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Original article

The Association between *Helicobacter Pylori* Infection in Subjects with Gastritis and Serum Levels of LL-37, MBL and M-Ficolin

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SUMMARY

***Helicobacter pylori* (*H. pylori*) can stimulate immune responses and lead to the release of proinflammatory factors and antimicrobial peptides as LL-37, mannose-binding lectin (MBL) and M –ficolin.**

The aim of this study was to determine the level of changes in serum levels of the three mentioned factors in people with gastritis and their association with the presence or absence of *H. Pylori*.

Subjects were divided into two groups of 35 gastritis individuals with *H. pylori* and 25 individuals without *H. pylori*. Biopsy and blood samples were collected from each subject. *H. pylori* positivity was investigated regarding the serum level by enzyme-linked immunosorbent assay (ELISA) kit and its presence in the tissue was examined by histopathology observations and rapid urease test (RUT). LL-37, MBL and M-ficolin serum levels indicated that 58% of the subjects were infected with *H. pylori*. Subjects with MBL levels lower than 500 ng/mL in the sera were significantly infected with *H. pylori*, and subjects with MBL levels higher than 1000 ng/ml often did not have *H. pylori* infection. The level of LL-37 was increased, while M-ficolin showed no significant change in the presence of *H. pylori*.

Findings indicated that lower levels of MBL and higher levels of LL-37 might be involved in *H. pylori* infection, while M-ficolin seems to be less effective in the infection.

Key words: Helicobacter pylori, **gastritis, LL-37, MBL, M-ficolin**

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INTRODUCTION

Gastritis is one of the most common types of gastrointestinal disorders, in which inflammation or mild infection occurs in the mucous membrane of the stomach. This disorder usually occurs in two forms - acute or chronic (1). If left untreated, gastric inflammation can turn chronic and lead to gastric motility disorder and, gradually, peptic ulcer (2). Among the factors causing inflammation, infection with *Helicobacter pylori* (*H. pylori*) is a common cause. *Helicobacter pylori* is a kind of spiral or spherical Gram-negative bacteria from the *Helicopter* family that infects more than half of the world's population (3, 4). The *H. pylori*-induced inflammation gradually affects the entire stomach and can lead to thinning and loss of the gastric mucosa (atrophy) (5, 6). The reason is that the immune system, despite the reaction, has no access to the bacterium. The main source and host of *H. pylori* is human, and it is estimated that in 70-90% of gastric inflammation cases, infection with *H. pylori* is the main cause. As immune cells become infected with *H. pylori*, the first immune responses are stimulated and IgG and IgA antibodies in the blood serum are increased (7). LL-37 is an antimicrobial peptide also found in epithelial cells of the gastrointestinal system, and plays other defensive roles such as inflammatory response regulation, chemoattraction of the cellular immune system cells into the infection and inflammation loci and attachment to neutralization of lipopolysaccharide (LPS) (8-10). Along with these responses, Mannose Binding Lectin (MBL) is an important factor for activeting the complement system and anti-microbial resistance, which facilitates phagocytosis and initiates inflammatory responses (11, 12). Ficolins, as another group of lectins, are similar to MBLs. Ficolin 1, commonly called M-ficolin, is a protein, mainly expressed on the peripheral blood leukocytes but also acts as a plasma protein with the activity of binding to elastin (13, 14). In addition to the three factors mentioned above, some other factors play their role in the response to *Helicobacter infection* in people with gastritis (15).

However, despite the importance of this controversial medical problem, relatively little study has been done on the three factors of LL-37, MBL and ficolin in gastric inflammation and the presence or absence of *H. Pylori*. The aim of this study was to determine the level of changes in serum levels of the three mentioned factors in people with gastritis and their association with the presence or absence of *H. Pylori*.

