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Association between *Helicobacter pylori* colonization and infection with anemia and diabetes

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Abstract

This study aimed to compare the incidence of anemia and diabetes between *Helicobacter pylori* (*H. pylori*) seropositive patients with those who were seronegative. *H. pylori* is an important pathogen that causes gastrointestinal disorders. In addition to gastrointestinal complications, *H. pylori* infection also could cause extra-digestive diseases including idiopathic thrombocytopenic purpura. This retrospective cross-sectional study was conducted on collected data from patients who had anti-*H. pylori* serological tests with no history of *H. pylori* peptic ulcer disease and treatment for anemia and diabetes. We evaluated the laboratory data of 140 patients with anti-*H. pylori* serological tests that 74 patients of them (53%) were categorized as seropositive and 66 (47%) were included in the seronegative group. We detected no significant difference between the two groups in the incidence of anemia, neither for male ($x^2(1, N=65)=0.380$, $p=0.538$) nor females ($x^2(1, N=75)=0.326$, $p=0.568$). Ferritin levels also showed no significant difference between the 2 groups in both males ($p=0.754$) and females ($p=0.133$). In the evaluation of the incidence of diabetes in seropositive patients, we also observed no significant differences compared to seronegative subjects ($x^2(1, N=140) =0.557$, $p=0.456$). Our findings indicated that *H. pylori* was not a main reason for anemia, in the population without significant upper gastrointestinal source of blood loss, or peptic ulcer disease, nor diabetes

Keywords: *Diabetes Mellitus, Anemia, Serologic Tests, Ferritins, Helicobacter pylori,*

Introduction

Helicobacter pylori (*H. pylori*) as a true pathogen, is responsible for various gastrointestinal disorders. Although *H. pylori* could result in different stages of gastritis, atrophy, metaplasia, and dysplasia of gastric mucosa and also mucosa-associated lymphoid tissue lymphoma, its infection may remain asymptomatic in most infected persons (1, 2). The prevalence of *H. pylori* infection was reported in 34.7% and 50.8% of in developed countries and developing countries respectively (2). The gold standard method to diagnose *H. pylori* infection is culture, but non-invasive laboratory methods particularly serologic tests are more comfortable for most patients (3). Serologic tests consist of the measurement of the serum anti-*H. pylori* immunoglobulins (IgG, IgM, and IgA) levels (3, 4). The assessment of the efficacy of these serologic tests to detect *H. pylori* infection showed that the IgG was a valid serological experiment for the diagnosis of *H. pylori* related infection with the highest sensitivity (75.75%) and accuracy (68.60%). The IgM had the highest specificity (94.73%) but the lowest sensitivity (5.97%). The sensitivity and specificity of IgA were moderate (33.33% and 80%, respectively) (3). Serum IgG and IgA could consider as good indicators to evaluate the severity of the Gastrointestinal (GI) complications of *H. pylori* (3-5).

The *H. pylori* infection could cause extra-digestive diseases by leading to systemic diffusion of proinflammatory cytokines (6). The association between *H. pylori* infection with hematological diseases including vitamin B12 deficiency, idiopathic thrombocytopenic purpura, and iron deficiency anemia (IDA) (7-9), ischemic heart disease (10), autoimmune thyroid diseases (11), neurologic diseases (12-14), hepatobiliary diseases (15), and type 2 diabetes mellitus (T2DM) (6) has been reported in some studies.

Methods

This study aimed to compare the incidence of anemia and diabetes among *H. pylori* seropositive patients with those who were seronegative.

Study design and data collection

This research was performed on collected data from patients who had anti-*H. pylori* serological tests and had been referred to a clinic in Tehran, Iran, between April 8, 2020, to December 10, 2021, included patients who had no history of *H. pylori* peptic ulcer disease and treatment for anemia and diabetes. In the case of women, it was important not to have them during menstruation. Baseline characteristics and laboratory data of the patients including age, sex, serum anti-*H. pylori* IgG, Ig M, and IgA levels, parameters related to anemia including Mean Corpuscular Hemoglobin (MCH), ferritin, Mean Corpuscular Volume (MCV), Hemoglobin (Hg), and HgA1C were recorded.

Definitions

Patients with ≥ 1 positive serum anti-*H. pylori* immunoglobulin was categorized as *H. pylori* seropositive (Table 1). Anemia was defined as Hg <14 g/dL in males and Hg <12.5 g/dL in females. HgA1C > 6.5 % was considered as a definition for diabetes.

Outcome

The incidence of anemia in seropositive patients compared to seronegative ones was evaluated as the primary outcome of the study. We also compared the ferritin level and incidence of diabetes between the two groups as secondary outcomes.

