Original Article

Role of the Lewis and ABO Blood Group Antigens in *Helicobacter pylori* Infection

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Abstract

Background: ***Helicobacter pylori*** **infection is a major risk factor for chronic gastritis and gastric cancer. Some findings show increased frequencies of these diseases in individuals with type O blood and in secretors (expressing Le^b antigen), but other studies have not found any relationship between blood groups and this infection. Given that *H. pylori* infection and gastric cancer are common in Iran, the assessment of the pathogenesis of this infection in relation to these blood groups could be valuable.**

Methods: **In a cross-sectional study, we determined the ABO and Lewis blood groups of participants using the tube method and evaluated the level of anti-*H. pylori* immunoglobulin G using an enzyme-linked immunosorbent assay. This study included 171 Iranian blood donors from Mashhad, Iran, during 2010. The significance of the differences in the frequencies of the Lewis and ABO phenotypes between individuals infected with and without *H. Pylori* infection were tested using the chi-square test. A *P*-value < 0.05 was considered significant.**

Results: ***H. pylori*** **infection was found in 76.6% of the study subjects (*n* = 131). The most common ABO blood group was O (33.9%), and the most common Lewis blood group was Le(a-b+) (54.7%). The frequencies of the ABO, Lewis, and secretion phenotypes were not significantly different between the infected and uninfected subjects.**

Conclusion: **We did not find any significant relationship between the Lewis, ABO, and secretion phenotypes and *H. pylori* infection.**

Keywords: *ABO blood groups, blood group antigens, Helicobacter pylori, Lewis blood group, secretor blood group*

Introduction

Helicobacter pylori infection is a high-prevalence worldwide; nonetheless, it is more common in underdeveloped and developing countries than in developed countries (1–3). *H. pylori* infection is most common in adults, with a prevalence of more than 90% in some countries (4). In Iran, the prevalence of this infection in adults has been reported to be approximately 80% (5,6). *H. pylori* infection is a major risk factor for chronic gastritis, peptic ulcers, and gastric cancer (7–9), which is the most common cancer in northern and northwestern Iran (6).

Lewis antigens, like ABO blood group antigens, are expressed in fluids and tissues such as the endothelium and the bowel mucosa. *H. pylori* expresses several lipopolysaccharides on its outer membrane that mediate the adhesion of the bacterium to the gastric epithelium and allow persistent colonisation (10). *H. pylori* binds to the H and Le^b blood group antigens in gastric mucosa; this binding most likely explains the increased incidence of gastritis and gastric cancer in individuals with type O blood and in secretors (expressing the Le^b antigen) (11,12). However, some other studies have not observed any relationship between *H. pylori* infection and the Lewis (4) and ABO blood groups (13). Therefore, the associations between the Lewis and ABO blood groups and *H. pylori* infection are controversial. There exists heterogeneity in the expression of outer membrane proteins, especially BabA, among different *H. pylori* strains, such that there is heterogeneity in the capacity of *H. pylori* to bind to the Le^b antigen on the surface of gastric epithelial cells. This heterogeneity may be a factor that explains some of the differences in the clinical outcomes of this infection (14). Given that *H. pylori* infection and gastric carcinoma are high-prevalence diseases in Iran, the assessment of the pathogenesis of *H. pylori* infection in relation to the blood groups could be valuable.

Materials and Methods

This cross-sectional study was financially supported and ethically approved by the research vice chancellor of Mashhad University of Medical Sciences, Iran. The study population included 171 healthy adult blood donors who were admitted to the Imam Reza Teaching Hospital and Blood Transfusion Center, Mashhad (a large city located in northeastern Iran), during 2010. Subjects who had a positive direct globulin test, were receiving treatment for *H. pylori* infection, or had a history of blood transfusion during the 3 months prior to admission were excluded from this study. We also excluded lipemic, icteric, and hemolytic samples. After obtaining informed consent, 2 mL of blood containing ethylenediaminetetraacetic acid was collected from each subject for blood group typing, and 2 mL blood without anticoagulant was collected for serologic evaluation of *H. pylori*. Red cell phenotyping was performed using commercial monoclonal antibodies in a direct agglutination test using the tube method according to manufacturer's protocol (Biotest AG, DE). Based on the expression of the Le^b antigen, subjects were divided into secretor and non-secretor groups. Because the secretory status was not obvious for the Le(a-b-) phenotype, subjects with this phenotype were not included in either of these groups (11).