MATERIALS AND METHODS

SUBJECTS

In this case-control study, carried out from April 2016 to June 2017, biopsy and blood samples were collected from 35 individuals with positive *H. pylori* gastritis as the case group and 25 individuals with negative *H. pylori* gastritis as the control group, in the division of gastroenterology of Ayatollah Rouhani Hospital, Babol University of Medical Sciences, Babol, Iran. In order to increase the reliability of results, the groups were adjusted regarding age and sex. Individual data of the subjects such as age, sex, type of diagnosis and medicine use were extracted from each patient's case and recorded for implementation in the study. Inclusion criteria in this study were medical history of prior gastric involvements (anorexia, nausea, and upper abdominal pain) and any disease that could be responsible for acute dyspeptic symptoms. People with high levels of gastric acid secretion, history of gastric cancer and transplantation as well as users of non-steroidal anti-inflammatory drugs (NSAIDs) were excluded from the study to avoid inaccuracy in the results. Moreover, the study cases underwent the upper gastrointestinal endoscopy of the antrum (Pentax EG-2940) for the purpose of obtaining biopsy specimens. This protocol was approved by the Ethics Committee of Babol University of Medical Sciences. All patients signed a written informed consent form.

DETERMINATION OF HELICOBACTER PYLORI STATUS

For the sera preparation, a 2-cc blood sample was collected from each subject in an EDTA-free tube before endoscopy. Samples were centrifuged immediately at the rate of 1300 × g for 30 minutes and the extracted sera were stored at -20 °C. The anti-*H. pylori* antibody titer in the sera was measured by ELISA kit (Hangzhou Eastbiopharm Co., Ltd., Hangzhou, China).The commercial kit was used in the manner explained in the factory manual. The optical density (OD) of the samples was measured at 450 nm by the ELISA reader. The cut-off point for positive IgG was higher than 10 U/mL. The presence of the bacterium in the biopsy samples was examined by histological reports. In order to select gastritis patients in the pathology section, paraffin blocks were produced from the samples fixed in 10% formalin solution and the prepared cuts were stained with hematoxylin-eosin and Giemsa. The hematoxylin method was used to deter-

mine the status of gastritis while Giemsa staining was used to determine the presence of *H. pylori*. This microorganism was observed in the shape of S or comma in the prepared LAMs during the histopathologic study by Giemsa staining. To measure urease activity, a rapid test kit was used. *H. pylori* specimens changed the primary yellow color of the reagent to red and eventually purple. The reduction in the reaction time was indicative of the severity of contamination. Upon performing RUT, histology and the ELISA test, the presence of *H. pylori* was confirmed according to the Sydney standard (two positive test results out of three) (16).

MEASURING THE SERUM LEVELS OF MBL, M-FICOLIN AND CATHELICIDIN LL-37

In order to measure the serum level of MBL in positive/negative *H. pylori* gastritis subjects, the Eastbiopharm ELISA kit (Hangzhou Eastbiopharm Co., Ltd., Hangzhou, China) was used according to the factory manual. This kit makes it possible to measure MBL at the range of 5-500 ng/mL. First, the serum samples were removed from the freezer and placed at the room temperature. A 40-μL serum sample was added to each well and then 10 μL of MBL antibody and 50 μL of streptavidin HRP were added to each well. Then, the well plate was covered and shaken gently until the contents were mixed and incubated at 37 °C for 60 minutes. The liquid was then removed and the wells were washed five times to disperse unattached enzymes. 50 μL of chromogen A solution followed by 50 μL of chromogen B (3, 3', 5, 5′-tetramethylbenzidine (TMB)) solution were added to each well. The plate was shaken gently and incubated for 10 minutes at 37 °C. For the last step, 50 μL of the stop solution was added to each well to stop the reaction (blue immediately changes to yellow). The linear regression equation of the standard diagram was drawn based on standard concentrations and proportional to acquired ODs. Then, the concentrations of samples were obtained. The serum levels of cathelicidin and LL37 were measured using Eastbiopharm ELISA kit (Hangzhou Eastbiopharm Co., Ltd., Hangzhou, China) in similar steps.

