 12 nmol/mL). The categorical variables were compared with the Pearson's χ^2 test, and a P value less than 0.05 was considered statistically significant.

3. Results

Based on the medical history of individuals referred to Negaresh Pathobiology Laboratory, 196 individuals with identified vitamin D data were selected for this study. The average age of these people was 42.5 years, of whom 111 (56.63%) were females. The exclusion criteria were as follows: having children below 6 years old, using antibiotics during the last 3 months, using vitamin D supplementation, and having substance abuse disorder. All participants were of the same racial and ethnic backgrounds. The demographic data of these individuals and the average level of their vitamin D and anti-H pylori IgG, IgM, and IgA antibodies are presented in Table 1. Our results revealed that the levels of vitamin D were not significantly different in various amounts of IgM, IgG, and IgA against *H. pylori* infection.

According to the obtained results, vitamin D levels did not differ significantly between the individuals with different high and low levels of anti-*H. pylori* IgG (P=0.368), IgM (P=0.661) and IgA (P=0.054) antibodies groups.

Based on Pearson's χ^2 test, normal and deficient groups of vitamin D did not associate significantly with positive or negative groups of anti-*H. pylori* antibodies: IgG (P=0.507), IgM (P=0.067) and IgA (P=0.781). The scatter plots in Figures 1, 2, and 3 demonstrate the association between vitamin D levels and *H. pylori* antibody levels.

4. Discussion

Stomach colonization with *H. pylori* is one of the most important risk factors for gastric cancer [17]. This cancer is a multistep and multifactorial process. The underlying cause of gastric cancer is not yet fully understood. However, several environmental factors, such as *H. pylori*, as a chronic gastritis metaplasia agent, are associated with different stages of gastric cancer [18].

Several studies have been conducted to determine whether vitamin D has a preventive function on various cancers, but the results have been contradictory. However, vitamin D has significantly enhanced the apoptosis rate in gastric cancer cell line [19]. In addition, vitamin D can also induce differentiation and cell cycle arrest in several cancer cells, such as colon, breast, and prostate cancers [20, 21].

Infection with *H. pylori* stimulates the cell proliferation of gastric epithelium and eventually induces apoptosis in these cells. An imbalance between cell proliferation and apoptosis can cause cell mutations [22]. The main cause of *H. pylori*-induced gastritis is increased infiltration in the inflammatory cells, which is usually the first detectable change in these patients [23, 24]. *H. pylori* in-

Table 1. Characteristics, vitamin D and anti-*H. pylori* antibody levels of included individuals

Variables		No.	Mean±SD	Min	Max
Age (y)		196	42.54±16.96	7	94
Vitamin D level (nmol/ml)		196	29.38±9.77	9.1	51.8
Anti-*H. pylori* IgG antibody (AU/ml)		166	23.75±35.5	0.4	149.7
Anti-*H. pylori* IgM antibody (AU/ml)		79	8.6±12.6	0.186	73.9
Anti-*H. pylori* IgA antibody (AU/ml)		106	10.54±17.76	0.7	145.23
Gender	Male	58 (43.37%)	-	-	-
	Female	111 (56.63%)	-	-	-