Serum samples were tested for anti-*H. pylori* immunoglobulin G using an enzyme-linked immunosorbent assay kit (Euroimmun AG Lubeck, DE). According to the kit's documentation, this test does not exhibit any cross-reactivity; however, high levels of lipemia, jaundice, and hemolysis may influence the results.

Statistical analyses

First, the prevalences of Le^a and Le^b antigen production, the Lewis phenotypes, and *H. pylori* infection were determined. Then, the correlations between *H. pylori* infection and the Lewis antigens as well as the Lewis and ABO phenotypes were tested by Fisher's exact test. A P-value < 0.05 was considered significant. All results were analysed by SPSS version 16 (SPSS Inc., Chicago, IL, US).

Results

We evaluated 171 individuals, 94.3% of whom were male and 5.7% of whom were female. The age range was 19–61 years with a mean (SD) of 33.8 (1) years. *H. pylori* infection was identified in 76.6% of the subjects (n = 131). No significant association was observed between sex and *H. pylori* infection. The most common ABO blood group was O (33.9%), followed by A (29.5%), B (28.7%), and AB (7.9%), and the most common Lewis blood group was Le (a-b+) (54.7%), followed by Le (a+b-) (34.9%), Le (a+b+) (8.9%), and Le (a-b-) (1.6%). Of 169 donors, 106 (62.7%) were secretors and secreted Lewis and ABO antigens in secretions.

As shown in Table 1, the frequencies of the ABO, Lewis, and secretion phenotypes were not significantly different between the infected and uninfected subjects. The Le (a-b-) phenotype was rare (n = 2), and the secretion status of this phenotype cannot be inferred; therefore, individuals with this phenotype were not included in the Lewis and the secretion phenotype analyses.

Discussion

The blood group antigens are important in the pathogenesis of some diseases (15,16). The Lewis antigens are biochemically related

Table 1: Comparison of the distributions of ABO, Lewis and secretion phenotypes between the 2 subject groups (with or without *Helicobacter Pylori infection*)

Characteristics	Total	Uninfected *n* (%)	Infected *n* (%)	*P*- value[a]
ABO phenotypes	171			0.669
O		15 (37.5)	48 (36.6)	
A		10 (25.0)	38 (29.0)	
B		11 (27.5)	31 (23.7)	
AB		4 (10.0)	14 (10.7)	
Lewis phenotypes	169			0.945
Le (a+b-)		16 (41.0)	47 (36.2)	
Le (a-b+)		21 (53.8)	71 (54.6)	
Le (a+b+)		2 (5.1)	12 (9.2)	
Secretion phenotypes	169			0.581
Secretor		23 (59.0)	83 (63.8)	
Non-secretor		16 (41.0)	47 (36.2)	

[a] *P* - value

to the ABO blood antigens. The *secretor* (*Se*) gene, encodes a fucosyltransferase that adds fucose to the terminal galactose of the type 1 precursor chain, forming a type 1 H chain. The Lewis gene encodes fucosyltransferase type III that can add fucose to type 1 precursor chains, forming the Le^a antigen, or fucose to type 1 H chains, forming the Le^b antigen. Persons lacking the *Se* gene, referred to as non-secretors, cannot produce type 1 H chains or the antigen derived from this type of chain, Le^b (11,12,17); therefore, non-secretors can only express the Le^a antigen. For this reason, we can use saliva for the determination of the Lewis phenotype in adults.

Some studies have shown that *H. pylori* binds to H and Le^b antigens (secretors) in the gastric mucosa. The binding of blood group antigen B to the outer membrane of *H. pylori* mediates the binding of *H. pylori* to Le^b antigens expressed on the gastric mucosa (10,18); this binding most likely causes the increased incidence of gastritis and gastric cancer in individuals with the O blood group and the Le (a-b+) phenotype (12).

Despite this, we did not observe any significant associations between *H. pylori* infection and the Lewis and ABO blood groups, as well as the secretion status (Table 1). The frequencies of the ABO blood group phenotypes in Iran have been reported to be the following: O in 37.62%, A in 30.25%, B in 24.36%, and AB in 7.77% of the population (19). These frequencies are similar to our results and those of other studies conducted in Iran (20). Heneghan et al. (17) determined the Lewis and ABO blood group phenotypes of 207 patients undergoing upper endoscopy and, similar to our study, did not observe any significant association between these blood groups or secretor status and *H. pylori* infection (17). Mattos et al. (4) studied the frequencies of the ABO and Lewis blood group phenotypes and secretor status in patients with or without *H. pylori* infection subjects by using breath and urea tests. They showed that *H. pylori* infection is more common in the O blood group patients, but they did not find significant associations between this infection and the Lewis blood groups and secretor status (4).