STATISTICAL ANALYSIS

GraphPad Prism 6 was used for statistical analysis of the collected data. Independent samples T-test and ANOVA were used for the comparison of two groups of quantitative data and more than two groups, respectively. The results were reported as mean ± SD and the rate of p-value less than 0.05 was considered significant.

RESULTS

DEMOGRAPHIC INFORMATION RELATED TO SUBJECTS

The sample of the study consisted of 60 participants who were divided into two groups. The case group consisted of 35 subjects with *H. pylori*, with the mean age of 45 ± 10.4 years. The control group consisted of 25 subjects with no detectable presence of *H. pylori* and the mean age of 47.4 ± 13.5 years (Table 1).

Table1. **Demographic information on the subjects**

Demographic and clinical complication	H.P+ (n= 35)	H.P- (n= 25)
Age (years) Mean ± SD	45 ± 13.5	55 ± 16.4
Range	25 - 81	21 - 71
Gender (F/M)	19/16	16/9
Smoking	2	1
Drinking	0	0
Drug	1	2

H.P+: *Helicobacter pylori* positive, H.P-: *Helicobacter pylori* negative

RESULTS OF H. PYLORI PRESENCE ANALYSIS

Pathological reports, RUT and ELISA tests performed for measuring IgG antibody titer against *H. pylori* indicated that approximately 57%, 59% and 58% of the subjects were infected with the bacterium, respectively. The mean concentration of IgG in both groups is shown in Table 2. Specimens that were reported positive in two tests were considered infected with *H. pylori.* Accordingly, 35(58%) of subjects were found to be infected with *H. pylori.*

RELATIONSHIP BETWEEN THE SERUM LEVELS OF MBL, M-FICOLIN AND LL-37 AND THE PRESENCE OF H. PYLORI

Measurement of the serum level of LL-37 in the case and the control group revealed a significant correlation between LL-37 serum concentration and *H. pylori* infection. The mean serum level in LL-37 *H. pylori*-positive subjects (81.92 ± 10.47) was higher than that in *H. pylori*-negative ones (50.29 ± 3.8) (p = 0.002). However, there was no statistical correlation (based on comparison of the total concentration of the two groups) between MBL serum level and *H. pylori* infection in terms of p value. This insignificant relationship was also observed be-tween M-ficolin serum level and *H. pylori* infection (Table 3). In addition, the serum levels of WBC, neutrophils and lymphocytes are shown in Table 4.

Table 2. **Evaluation of the presence of *H. pylori* based on anti-*H. pylori* IgG antibody**

IgG Unit in serum		Number(%)	IgG Serum con. U/ml
H. pylori	Positive (> 10 U/ml)	36 (60%)	50.2
	Negative (< 10 U/ml)	24 (40%)	21.6
Total		60	-

Table 3. **Evaluation of the serum levels of ficolin, MBL and LL-37 as measured in two groups**

Measured factors	*H. Pylori* status	Mean ± SEM number	P value
Ficolin	H.P+	263.2 ± 54.47, n = 35	0.81
	H.P-	249.8 ± 50.98, n = 25	
MBL	H.P+	898.5 ± 106.5, n = 35	0.07
	H.P-	1183 ± 106.2, n = 25	
LL-37	H.P+	81.92 ± 10.47, n = 35	0.002**
	H.P-	50.29 ± 3.867, n = 25	

H.P+: *Helicobacter pylori* positive,
H.P-: *Helicobacter pylori* negative,
MBL: Manose Binding Lectin (MBL)