Statistical analysis

To calculate the normal and non-normal distribution, we used from mean ± standard deviation (SD) and median (interquartile range (IQR), respectively. Quantitative data were tested for normality of distributions by Kolmogorov–Smirnov test, and then compared by Unpaired Student's *t*-test, Mann-Whitney U test for normal and non-normal distribution data, respectively. Qualitative data were analyzed by the Chi-square test. SPSS software was used for the analysis of data (Version 21.0; SPSS Inc., Chicago, IL, USA). A *P-value* less than 0.05 was considered as a significant result.

Results

We evaluated the laboratory data of 140 patients with anti-*H. pylori* serological tests. Out of 140 patients investigated, 74 (53%) were seropositive and 66 (47%) were seronegative. No significant differences were observed in the basic characteristics of the participants, parameters related to anemia including Hg, ferritin, MCV, MCH, and also HbA1C between the two groups (Table 2). We detected 5 males (14.7%) with anemia in the seropositive group which was not significantly higher than those with anemia in the seronegative group (9.6%) ($x^2(1, N=65)=0.380$, $p=0.538$). The findings were also similar for females (15% in the seropositive group and 20% in the seronegative arm, $x^2(1, N=75)=0.326$, $p=0.568$) (Figure 1).

Ferritin levels also showed no significant difference between the 2 groups in both males ($p=0.754$) and females ($p=0.133$). In the evaluation of the incidence of diabetes in seropositive patients, we also detected no significant differences compared to seronegative patients (9.4% vs 6%, respectively, $x^2(1, N=140) =0.557$, $p=0.456$) (Figure 2).

Discussion

This study showed no significantly increase in the incidence of anemia in *H. pylori* seropositive patients compared to seronegative participants. We also observed no significant difference in ferritin levels between the two groups. The role of *H. pylori* infection in inducing Iron Deficiency (ID) and IDA was evaluated by some studies but findings are still conflicting (7, 16-19). ID may be observed by *H. pylori* following chronic gastritis and consequently reduced intestinal iron absorption, hypo- or achlorhydria, and reduced ascorbic acid secretion (18). Sever ID impact on reducing erythropoiesis and IDA occurs by a chronic process (19). *H. pylori* can also lead to peptic ulcer disease and GI bleeding. Obvious or occult GI bleeding is considered a major cause of IDA (16). The IDA due to *H.pylori* infection in the absence of peptic ulcer disease is controversial (17). We detected no significant association between anemia and *H. pylori* infection in our study conducted on patients without *H. pylori*-related peptic ulcer disease.

Our data did not indicate an increasing rate in the incidence of diabetes in *H. pylori* seropositive patients compared to seronegative participants. The results of studies about the association between *H. pylori* and the prevalence of T2DM were controversial (20-23). The pathophysiology of diabetes is multifactorial, many factors such as lifestyle and diet, family history, and socioeconomic status are involved in developing diabetes. Consequently, there is potential for confounding factors that may impress the link between the infection and T2DM (24).

In addition to ferritin, we need Total Iron-Binding Capacity (TIBC) and serum iron level to evaluate the ID and the lack of these data was the main limitation of this study. Thus, we could not definitely roll out the association between *H. pylori* with ID and IDA. Similarly, In the first step, we only evaluated the incidence of diabetes in seropositive participants regardless of confounding factors such as age, family history, and socioeconomic status. A large prospective study with adjusting confounding factors is needed to evaluate the impact of *H. pylori* on the incidence of T2DM. lack of culture-based confirmation of *H. pylori* infection was another limitation of this study.

Conclusion

Our findings indicated that *H. pylori* was not a main reason for anemia, in the population without significant upper gastrointestinal source of blood loss, or peptic ulcer disease, nor diabetes

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Conflict of Interest

All authors declare no potential conflicts of interest for the research, authorship, and/or publication of this article.

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Ethical statements. The entire procedures were approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences in Tehran, Iran. A written informed consent was obtained from participants.