A study by Rothenbacher et al. (10) investigated the role of Lewis antigens in ongoing *H. pylori* infection in 712 women of different nationalities who were admitted to the Department of Gynecology and Obstetrics, University of Ulm, Germany, between November 2000 and November 2001; in contrast to the results of many other studies, they found a higher frequency of *H. pylori* infection in individuals with the Le (a+b-) phenotype than in individuals with the Le (a-b+) phenotype. Therefore, they presented the hypothesis that individuals with a Le (a+b-) phenotype secrete only Le^a and no other ABH substances in secretions such as

gastric fluids; in contrast, individuals with the Le (a–b+) phenotype (secretors) secrete Le^a as well as Le^b and ABH substances in body fluids. Thus, it is possible that the Le^b present in other body secretions such as gastric mucus may bind to specific glycoproteins of *H. pylori* and hinder the binding of *H. pylori* to the gastric mucosa (10).

Recent findings on strains of *H. pylori* from different areas of the world have revealed that different strains differed by approximately 1500-fold with respect to binding affinities, and there was considerable diversity related to the babA gene sequences (14,16,21). Not all strains are equally specific for O and Le^b; many strains from outside South America can bind to A and Leb in addition to O and Le^b. For example, Peruvian strains are related to Spanish strains but not to Asian strains (16,21). A study by Con et al. (22), in which 95 Costa Rican and 95 Japanese *H. pylori* isolates were genotyped, revealed a higher frequency of babA2 in Japan (96.8%) than in Costa Rica (73.7%). In comparison, the frequency of babA2/B was higher in Costa Rica (11.6%) than in Japan (1.1%). Con et al. (22) also suggest that frequencies of babA2 and babA2/B exhibit geographic differences (22). Another virulence factor characterised recently in *H. pylori* is a sialic acid–binding adhesin, SabA. The frequency of SabA also exhibits geographic differences and is more common in European than Japanese *H. pylori* isolates (23,24). As a result, this diversity in *H. pylori* strains may explain why our findings were different from those of some other studies from different geographic area. We suggest that a future study should characterise the strains of *H. pylori* in infected patients in addition to determine the ABO and Lewis blood groups.

Conclusion

We did not observe any significant relationship between the Lewis, ABO, and secretion phenotypes and *H. pylori* infection.

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Authors' Contributions

Conception and design, analysis and interpretation of the data, statistical expertise: MRK
Obtaining of funding, collection and assembly of the data: AMR
Provision of study materials, drafting of the article: MHS
Critical revision of the article: HA
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References

1. Keramati MR, Siadat Z, Mahmoudi M. The correlation between *H. pylori* infection with serum ferritin concentration and iron deficiency anemia. *Int J Pediat Hem Onc.* 2007;**17(1)**:16–20.

2. Magalhaes Queiroz DM, Luzza F. Epidemiology of *Helicobacter pylori* infection. *Helicobacter.* 2006;**11(Suppl 1)**:1–5.

3. Mitchell H, Megraud F. Epidemiology and diagnosis of *Helicobacter pylori* infection. *Helicobacter.* 2002;**7(Suppl 1)**:8–16.

4. de Mattos LC, Rodrigues Cintra J, Sanches FE, Alves da Silva Rde C, Ruiz MA, Moreira HW. ABO, Lewis, secretor and non-secretor phenotypes in patients infected or uninfected by the *Helicobacter pylori* bacillus. *Sao Paulo Med J.* 2002;**120(2)**:55–58.

5. Babamahmoodi F, Ajemi A, Kalhor M, Shfiei GR, Khalilian AR. A seroepidemiological study of *Helicobacter pylori* infection in Sari in 2001-02. *J Mazand Univ Med Sci.* 2004;**43(14)**:39–48.

6. Malekzadeh R, Derakhshan MH, Malekzadeh Z. Gastric cancer in Iran: Epidemiology and risk factors. *Arch Iran Med.* 2009;**12(6)**:576–583.

7. Compare D, Rocco A, Nardone G. Risk factors in gastric cancer. *Eur Rev Med Pharmacol Sci.* 2010;**14(4)**:302–308.

8. Fock KM, Ang TL. Epidemiology of Helicobacter pylori infection and gastric cancer in Asia. *J Gastroenterol Hepatol.* 2010;**25(3)**:479–486.