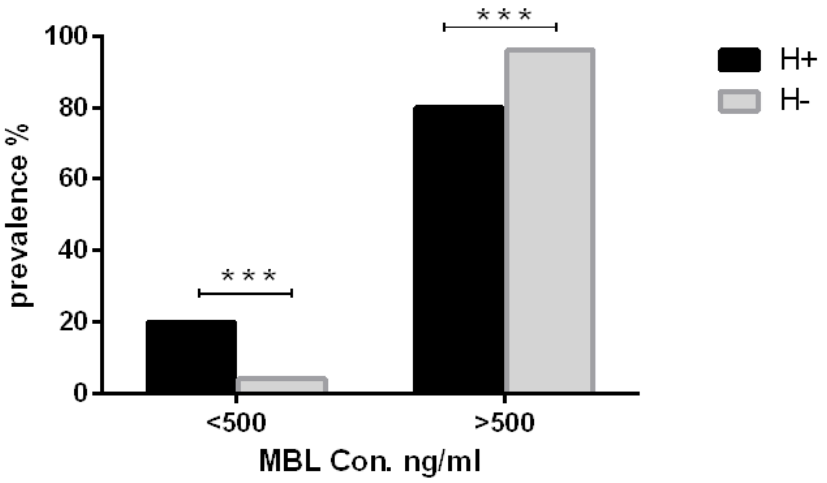
Table 4. **Evaluation of the serum levels of WBC, neutrophil and lymphocyte as measured in two groups**

Measured factors	*H. Pylori* status	Mean ± SEM number	P value
WBC	H.P+	8360 ± 305.4, n = 35	0.04*
	H.P-	7429 ± 335.3, n = 24	
Neutrophil	H.P+	60.09 ± 1.740, n = 35	0.04*
	H.P-	55.22 ± 1.503, n = 25	
Lymphocyte	H.P+	32.69 ± 1.658, n = 35	0.2
	H.P-	35.62 ± 1.751, n = 25	

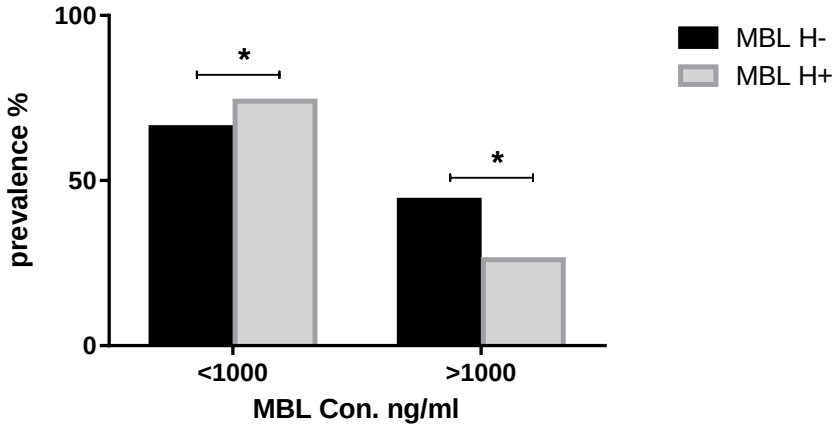
H.P+: *Helicobacter pylori* positive,
H.P-: *Helicobacter pylori* negative,
WBC: White Blood Cells

RELATIONSHIP BETWEEN MBL SERUM LEVEL AND H. PYLORI POSITIVITY BASED ON DEFINED CUT-OFF POINTS

According to Miranda et al., the ranges of 0-500 ng/mL, 501-1000 ng/mL, and > 1000 ng/mL represent low, medium and high levels of MBL, respectively. Van Till et al. reported that subjects with MBL levels less than 500 ng/mL were more susceptible to abdominal yeast infection, and Damiens et al. showed that < 100 ng/mL MBL levels can be considered as high MBL deficiencies. As shown in tables 3-5, 20% of *H. pylori*-infected subjects had MBL levels of < 500 ng/mL compared to the 4% of *H. pylori*-uninfected ones. Subjects with MBL levels of < 500 ng/mL are six times more susceptible to *H. pylori* infection. In addition, 44% of *H. pylori*-uninfected subjects show MBL levels of > 1000 ng/ml compared to 26% of *H. pylori*-infected ones. Subjects with higher MBL levels are less susceptible to *H. pylori* infection (Graph 1 and 2).