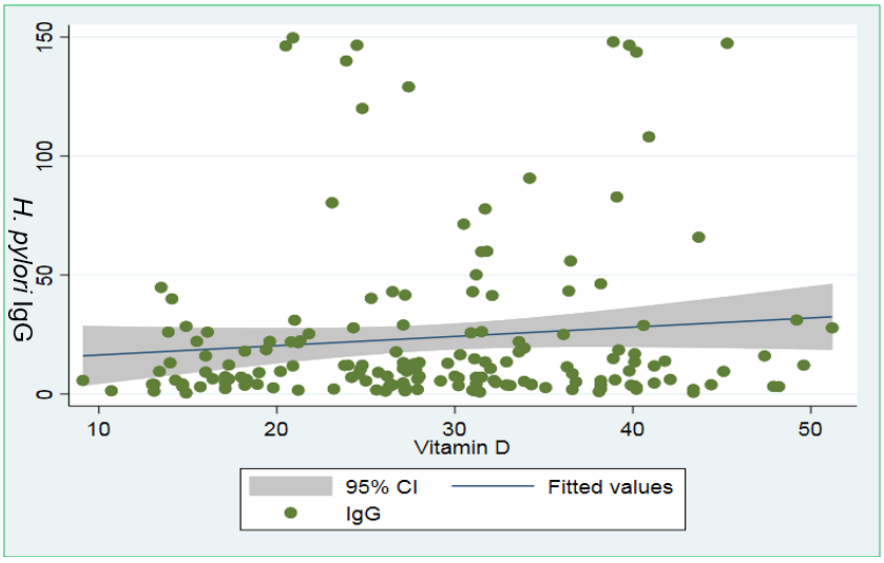

Figure 1. Association between vitamin D levels and *H. pylori* IgG antibody levels

According to the result, there is no significant relationship between the levels of vitamin D and *H. pylori* IgG antibody (Correlation coefficient=0.104, P=0.181).

fection has become a public health issue that has drawn the attention of many researchers. *H. pylori* gastritis is an infectious disease transmitted through the oral-oral or fecal-oral routes. This infectious agent can be detected in dental plaques, human and animal feces, and natural environmental waters [25]. Eradication of the *H. pylori* infection has been reported as an effective strategy for the treatment of gastritis and gastric ulcer as well as the prevention of gastric cancer [26, 27].

Urea breath tests, serum levels of anti-*H. pylori* antibodies, stool antigen tests, rapid urease tests, culture, and pathology are the most important diagnostic methods for *H. pylori* infection [28]. Diagnostic tests based on serum anti-*H. pylori* antibodies are inexpensive and easy, and the existing commercial kits of these serological tests have high accuracy, sensitivity, and specificity for diagnosing this infection [29].

In the present retrospective study, we evaluated the association between vitamin D levels and levels of different

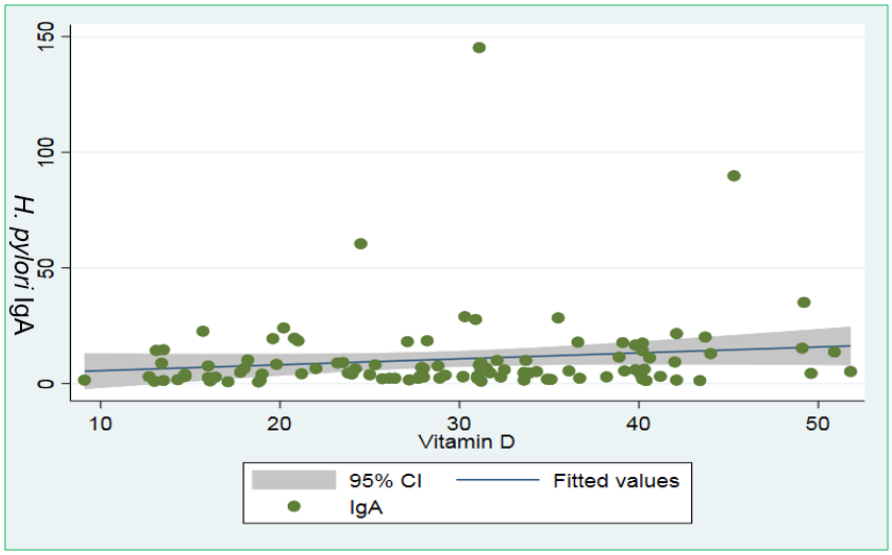

Figure 2. Association between vitamin D levels and *H. pylori* IgA antibody levels

According to the result, there is no significant relationship between the levels of vitamin D and *H. pylori* IgA antibody (Correlation coefficient=0.145, P=0.137).

