

Influence of H. Pylori and Sex on Leukocyte Differentials

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Abstract

Background: Influence of *Helicobacter pylori* infection and sex difference on leukocyte differentials was insufficiently understood. We therefore conducted the current study to evaluate influence of *H. pylori* and sex on peripheral leukocyte differentials as well as influence of *Helicobacter pylori* eradication.

Methods: Dyspeptic patients and persons asked to examine gastroduodenal lesions at medical check were included. Total leukocytes, differentials, and anti-*H.pylori* IgG antibody were measured. Those change after eradication was also measured. *H. pylori* infection was assessed by anti-*H. pylori* IgG antibody, rapid urease test, and pathologic findings. *H. pylori*-uninfected patients and non-dyspeptic/seronegative persons were regarded as negative controls.

Results: Totally 374 patients and 299 controls were evaluated, and 167 patients were successfully eradicated. Peripheral counts of neutrophil and monocyte elevated with *H. pylori* infection: 3221.7+/-1108.7 vs. 2911.9+/-1027.3/ μ L and 307.5+/-130.5 vs. 281.5+/-106.4/ μ L, (p =.0002 and .0054). Compared to females, males manifested elevated counts of every leukocyte, but the difference was insignificant in basophil (p =.0089, 0.0316, <.0001, and .0384 for neutrophil, lymphocyte, monocyte, and eosinophil, respectively).

After eradication, counts of neutrophil, lymphocyte, and monocyte declined: 3111.0+/-966.8 to 2785.1+/-997.2/ μ L, 1905.9+/-603.2 to 1831.6+/-613.5/ μ L, and 293.1+/-113.3 to 264.3+/-93.6/ μ L by 2 months (p <.0001, .0189, and .0004). In contrast, eosinophil counts elevated from 123.2+/-97.0 to 139.8+/-115.4 by 2 months, and to 159.6+/-132.8/ μ L by 6 months (p =.0349 and <.0001).

Conclusions: We confirmed increases in neutrophils and monocytes in *H. pylori*-infected patients. Successful eradication reduced peripheral counts of neutrophil, lymphocyte, and monocyte, whereas it increased eosinophil counts. Males manifested elevated counts of every leukocyte, comparing to females. *H. pylori* infection influences systemic immune response and may not predispose to allergic disorders.

Trial registration: The study protocol was registered on UMIN (University hospital Medical Information Network system) in Japan (R000017345) in 2014.

Background

Helicobacter pylori (*H. pylori*) infection had been reported to alter leukocyte differentials [1–6], and most of researchers reported increased numbers of total leukocytes, neutrophil, and monocyte, comparing to those uninfected. Concerning eosinophil and basophil, no specific alterations were reported. In addition, most of researchers did not pay attention to some factors that could influence the leukocyte differentials such as smoking, medications, sex difference, and additional morbidity. We therefore conducted the

current study to elucidate influence of *H. pylori* infection and sex difference on leukocyte differentials in detail.

Methods

Dyspeptic patients and persons recommended to receive close examination at medical check were included in the current study. After obtaining informed/written consents to check immunohematologic parameters and *H. pylori* infection, they were venipunctured to examine blood tests including complete blood counts, leukocyte differentials, and anti-*H. pylori* IgG antibody. Because *H. pylori* eradication therapy applies only to endoscopically diagnosed gastritis in Japan, patients received endoscopic examination when they wanted to eradicate *H. pylori*. Diagnosis of gastritis was made according to the Kyoto classification of gastritis and that of gastroduodenal ulcer did according to the classification of Sakita and Miwa [7, 8]. To evaluate *H. pylori* status, biopsy specimens were obtained from the antrum and body in the greater curvature of the stomach. The samples were placed into rapid urease test (RUT) kits, and the results were evaluated 5 hrs. later. These samples were also prepared for pathologic evaluation. Anti-*H. pylori* IgG antibody more than 10 U/ml was accepted as seropositive. We defined *H. pylori*-infected patients to be positive for anti-*H. pylori* IgG antibody as well as for RUT or pathologic findings of gastromucosal biopsy. The difference in total leukocytes counts and differentials were evaluated according to the presence or absence of *H. pylori* infection. We also evaluated the influence of sex difference on the parameters. Moreover, some of *H. pylori*-infected patients received triple therapy mainly consisted of amoxicillin 1500 mg/day, clarithromycin 400 mg/day, and proton-pump inhibitor for a week. The change in the parameters after successful eradication was evaluate at 2, 6, and 12 months after the treatment.