References

1. Holmes L, Rios J, Berice B, Benson J, Bafford N, Parson K, et al. Predictive Effect of Helicobacter pylori in Gastric Carcinoma Development: Systematic Review and Quantitative Evidence Synthesis. Medicines. 2021;8(1):1.
2. Zamani M, Ebrahimtabar F, Zamani V, Miller W, Alizadeh-Navaei R, Shokri-Shirvani J, et al. Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection. Alimentary pharmacology & therapeutics. 2018;47(7):868-76.
3. Saadi H, Saeed A. Evaluation of the Efficacy of ELISA IgG, IgM, and IgA Tests for Diagnosis of Helicobacter pylori. Kurdistan Journal of Applied Research. 2018.
4. Li S, Lu AP, Zhang L, Li YD. Anti-Helicobacter pylori immunoglobulin G (IgG) and IgA antibody responses and the value of clinical presentations in the diagnosis of H. pylori infection in patients with precancerous lesions. World journal of gastroenterology. 2003;9(4):755-8.
5. Knekt P, Teppo L, Aromaa A, Rissanen H, Kosunen TU. Helicobacter pylori IgA and IgG antibodies, serum pepsinogen I and the risk of gastric cancer: changes in the risk with extended follow-up period. International journal of cancer. 2006;119(3):702-5.
6. Gravina AG, Priadko K, Ciamarra P, Granata L, Facchiano A, Miranda A, et al. Extra-Gastric Manifestations of Helicobacter pylori Infection. Journal of Clinical Medicine. 2020;9(12):3887.
7. Hudak L, Jaraisy A, Haj S, Muhsen K. An updated systematic review and meta-analysis on the association between Helicobacter pylori infection and iron deficiency anemia. Helicobacter. 2017;22(1):e12330.
8. Green R. Vitamin B12 deficiency from the perspective of a practicing hematologist. Blood. 2017;129(19):2603-11.
9. Vanegas YAM, Vishnu P. Management of Helicobacter pylori in patients with immune thrombocytopenia. Hämostaseologie. 2019;39(03):279-83.
10. Mladenova I. Helicobacter pylori and cardiovascular disease: update 2019. Minerva Cardioangiol. 2019;67(5):425-32.
11. Figura N, Di Cairano G, Moretti E, Iacoponi F, Santucci A, Bernardini G, et al. Helicobacter pylori infection and autoimmune thyroid diseases: the role of virulent strains. Antibiotics. 2020;9(1):12.
12. Dardiotis E, Sokratous M, Tsouris Z, Siokas V, Mentis AFA, Aloizou AM, et al. Association between Helicobacter pylori infection and Guillain-Barré Syndrome: A meta-analysis. European journal of clinical investigation. 2020;50(5):e13218.
13. Tan AH, Lim SY, Mahadeva S, Loke MF, Tan JY, Ang BH, et al. Helicobacter pylori Eradication in Parkinson's Disease: A Randomized Placebo-Controlled Trial. Movement Disorders. 2020.
14. Doulberis M, Kotronis G, Gialamprinou D, Polyzos SA, Papaefthymiou A, Katsinelos P, et al. Alzheimer's disease and gastrointestinal microbiota; the impact of Helicobacter pylori infection involvement. International Journal of Neuroscience. 2020:1-13.
15. Cen L, Pan J, Zhou B, Yu C, Li Y, Chen W, et al. Helicobacter Pylori infection of the gallbladder and the risk of chronic cholecystitis and cholelithiasis: A systematic review and meta-analysis. Helicobacter. 2018;23(1):e12457.
16. De Franceschi L, Iolascon A, Taher A, Cappellini MD. Clinical management of iron deficiency anemia in adults: Systemic review on advances in diagnosis and treatment. European Journal of Internal Medicine. 2017;42:16-23.
17. John S, Baltodano JD, Mehta N, Mark K, Murthy U. Unexplained iron deficiency anemia: do Helicobacter pylori have a role to play? Gastroenterology Report. 2018;6(3):215-20.
18. DuBois S, Kearney DJ. Iron-Deficiency Anemia and Helicobacter pylori Infection: A Review of the Evidence. Official journal of the American College of Gastroenterology | ACG. 2005;100(2):453-9.
19. Bermejo F, García-López S. A guide to the diagnosis of iron deficiency and iron deficiency anemia in digestive diseases. World journal of gastroenterology. 2009;15(37):4638-43.
20. Devrajani BR, Shah SZA, Soomro AA, Devrajani T. Type 2 diabetes mellitus: A risk factor for Helicobacter pylori infection: A hospital-based case-control study. International journal of diabetes in developing countries. 2010;30(1):22.
21. Bener A, Micallef R, Afifi M, Derbala M, Al-Mulla HM, Usmani MA. Association between type 2 diabetes mellitus and Helicobacter pylori infection. Turk J Gastroenterol. 2007;18(4):225-9.
22. Gulcelik N, Kaya E, Demirbas B, Culha C, Koc G, Ozkaya M, et al. Helicobacter pylori prevalence in diabetic patients and its relationship with dyspepsia and autonomic neuropathy. Journal of endocrinological investigation. 2005;28(5):214-7.
23. Ko GT, Chan FK, Chan W-B, Sung JJ, Tsoi C, To K, et al. Helicobacter pylori infection in Chinese subjects with type 2 diabetes. Endocrine research. 2001;27(1-2):171-7.
24. He C, Yang Z, Lu N-H. Helicobacter pylori infection and diabetes: is it a myth or fact? World Journal of Gastroenterology: WJG. 2014;20(16):4607.