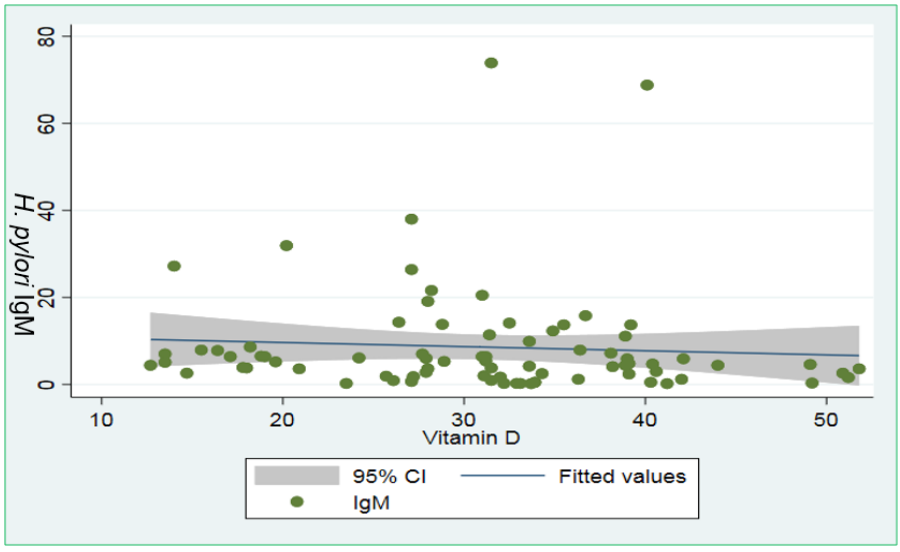

Figure 3. Association between vitamin D levels and *H. pylori* IgM antibody levels

Judishapur Journal of Oncology (JJO)

According to the results, there is no significant relationship between the levels of vitamin D and *H. pylori* IgM antibody (Correlation coefficient=0.071, P=0.533).

anti-*H. pylori* antibodies (IgG, IgM, and IgA) separately to identify any significant relationship. As discussed above, according to the obtained results, no significant relationship was identified between the vitamin D level in individuals and the amount of different anti-*H. pylori* antibodies, including IgG, IgM, and IgA.

In research and clinical studies, there is still debate on the relationship between vitamin D levels and *H. pylori* infection, especially about the effect of vitamin D on eradicating *H. pylori* infection. However, the relationship between vitamin D and *H. pylori* remains to be determined. In a recent meta-analysis study by Yang et al., they collected published articles on vitamin D association with *H. pylori* infection to substantiate adequate evidence on the relationship between vitamins D and *H. pylori* infection, as well as vitamin D and *H. pylori* eradication [8]. The results of this review showed that patients with *H. pylori* infection had lower levels of vitamin D. In addition, patients who had successful eradication of *H. pylori* infection had higher levels of serum vitamin D, and conversely, those with vitamin D deficiency had lower rates of success in eradicating *H. pylori* infection. Eventually, it was revealed that vitamin D could be an important protective factor against *H. pylori* infection [8]. Surmeli et al., in another recent related study, reported that vitamin D deficiency could be associated with an increased risk of *H. pylori* infection. Furthermore, they also stated that the potential protective effect of vitamin D against *H. pylori* infection and its possible role in the treatment of *H. pylori* should be evaluated in future trials [30]. In a previous similar study, El Shahawy et al. examined the effect of serum levels of 25-hydroxy-vitamin D on eradication rates of *H. pylori* infection. They also have demonstrated that vitamin D deficiency can be considered a risk factor related to eradication failure of *H. pylori* infection.

5. Conclusion

The relationship between vitamin D and *H. pylori* has remained to be determined. In conclusion, in the present study, we have identified no significant relationship between the serum level of vitamin D and the amount of different anti-*H. pylori* antibodies, including IgG, IgM, and IgA.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This study was supported financially by the Negaresh Pathobiology Laboratory, Tehran, Iran, and was carried out in collaboration with the Shahid Beheshti and Tehran universities of medical sciences, Tehran, Iran.

Authors' contributions

Conceptualization and supervision: Reza Ghanbari; Methodology: Mehrdad Haghighi, Amir Mohammad

Alborzi; Investigation, writing – original draft, and writing – review & editing: All authors; Data collection: Mehrdad Haghighi, Amir Mohammad Alborzi; Data analysis: Mehrdad Haghighi, Reza Ghanbari.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

We thank the staff of the Negaresh Pathobiology Laboratory, Tehran, Iran, for assistance with this project.