Controls

Patients unmatched to have *H. pylori* infection and non-dyspeptic persons confirmed as seronegative for *H. pylori* were regarded as *H. pylori*-uninfected controls.

Patient exclusion

Patients with immunohematologic, rheumatic, malignant, peptic ulcer, and infectious diseases any other than *H. pylori* infection such as pneumonia, tuberculosis, hepatitis etc. were excluded. In addition, persons aged < 15yrs and those with prior eradication were excluded. Current smokers and ex-smokers who quitted smoking within 5 or less years were excluded [9, 10]. Because non-steroidal anti-inflammatory drugs (NSAIDs) might induce neutropenia and tend to bleed, NSAID users were also excluded. To further evaluate eosinophil counts, allergic patients were excluded when required.

Statistics

Data were expressed as mean+/-SD. Statistical difference was evaluated using Student's paired and unpaired *t*-tests, and p values less than .05 were accepted as significantly different.

Ethics and trial registration

The study protocol was registered on UMIN (University hospital Medical Information Network system) in Japan (R000017345). The institutional ethical committee of the Itabashi Hospital, Nihon University School of Medicine, approved the study protocol (RK141114-3, 2014.12.29).

Results

Initially, 1,314 Japanese persons were recruited: 426 *H. pylori*-infected males, 203 *H. pylori*-uninfected males, 392 *H. pylori*-infected females, and 293 *H. pylori*-uninfected females. There were 165 persons taking NSAIDs (M:F = 70:95), 331 having gastric or duodenal ulcer (M:F = 202:129), 358 current smokers (M:F = 259:99), and 107 ex-smokers quitted smoking within 5 years (M:F = 87:20). Those participants were excluded from the study.

Totally 673 persons were evaluated: 374 infected (M:F = 129:245) and 299 uninfected (M:F = 98:201) (Tables 1). There were 129 persons with allergic disorders (M:F = 35:93): 94 pollinosis, 16 bronchial asthma, 14 drug allergy, 6 atopic dermatitis, 4 food allergy, and 4 urticaria (some patients had 2 allergic disorders). A hundred and ninety-five patients received *H. pylori* eradication therapy. As a result, 167 patients were successful eradicated and data of 153 patients were able to be evaluated.

Table 2 depicts effect of *H. pylori* infection on leukocyte differentials. *H. pylori*-infected patients showed elevated counts of total leukocytes, neutrophil, lymphocyte, and monocyte: 5578.1+/-1438.7 vs. 5192.0+/-1312.9/ μ L, 3221.7+/-1108.7 vs. 2911.9+/-1027.3/ μ L, 1853.6+/-600.7 vs. 1787.5+/-612.5/ μ L, 307.5+/-130.5 vs. 281.5+/-106.4/ μ L, although the difference in lymphocyte counts was insignificant ($p = .0003, .0002, .1605, \text{ and } .0054$) (Table 2a). Compared to uninfected, *H. pylori*-infected male patients manifested elevated counts of neutrophil and monocyte: 3392.0+/-1229.3 vs. 3033.0+/-1057.0/ μ L, and 352.5+/-152.3 vs. 315.1+/-117.2/ μ L, ($p = .0216 \text{ and } .0123$), whereas they insignificantly manifested decreased counts of lymphocyte and eosinophil: lymphocyte 1866.9+/-615.2 vs. 1931.4+/-692.8/ μ L, and 150.8+/-126.4 vs. 184.8+/-259.7/ μ L ($p = .4596 \text{ and } .1945$) (Table 2b). Except for basophil, female patients with *H. pylori* infection showed elevated counts of every leukocyte subgroup, although the statistical difference was confirmed in total leukocytes, neutrophil, and lymphocyte: 5452.3+/-1332.0 vs. 5034.8+/-1270.0/ μ L, 3132.0+/-1031.0 vs. 2852.9+/-1009.9/ μ L, and 1846.7+/-594.1 vs. 1717.4+/-559.3/ μ L, ($p = .0008, .0045, \text{ and } .0194$), respectively (Table 2c).