Table 1. Laboratory test cut-off

Laboratory test	**Reference range**		
IgG	Negative: < 8	Borderline: 8 – 12	Positive: > 12
IgM	Negative: < 8	Borderline: 8 – 12	Positive: > 12
IgA	Negative: < 15	Borderline: 15 – 20	Positive: > 20
Hg [a]	Female: 12.5 – 16 g/dL	Male: 14 – 18 g/dL	
MCV [b]	Female: 80 – 96 μm^3	Male: 80 – 96 μm^3	
MCH [c]	Female: 27 – 31 pg	Male: 27 – 31 pg	
Ferritin	Female: 10 – 200 ng/mL	Male: 20 – 350 ng/mL	
HgA1C [d]	Nondiabetic: 3.5-6%	Prediabetes: 6-6.5%	Diabetic: >6.5%

a, Hg: Hemoglobin; b, MCV: Mean Corpuscular Volume; c, MCH: Mean Corpuscular Hemoglobin; d, HgA1C: Hemoglobin A1C

Table 2.Basic characteristics of participation

		Groups				sig[a, b,c]
		H. pylori seropositive		H. pylori seronegative		
		Count	Mean ± SD /median(IQR)[d]	Count	Mean ± SD /median(IQR)[d]	
Sex	Male	34		31		0.903
	Female	40		35		
Age (years)		74	41.2±16.5	66	41.2±20.4	0.995
IgG			17.7(10.6-43)		3.7(2.2-6.3)	0.000
IgM			8.3(4.6-13.8)		3.9(2.6-6.4)	0.001
IgA			5.5(3.1-15.3)		4.3(2.3-6.5)	0.034
Hb [e] (g/dL)	Male		15±1.1		15.2±1	0.548
	Female		13.3±1.1		13.1±1.6	0.503
Ferritin (ng/mL)	Male		95.1(43.5-104.2)		78(31-69.1)	0.754
	Female		28.3(16.7-49.3)		36.9(31-69.1)	0.133
MCV [f] (μm^3)			84.1(81.8-87)		82.7(80.4-86.3)	0.134
MCH [g] (pg)			28.4(27.5-29.5)		28.6(27.6-29.8)	0.532
HbA1C [h] (%)			5.4(5.1-5.9)		5.5(5.1-5.9)	0.981

a, Unpaired t-test; b, Mann-Whitney U test; c, Chi-square test; d, mean± standard deviation or median (interquartile range:25%,75%) for quantitative or categorical data, respectively; e, Hg: Hemoglobin; f, MCV: Mean Corpuscular Volume; g, MCH: Mean Corpuscular Hemoglobin; h, HgA1C, Hemoglobin A1C

Figure legends

Figure 1. The number of males and females with anemia in both *Helicobacter pylori* seropositive and seronegative patients

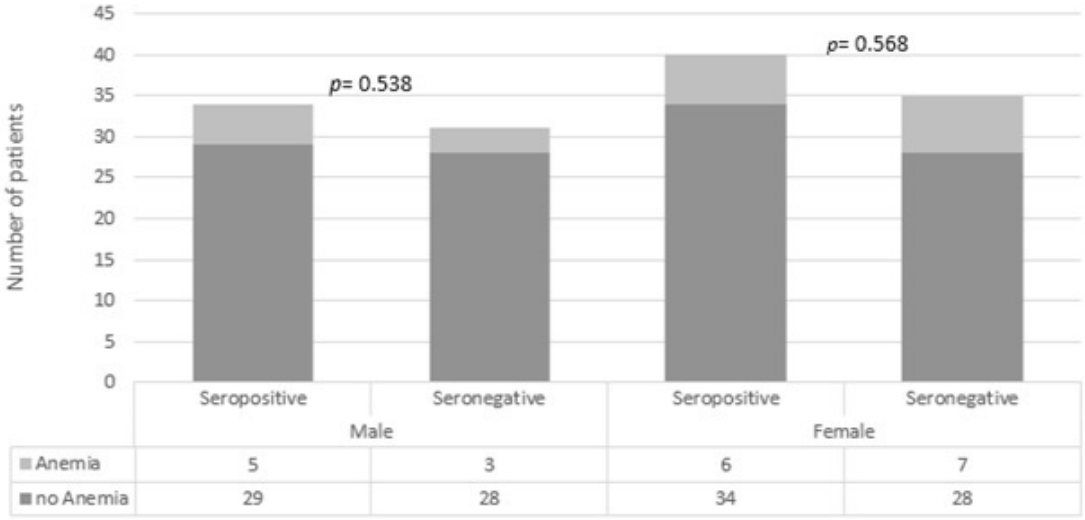

Figure 2. The number of patients with diabetes (DM) in both *Helicobacter pylori* seropositive and seronegative patients