References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: A Cancer Journal For Clinicians. 2011; 61(2):69-90. [DOI:10.3322/caac.20107] [PMID]

[2] Kim SS, Ruiz VE, Carroll JD, Moss SF. *Helicobacter pylori* in the pathogenesis of gastric cancer and gastric lymphoma. Cancer Letters. 2011; 305(2):228-38. [DOI:10.1016/j.canlet.2010.07.014] [PMID] [PMCID]

[3] Sgouras D, Tegtmeyer N, Wessler S. Activity and functional importance of *Helicobacter pylori* virulence factors. *Helicobacter pylori* in Human Diseases. 2019:35-56. [DOI:10.1007/5584_2019_358] [PMID]

[4] Fontham ET, Ruiz B, Perez A, Hunter F, Correa P. Determinants of *Helicobacter pylori* infection and chronic gastritis. American Journal of Gastroenterology (Springer Nature). 1995; 90(7):1094-101. [Link]

[5] Jonaitis L, Pellicano R, Kupcinskas L. *Helicobacter pylori* and nonmalignant upper gastrointestinal diseases. Helicobacter. 2018; 23:e12522. [DOI:10.1111/hel.12522] [PMID]

[6] Lu C, Yu Y, Li L, Yu C, Xu P. Systematic review of the relationship of *Helicobacter pylori* infection with geographical latitude, average annual temperature and average daily sunshine. BMC Gastroenterology. 2018; 18(1):1-9. [DOI:10.1186/s12876-018-0779-x] [PMID] [PMCID]

[7] Bouillon R, Carmeliet G, Verlinden L, Van Etten E, Verstuyf A, Luderer HF, Lieben L, Mathieu C, Demay M. Vitamin D and human health: Lessons from vitamin D receptor null mice. Endocrine Reviews. 2008; 29(6):726-76. [DOI:10.1210/er.2008-0004] [PMID] [PMCID]

[8] Yang L, He X, Li L, Lu C. Effect of vitamin D on *Helicobacter pylori* infection and eradication: A meta-analysis. Helicobacter. 2019; 24(5):e12655. [DOI:10.1111/hel.12655] [PMCID]

[9] Sugano K. Effect of *Helicobacter pylori* eradication on the incidence of gastric cancer: A systematic review and meta-analysis. Gastric Cancer. 2019; 22(3):435-45. [DOI:10.1007/s10120-018-0876-0]

[10] Kwak JH, Paik JK. Vitamin D status and gastric cancer: A cross-sectional study in Koreans. Nutrients. 2020; 12(7):2004. [DOI:10.3390/nu12072004]

[11] Vyas N, Companioni RC, Tiba M, Alkhawam H, Catalano C, Sogomonian R, et al. Association between serum vitamin D levels and gastric cancer: A retrospective chart analysis. World Journal of Gastrointestinal Oncology. 2016; 8(9):688. [DOI:10.4251/wjgo.v8.i9.688]

[12] Ofman JJ, Etchason J, Fullerton S, Kahn KL, Soll AH. Management strategies for *Helicobacter pylori*-seropositive patients with dyspepsia: Clinical and economic consequences. Annals of Internal Medicine. 1997; 126(4):280-91. [DOI:10.7326/0003-4819-126-4-199702150-00004] [PMID]

[13] Sheu BS, Shiesh SC, Yang HB, Su IJ, Chen CY, Lin XZ. Implications of *Helicobacter pylori* serological titer for the histological severity of antral gastritis. Endoscopy. 1997; 29(01):27-30. [DOI:10.1055/s-2007-1004057] [PMID]

[14] Sim JG, Kim CJ, Seo JK. The value of *Helicobacter pylori* IgG antibody in estimating the severity of gastritis in children. Journal of Korean Medical Science. 1995; 10:329-33. [DOI:10.3346/jkms.1995.10.5.329] [PMID] [PMCID]

[15] Yamamoto I, Fukuda Y, Mizuta T, Fukada M, Nishigami T, Shimoyama T. Serum anti-*Helicobacter pylori* antibodies and gastritis. Journal of Clinical Gastroenterology. 1995; 21:S164-8. [PMID]

[16] Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. *Helicobacter pylori* infection and the development of gastric cancer. The New England Journal of Medicine. 2001; 345(11):784-9. [DOI:10.1056/NEJMoa001999] [PMID]