Concerning sex difference, males showed elevation of every leukocyte count, although the difference in basophil did not reach statistical significance: total leukocytes 5686.4+/-1500.4 vs. 5264.1+/-1319.5/ μ L, neutrophil 3237.0+/-1169.2 vs. 3006.2+/-1029.8/ μ L, lymphocyte 1894.7+/-649.1 vs. 1788.4+/-581.7/ μ L, monocyte 341.5+/-142.1 vs. 272.8+/-101.4/ μ L, eosinophil 165.5+/-195.1 vs. 136.0+/-162.9/ μ L, and basophil 34.9+/-29.8 vs. 32.2+/-26.1/ μ L ($p = .0002, .0089, .0316, < .0001, .0384, \text{ and } .2164$) (Table 3a). In *H. pylori*-infected patients, the difference was verified in total leukocytes, neutrophils, and monocytes: 5817.0+/-1600.5 vs. 5452.3+/-1332.0/ μ L, 3392.0+/-1229.3 vs. 3132.0+/-1031.0/ μ L, and 362.0+/-155.8 vs. 278.9+/-104.4/ μ L ($p = .0196, .0310 \text{ and } < .0001$) (Table 3b). Such elevations were similarly observed in *H. pylori*-uninfected persons, although the difference in neutrophil and basophil was insignificant: total

leukocytes 5514.4+/-1346.3 vs. 5034.8+/-1270.2/ μ L, neutrophil 3033.0+/-1057.0 vs. 2852.9+/-1009.9/ μ L, lymphocyte 1931.4+/-692.8 vs. 1717.4+/-559.5/ μ L, monocyte 314.5/-117.0 vs. 269.4+/-97.1/ μ L, eosinophil 184.8+/-258.7 vs. 134.7+/-126.5/ μ L, and basophil 36.6+/-26.6 vs. 32.5+/-29.8/ μ L ($p = .0029, .1551, .0045, .0002, .0253, \text{ and } .2486$) (Table 3c).

Table 4 depicts effect of *H. pylori* eradication on leukocyte differentials. After successful eradication, peripheral counts of total leukocytes, neutrophil, lymphocyte, and monocyte declined: 5470.5+/-1288.6 to 5048.7+/-1369.5/ μ L, 3111.0+/-966.8 to 2785.1+/-997.2/ μ L, 1905.9+/-603.2 to 1831.6+/-613.5/ μ L, and 293.1+/-113.3 to 264.3+/-93.6/ μ L, by 2 months ($p = < .0001, < .0001, .0189, .0003$). In contrast, eosinophil counts elevated from 123.2+/-97.0 to 139.8+/-115.4/ μ L by 2 months, and to 159.6+/-132.8/ μ L by 6 months ($p = .0349 \text{ and } < .0001$).

Discussion

We here showed *H. pylori* infection elevates peripheral counts of both neutrophil and monocyte, and it elevates lymphocyte counts in females. We also showed males definitely manifest elevated counts of monocyte, irrespective of *H. pylori* infection. Likewise, *H. pylori*-uninfected males showed elevated counts of eosinophil and lymphocyte, comparing to uninfected females. In addition, we disclosed successful *H. pylori* eradication cancelled such elevations in peripheral counts of neutrophil, lymphocyte, and monocyte, whereas it elevated peripheral eosinophil counts. The infection seemed to down-regulate peripheral eosinophil counts in males.