Graph 1. **The frequency of individuals with serum MBL levels of more and less than 500 ng / ml. Subjects with MBL levels of < 500 ng/ml are 6 times more susceptible to *Helicobacter pylori* infection (p = 0.0008)**



Graph 2. **The frequency of subjects with serum MBL levels of more and less than of 1000 ng / ml. Subjects with levels of > 1000 ng/ml are significantly less *H. pylori*-infected (p = 0.04)**

DISCUSSION

Gastritis is inflammation of the gastric mucosa caused by various conditions. This inflammation can be initiated or intensified by the presence and colonization of *H. Pylori*. It has been observed that more than half of the world's population is infected with *H. pylori*. *H. pylori*-induced inflammations are associated with the persistence of this microorganism in the gastric mucosal epithelium (1, 2). It is generally accepted that *H. pylori* in gastric epithelial cells in patients with gastritis as well as human monocytes leads to the expression and release of proinflammatory factors, free radicals and antimicrobial peptides (3). Therefore, it is conceivable to hypothesize that the serum level of some elements may be affected in individuals infected with the bacterium. Findings have demonstrated that antimicrobial peptide LL-37 plays a key role in the regulation of inflammatory and protective responses of human neutrophil bacterial activity and release of inflammatory mediators when antimicrobial activity of neutrophils is increased (10). Along the same lines, our results indicated that the serum level of LL-37 is significantly higher in *H. pylori*-positive individuals in comparison to *H.pylori*-negative ones (81.92 ± 10.47 vs 50.29 ± 3.867). Leszczyńska K et al. also revealed that the amount of LL-37 serum produced in mucosa increased in individuals with *H. pylori* infection in comparison with the control group. It can be inferred that this peptide can be effective in the regulation of immune-inflammatory responses apart from its antimicrobial activity against *H. pylori* (17). Generally, it is considered that MBL plays an essential role in the protection against *H. pylori* infection via initiating the lectin complement pathway and its opsonic activity in facilitating phagocytosis (18). However, in this study, we found that MBL had a lower presence in the serum of *H. pylori*-infected subjects and that the difference of MBL concentration changes between the case and the control group was not statistically significant. Given the fact that this lack of significant correlation might be due to the small sample size, MBL concentration was assessed based on cut-offs (< 500 ng/ml as low, 500-1000 ng/ml as medium and > 1000 ng/ml as higher level) defined by Miranda et al. Our study showed that individuals with MBL levels lower than 500 ng/ml were significantly infected with *H. pylori*. People with MBL levels higher than 1000 ng/ml often did not have H. pylori infection.

Bak-Romaniszyn L et al. studied the association of MBL serum level with chronic gastritis and duodenal ulcer in 174 children aged 6-17. They observed that *H. pylori*-infected (1809 ng / ml) children with gastritis (1439 ng/ml) had significantly lower MBL levels than the controls (2545 ng/ml) (19). An explanation for the decreased level of MBL in *H. pylori*-infected cases is that *H. pylori* can escape phagocytosis when covered with MBL, a phenomenon that was previously reported for vitronectin and sialic acid by Chmiela et al. (20). This effect occurs in part to the fact that MBL covers *H. pylori*-associated important adhesion molecules and attenuates *H. pylori* engulfment by phagocytes (21). On the other hand, MBL binding ability can be neutralized by *H. pylori* urease in gastric mucosa (22). Stimulation of the release of inflammatory cytokines such as TNFα, as an MBL activity, can be a reason for the low presence of

MBL in *H. pylori* infection (23). Keeping in view these results, the present study suggests that the presence and employment of MBL in immune responses against *H. pylori* infection might be necessary.