[17] Correa P. Human gastric carcinogenesis: A multistep and multifactorial process—first American Cancer Society award lecture on cancer epidemiology and prevention. Cancer Research. 1992; 52(24):6735-40. [Link]

[18] Pan L, Matloob AF, Du J, Pan H, Dong Z, Zhao J, Feng Y, Zhong Y, Huang B, Lu J. Vitamin D stimulates apoptosis in gastric cancer cells in synergy with trichostatin A/sodium butyrate-induced and 5-aza-2′-deoxycytidine-induced PTEN upregulation. The FEBS Journal. 2010; 277(4):989-99. [DOI:10.1111/j.1742-4658.2009.07542.x] [PMID]

[19] Polek TC, Weigel NL. Vitamin D and prostate cancer. Journal of Andrology. 2002; 23(1):9-17. [DOI:10.1002/j.1939-4640.2002.tb02596.x] [PMID]

[20] Holick MF. Vitamin D: Importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. American Journal of Clinical Nutrition. 2004; 79(3):362-71. [DOI:10.1093/ajcn/79.3.362] [PMID]

[21] Kerr JF, Winterford CM, Harmon BV. Apoptosis. Its significance in cancer and cancer therapy. Cancer. 1994; 73(8):2013-26. [DOI:10.1002/1097-0142(19940415)73:83.0.CO;2-J]

[22] Kronsteiner B, Bassaganya-Riera J, Philipson C, Viladomiu M, Carbo A, Abedi V, et al. Systems-wide analyses of mucosal immune responses to *Helicobacter pylori* at the interface between pathogenicity and symbiosis. Gut Microbes. 2016; 7(1):3-21. [DOI:10.1080/19490976.2015.1116673] [PMID] [PMCID]

[23] Bagheri N, Salimzadeh L, Shirzad H. The role of T helper 1-cell response in Helicobacter pylori-infection. Microbial Pathogenesis. 2018; 123:1-8. [DOI:10.1016/j.micpath.2018.06.033] [PMID]

[24] Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al. Kyoto global consensus report on *Helicobacter pylori* gastritis. Gut. 2015; 64(9):1353-67. [DOI:10.1136/gutjnl-2015-309252] [PMID] [PMCID]

[25] Lee YC, Chiang TH, Chou CK, Tu YK, Liao WC, Wu MS, et al. Association between *Helicobacter pylori* eradication and gastric cancer incidence: A systematic review and meta-analysis. Gastroenterology. 2016; 150(5):1113-24. e5. [DOI:10.1053/j.gastro.2016.01.028] [PMID]

[26] Sakitani K, Nishizawa T, Arita M, Yoshida S, Kataoka Y, Ohki D, et al. Early detection of gastric cancer after *Helicobacter pylori* eradication due to endoscopic surveillance. Helicobacter. 2018; 23(4):e12503. [DOI:10.1111/hel.12503] [PMID] [PMCID]

[27] Nishizawa T, Suzuki H. Mechanisms of *Helicobacter pylori* antibiotic resistance and molecular testing. Frontiers in Molecular Biosciences. 2014; 1:19. [DOI:10.3389/fmolb.2014.00019] [PMID] [PMCID]

[28] Talley N, Kost L, Haddad A, Zinsmeister A. Comparison of commercial serological tests for detection of *Helicobacter pylori* antibodies. Journal of Clinical Microbiology. 1992; 30(12):3146-50. [DOI:10.1128/jcm.30.12.3146-3150.1992] [PMID] [PMCID]

[29] Surmeli DM, Surmeli ZG, Bahsi R, Turgut T, Oztorun HS, Atmis V, et al. Vitamin D deficiency and risk of *Helicobacter pylori* infection in older adults: A cross-sectional study. Aging Clinical and Experimental Research. 2019; 31(7):985-91. [DOI:10.1007/s40520-018-1039-1] [PMID]

[30] El Shahawy MS, Hemida MH, El Metwaly I, Shady ZM. The effect of vitamin D deficiency on eradication rates of *Helicobacter pylori* infection. JGH Open. 2018; 2(6):270-5. [DOI:10.1002/jgh3.12081] [PMID] [PMCID]