Karttunen et al. first reported elevated counts of total leukocytes, lymphocyte, and basophil in 96 dyspeptic patients, all received gastroscopy (M:F = 40:56, *H. pylori* positive: *H. pylori*-negative = 58:38), irrespective of smoking status and endoscopic findings. They also reported insignificant elevation of monocyte counts in *H. pylori*-infected patients among non-smokers ($p = .052$) [1]. Our observation appears in accordance with the data of Karttunen et al., except for basophil counts. The difference in basophil could be explained by the small sample size and the difference in diagnosing *H. pylori* infection. Similar to our observation, Kondo et al. retrospectively reported decreased counts of peripheral neutrophil, lymphocyte, and monocyte after successful eradication [2].

Recently, some researchers paid attention to neutrophil/lymphocyte (N/L) ratio in investigating organ damage: they reported elevation of N/L ratio in *H. pylori*-infected patients, compared to uninfected controls [3–6]. Among them, Jafarzadeh A et al. reported elevated neutrophil counts in *H. pylori*-infected patients with gastric ulcer, compared to those of asymptomatic *H. pylori*-infected controls [3]. Sahin Y et al. reported elevated neutrophil counts and the decline after successful eradication among children [4]. Farah R et al. and Zeren S et al. reported elevated neutrophil counts and N/L ratio in *H. pylori*-infected patients [5, 6]. The both researchers also reported lowered lymphocyte counts in *H. pylori*-infected patients, although they did not assess sex difference in the counts. In contrast, we disclosed elevated lymphocyte counts in *H. pylori*-infected females while we observed insignificant reduction of lymphocyte counts in *H. pylori*-infected males. These 6 studies and the current data showed increases in peripheral

neutrophils in *H. pylori*-infected patients. In addition, Hansen PS et al. had reported proinflammatory activation of neutrophils and monocytes in *H. pylori*-infected patients [11]. Taking these 7 studies and the current study into account, the increase in peripheral neutrophil counts could be a hall mark of *H. pylori* infection, and the increase in monocyte counts appears characteristic phenomenon in this infection.

We firstly present *H. pylori* infection could down-regulate peripheral eosinophil counts and its eradication definitely elevated peripheral eosinophil counts, in the first six months with a subsequent decline. *H. pylori* infection have been increasingly reported to inversely associate with allergic disorders probably due to the induction of regulatory T cells (T-regs) and skewed property to type 1 helper T cells (Th1) [12–22], although some of researchers expressed opposite opinion [23]. Our data could support such anti-allergic effect of the infection. When we accepted the increase in peripheral eosinophils as a predisposed parameter to allergic disorders, the current observations of both the decrease in eosinophils in *H. pylori*-infected patients and the increase after successful eradication could indicate anti-allergic effect of the organism. The current data at least means *H. pylori* infection cannot predispose to allergic disorders. Likewise, some researchers reported aberration of eosinophil after successful eradication of *H. pylori* [24, 25].

The reports assessing sex difference in leukocyte differentials are lacking, and few researchers paid attention to smoking status. Male sex has been reported to up-regulate peripheral monocyte counts [26–28], and Nah E et al. solely reported higher eosinophil counts in males than in females [26]. Taking their observations and the current data, the elevated monocyte counts in males over females seems definitely and uniquely derived from male-sex. The current data further indicates males have significantly elevated counts of another sub-group of leukocytes, comparing to females in Japanese.

Conclusion

We here confirmed elevated counts of neutrophil and monocyte in *H. pylori*-infected patients. Successful eradication reduced peripheral counts of neutrophil, lymphocyte, and monocyte, whereas it increased eosinophil counts. *H. pylori* infection influences systemic immune response and may not predispose to allergic disorders. In addition, males manifested definite elevation of monocyte counts, comparing to females. Without influence of *H. pylori* infection, males showed elevation of every sub-group of leukocytes in the peripheral blood, although the difference in neutrophil and basophil was insignificant.

Limitations Of The Current Study

First, we evaluated the patients aged near 60-year-old in the current study. We therefore may not apply the current data for the youth. Second, due to a large number of excluded males such as smokers and ulcer patients, we were forced to evaluate a smaller number of male participants: male vs. female 219:438. Therefore, the difference derived from males could be underestimated.