The complement lectin pathway can be activated in both the presence and absence of MBL by ficolins, which can bind GlcNAc and mannose on the surface of *H. pylori* (11). Considering this, ficolin serum level was measured in this study despite an increase and it was not statistically significant (263.2-± 54.47 VS 249.8 ± 50.98). It was due to the higher presence of M-ficolin on the surface of leukocyte membrane in comparison to sera. In 2005, Yu Liu conducted a comprehensive study on M-ficolin and reported that M-ficolin is a secondary protein in activating the complement lectin pathway. Based on their studies, M-ficolin can also form homopolymers using intermolecular disulfide bonding, similar to L-ficolin and MBL. However, after trying to isolate M-ficolin from the serum with GlcNAc-agarose, they did not obtain a detectable level. Compared with L-ficolin, M-ficolin appears to be an acute protein that is temporarily stored in secondary granules of leukocytes to secrete properly in the local areas upon stimulation of immune system (24).

The present study revealed that the serum levels of white blood cells and neutrophils were significantly higher in *H. pylori*-infected cases, whereas the serum level of lymphocytes were not statistically significant. In a similar study, white blood cell count was evaluated in 94 patients with duodenal ulcer during and after the infection. They found that successful treatment of patient results in a significant reduction in the number of white blood cells (7413 ± 520 /μL to 6738 ± 410 /μL).This correlation was also observed in circulating polymer-phonuclear leukocyte cells (4594 ± 370 / μL to 3855 ± 270/ μL) (25). From a practical point of view, an increase in the number of cells could be related to either drainage of cellular reservoirs or increased production of WBCs (26). However, this merits further research. These increased the levels of leukocytes, especially neutrophils as cells that cause inflammation, must be controlled because of the inflammation-associated damages they can inflict.

CONCLUSION

This study indicated that MBL and LL-37 serum levels were more associated with the presence of *H. pylori* than M-ficolin. Findings indicated that lowel levels of MBL and higher levels of LL-37 were involved in *H. pylori* infection, while M-ficolin with no significant change had no important part in it. These three factors might be protective or aggregative in immunomodulation.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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Povezanost infekcije izazvane bakterijom *Helicobacter Pylori* kod ispitanika sa gastritisom i serumskih nivoa LL-37, MBL i M-fikolina

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SAŽETAK

***Helicobacter pylori (H. pylori)* može da stimuliše imunske odgovore i da dovede do oslobađanja proinflamatornih faktora i antimikrobnih peptida poput LL-37, proteina koji vezuje manozu (mannose-binding lectin (MBL)-eng.) i M-fikolina.**

Cilj ove studije bio je ispitivanje promena serumskih nivoa pomenutih faktora kod ispitanika sa gastritisom i njihove povezanosti sa prisustvom ili odsustvom bakterije *H. Pylori*.

Ispitanici su bili podeljeni u dve grupe: kod 35 ispitanika utvrđeno je prisustvo bakterije *H. pylori*, a kod 25 ispitanika nije. Biopsije i uzorci krvi uzimani su kod svakog ispitanika. Prisustvo *H. Pylori* utrđivano je enzimskim imunotestom ELISA, dok je njeno prisustvo u tkivu utvrđeno histopatološkim analizama, kao i brzim ureaza testom (rapid urease test - RUR-eng). Serumski nivoi LL-37, MBL-a i M-fikolina pronađeni su kod 58% ispitanika inficiranih bakterijom *H. pylori*. Ispitanici kod kojih su nivoi MBL-a bili ispod 500 ng/mL, bili su značajno inficirani bakterijom *H. pylori*, dok kod ispitanika kod kojih su nivoi MBL-a bili iznad 1000 ng/ml prisustvo bakterije nije utvrđeno. Nivo LL-37 bio je povećan, dok se nivo M-fikolina nije značajno promenio u prisustvu bakterije *H. pylori*.

Nalazi su pokazali da niži nivoi MBL-a i viši nivoi LL-37 mogu biti detektovani kod infekcije izazvane bakterijom *H. pylori*, dok je M-fikolin manje aktivan kod ove infekcije.

***Ključne reči: Helicobacter pylori*, gastritis, LL-37, MBL, M-fikolin**