9. Ramirez Ramos A, Sanchez Sanchez R. Helicobacter pylori and gastric cancer. *Rev Gastroenterol Peru*. 2008;**28(3)**:258–266.

10. Rothenbacher D, Weyermann M, Bode G, Kulaksiz M, Stahl B, Brenner H. Role of Lewis A and Lewis B blood group antigens in *Helicobacter pylori* infection. *Helicobacter*. 2004;**9(4)**:324–329.

11. Schmaier AH, Thornburg CD, Pipe SW. Coagulation and fibrinolysis. In: Mcpherson RA, Pincus MR, editors. *Henry's clinical diagnosis and management by laboratory methods*. 21st ed. Philadelphia (PA): Saunders Elsevier; 2007. p. 729–733.

12. Beadling WV, Cooling L. Immunohematology. In: Mcpherson RA, Pincus MR, editors. *Henry's clinical diagnosis and management by laboratory methods*. 21st ed. Philadelphia (PA): Saunders Elsevier; 2007. p. 636–637.

13. Keller R, Dinkel KC, Christl SU, Fischbach W. Interrelation between ABH blood group O, Lewis (B) blood group antigen, *Helicobacter pylori* infection, and occurrence of peptic ulcer. *Z Gastroenterol*. 2002;**40(5)**:273–276.

14. Hennig EE, Mernaugh R, Edl J, Cao P, Cover TL. Heterogeneity among *Helicobacter pylori* strains in expression of the outer membrane protein BabA. *Infect Immun*. 2004;**72(6)**:3429–3435.

15. Ayatollahi H, Rafatpanah H, Khayyami ME, Sayyadpour D, Ravarian M, Sadeghian MH, et al. Association between ABO and Rhesus blood group systems among confirmed human T lymphotropic virus type 1-infected patients in Northeast Iran. *AIDS Res Hum Retroviruses*. 2008;**24(9)**:1155–1158.

16. Anstee DJ. The relationship between blood groups and disease. *Blood*. 2010;**115(23)**:4635–4643.

17. Heneghan MA, Moran AP, Feeley KM, Egan EL, Goulding J, Connolly CE, et al. Effect of host Lewis and ABO blood group antigen expression on *Helicobacter pylori* colonisation density and the consequent inflammatory response. *FEMS Immunol Med Microbiol*. 1998;**20(4)**:257–266.

18. Backstrom A, Lundberg C, Kersulyte D, Berg DE, Borén T, Arnqvist A. *Metastability of Helicobacter pylori bab adhesin genes and dynamics in Lewis b antigen binding*. Proceedings of the National Academy of Sciences of the United States of America. 2004;**101(48)**:16923–16928.

19. Pour Fathollah A, Oodi A, Honarkaran N. Geographical distribution of ABO and Rh (D) blood groups among Iranian blood donors in the year 1361 (1982) as compared with that of the year 1380 (2001). *Blood*. 2004;**1(1)**:11–17.

20. Keramati MR, Shakibaei H, Kheiyyami MI, Ayatollahi H, Badiei Z, Samavati M, et al. Blood group antigens frequencies in the northeast of Iran. *Transfus Apher Sci*. 2011;**45(2)**:133–136.

21. Aspholm-Hurtig M, Dailide G, Lahmann M, Kalia A, Ilver D, Roche N, et al. Functional adaptation of BabA, the *H. pylori* ABO blood group antigen binding adhesin. *Science*. 2004;**305(5683)**:519–522.

22. Con SA, Takeuchi H, Nishioka M, Morimoto N, Sugiura T, Yasuda N, et al. Clinical relevance of *Helicobacter pylori* babA2 and babA2/B in Costa Rica and Japan. *World J Gastroenterol*. 2010;**16(4)**: 474–478.

23. Molnar B, Galamb O, Sipos F, Leiszter K, Tulassay Z. Molecular pathogenesis of *Helicobacter pylori* infection: The role of bacterial virulence factors. *Dig Dis*. 2010;**28(4-5)**:604–608.

24. Shao L, Takeda H, Fukui T, Mabe K, Han J, Kawata S, et al. Genetic diversity of the *Helicobacter pylori* sialic acid-binding adhesin (sabA) gene. *Biosci Trends*. 2010;**4(5)**:249–253.