Abbreviations

H. pylori

Helicobacter pylori

RUT

Rapid urease test

Declarations

We performed the study according to our ethical standards as follows. After obtaining informed/written consents to check immunohematologic parameters and *H. pylori* infection, they were venipunctured to examine blood tests including complete blood counts, leukocyte differentials, and anti-*H. pylori* IgG antibody. The personal information of the participants is kept strictly confidential. The study protocol was registered on UMIN (University hospital Medical Information Network system) in Japan (R000017345). The institutional ethical committee of the Itabashi Hospital, Nihon University School of Medicine, approved the study protocol (RK141114-3, 2014.12.29). Disclosure of potential conflicts with interest

YM received honoraria for the lectures from Astra-zeneca and Takeda Pharmaceutical. Dr. Kitamura received personal fees from Astellas Pharma Inc., Bristol-Myers Squibb K.K, Daiichi Sankyo Co., Ltd., Esai Co., Ltd., GlaxoSmithKline K.K., Mitsubishi Tanabe Pharma Corporation, Pfizer Inc.. Fukui Y, Yamanaka H, Takei M, Iwamoto M, Moriyama M, Kato K, Maejima M, and Shirinskaya N have no conflicts of interests to report.

Authors' contributions

YF, KK, MI, NS, and YM contributed to the study conception and design. HY, NK, MT, MM, and MM collected the data. YF, KK, NS, TM, MM, and YM analyzed and interpreted the data. YF and YM drafted the manuscript. PP, JM, and MG criticized the manuscript. All authors approved the final version of the manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Compliance with Ethical Standards

We performed the study according to our ethical standards as follows.

After obtaining informed/written consents to check immunohematologic parameters and *H. pylori* infection, they were venipunctured to examine blood tests including complete blood counts, leukocyte differentials, and anti-*H. pylori* IgG antibody.

The personal information of the participants is kept strictly confidential.

The study protocol was registered on UMIN (University hospital Medical Information Network system) in Japan (R000017345). The institutional ethical committee of the Itabashi Hospital, Nihon University School of Medicine, approved the study protocol (RK141114-3, 2014.12.29)

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

Disclosure of potential conflicts with interest

YM received honoraria for the lectures from Astra-zeneca and Takeda Pharmaceutical.

NM received personal fees from Astellas Pharma Inc., Bristol-Myers Squibb K.K, Daiichi Sankyo Co., Ltd., Esai Co., Ltd., GlaxoSmithKline K.K., Mitsubishi Tanabe Pharma Corporation, Pfizer Inc..

F Y, YH, TM, IM, MM, KK, MM, and SN have no conflicts of interests

to report.

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Tables

Table 1. Participants' profiles

Patients	Males	Females	Total
Number	227	446	673
Age	57.0+/-15.4	57.7+/-14.7	
56. <i>pylori</i> (+)	129 (56.8%)	245 (54.9%)	374 (55.6%)
57. <i>pylori</i> (-)	98 (43.2%)	201 (45.1%)	299 (54.4%)

Table 2. Effect of *H. pylori* on leukocyte differentials

Table 2a. All participants

1. <i>pylori</i> Positive	Negative
p	

Number	374		298
Leukocyte	5578.1+/-1438.7	5192.0+/-1312.9	.0003
Neutrophil	3221.7+/-1108.7	2911.9+/-1027.3	.0002
Lymphocyte	1853.6+/-600.7	1787.5+/-613.5	.1605
Monocyte	307.5+/-130.5	281.5+/-106.4	.0054
Eosinophil	141.8+/-169.1	151.2f+/-181.9	
.4901*			
Basophil	32.5+/-26.2	33.9+/-28.8	
.5165			

*.6145 when allergic patients excluded

Table 2b. Male patients

	1. <i>pylori</i> Positive	Negative	
	p		
Number	129		98
Leukocytes	5817.0+/-1600.4	5514.4+/-1346.3	.1325
Neutrophil	3392.0+/-1229.3	3033.0+/-1057.0	.0216
Lymphocyte	1866.9+/-615.2	1931.4+/-692.8	.4596
Monocyte	352.5+/-152.3	315.1+/-117.2	
.0123			
Eosinophil	150.8+/-126.4	184.8+/-259.7	
.1945*			
Basophil	33.4+/-32.7	36.5+/-26.2	
.4729			

*.1263 when allergic patients excluded

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Table 2c. Female patients

1. <i>pylori</i> Positive	Negative	p	
Number	245	201	
Leukocytes	5452.3+/-1332.0	5034.8+/-1270.0	.0008
Neutrophil	3132.0+/-1031.0	2852.9+/-1009.9	.0045
Lymphocyte	1846.7+/-594.1	1717.4+/-559.3	
.0194			
Monocyte	278.9+/-104.4	265.4+/-97.1	
.1619			
Eosinophil	137.0+/-187.7	134.7+/-126.5	
.8836*			
Basophil	31.9+/-22.6	32.6+/-29.8	
<u>.7827</u>			

*.5463 when allergic patients excluded

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Table 3. Effect of sex difference on leukocyte differentials

Table 3a. All participants

Sex	Male	Female	
	p		
Number	227	446	
Leukocytes	5686.4+/-1500.4	5264.1+/-1319.5	.0002
Neutrophil	3237.0+/-1169.2	3006.2+/-1029.8	.0089

Lymphocyte	1894.7+/-649.1	1788.4+/-581.7
.0316		
Monocyte	341.5+/-142.1	272.8+/-101.3
<.0001		
Eosinophil	165.5+/-195.1	136.0+/-162.9
.0384*		
Basophil	34.9+/-29.8	32.2+/-26.1
<u>.2164</u>		

*.1131 when allergic patients excluded

Table 3b. *H. pylori* positive patients

Sex	Male		
Female	p		
Number	129		245
Leukocytes	5817.0+/-1600.5	5452.3+/-1332.0	.0196
Neutrophil	3392.0+/-1229.3	3132.0+/-1031.0	.0310
Lymphocyte	1866.9+/-615.2	1846.7+/-594.1	.7579
Monocyte	362.0+/-155.8	278.9+/-104.4	
<.0001			
Eosinophil	150.8+/-126.4	137.0+/-187.7	
.4535*			
Basophil	33.7+/-32.0	31.9+/-22.6	
<u>.5393</u>			

*.9389 when allergic patients excluded

Table 3c. *H. pylori* negative participants

Sex	Male	
Female	p	

Number	98		200
Leukocytes	5514.4+/-1346.3	5034.8+/-1270.2	.0029
Neutrophil	3033.0+/-1057.0	2852.9+/-1009.9	.1551
Lymphocyte	1931.4+/-692.8	1717.4+/-559.5	
.0045			
Monocyte	314.5/-117.0	269.4+/-97.1	
.0002			
Eosinophil	184.8+/-258.7	134.7+/-126.5	
.0253*			
Basophil	36.6+/-21.6	32.5+/-29.8	
.2486			

*.0235 when allergic patients excluded

Table 4. Changes in peripheral leukocyte counts after successful eradication

Before	12 months	2 months	6 months
Number of patients			
153		153	
93		52	
Leukocytes			
5470.5+/-1288.6	5048.7+/-1369.5 ¹	5364.2+/-1224.1	5178.3+/-1244.3
Neutrophil			
3111.0+/-966.8	2785.1+/-997.2 ¹	2934.8+/-989.8	
2947.4+/-991.6			
Lymphocyte			

1905.9+/-603.2
1821.6+/-608.9

1831.6+/-613.5²

1917.5+/-613.9

Monocyte

293.1+/-113.3
285.0+/-110.8

264.3+/-93.6³

295.1+/-97.8

Eosinophil

123.2+/-97.0

139.8+/-115.4^{4,*}

159.6+/-132.8^{1,**}

126.0+/-103.7

Basophil

29.9+/-17.7

30.6+/-26.9

33.3+/-24.1

31.8+/-18.8

1: <.0001, 2 :.0189, 3 :.0004, 4 :.0349

*.0960 and **.0009 when allergic patients excluded