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Relationship between *Helicobacter pylori* cytotoxin-associated gene A protein with clinical outcomes in patients with rheumatoid arthritis

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ABSTRACT

Introduction: The *Helicobacter pylori (H. pylori)* infection leads to intensification of symptoms and calenture of autoimmune diseases. This study aimed to evaluate the relationship between *H. pylori* infection and clinical outcomes in rheumatoid arthritis (RA) patients.

Methodology: This study was performed on 100 RA patients. Blood samples were collected for measuring Anti-*H. pylori* IgG antibodies and cytotoxin-associated gene A (CagA) protein. Fresh fecal samples were also collected and the fecal *H. pylori* antigen was extracted. Clinical condition as well as severity and type of RA symptoms in both groups of *H. pylori* positive and *H. pylori* negative were also compared.

Results: Serum levels of rheumatoid factor (RF), ESR, CRP, anti-cyclic citrullinated peptide (Anti−CCP), and anti-mutated citrullinated vimentin (Anti-MCV) were significantly higher in *H. pylori* positive patients than in *H. pylori* negative patients ($P < 0.05$). Serum RF, ESR, CRP and Anti-MCV levels were significantly higher in CagA positive patients than in CagA negative patients ($P < 0.05$). There were no significant differences in DAS-28 scores between *H. pylori* positive and *H. pylori* negative patients ($P = 0.064$) as well as between patients with positive and negative fecal *H. pylori* antigen ($P = 0.237$). However, DAS-28 score was significantly higher in CagA positive patients than in CagA negative patients ($P < 0.001$). Furthermore, mean VAS score was significantly higher in *H. pylori* positive patients ($P = 0.031$) and CagA positive patients ($P = 0.004$); however, there were no significant differences in VAS scores between patients with positive and negative fecal *H. pylori* antigen ($P = 0.310$).

Conclusion: Follow-up and examination of RA patients in terms of infection with serum and fecal *H. pylori* organism and CagA seems necessary that will contribute to better and further control and treatment of the patients.

1. Introduction

Rheumatoid arthritis (RA) is a common chronic inflammatory and systemic disease that causes major disabilities in adulthood [1]. Disease prevalence is approximately one percent of the world population (between 0.4–2.1%) and affects women nearly three times more than men [1]. This disease affects 750 per million people every year. The incidence rate is approximately 1:100,000 and 600,000 of Iranian population [2]. RA, a disease with unknown etiology, is characterized by peripheral symmetric polyarthritis [1]. The main characteristic of the disease is inflammation of the synovial membrane of cartilage, swelling, pain and joint dysfunction, which can destroy cartilage and bone and cause joint deformation [2]. RA is directly correlated with the risk of other chronic diseases including cardiovascular diseases, making it one of the major public health problems [2]. Combined treatment protocols (including Non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), biological agents and *etc*) are used for this disease [2].

Several factors such as microbial and infectious causes have been ever known as triggering, exacerbating or creating resistance to therapy in RA. *Helicobacter pylori* (*H. pylori*) is one of the most commonly studied infectious agents suggested as agents triggering autoimmune response. Foreign invaders such as infectious agents are dealt with the immune system via the secretion of inflammatory cytokines, cellular

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activation, and oxidative burst, thereby infection is terminated. However, *H. pylori* is not killed, as it disguises itself; the pathogen is covered by structures identical to the human Lewis antigens, repeated many times in the bacterial lipopolysaccharide (LPS). Moreover, variety of *H. pylori* antigens are recognized as self by the human immune system which may lead to the autoimmunity such as autoimmune gastritis, thyroiditis, infertility, and etc. The persistence of *H. pylori* equates with the persistence of chronic inflammatory molecules and chronic inflammation [3,4]. The strains of the bacterium coding for the cytotoxin-associated gene A (CagA) protein are endowed with an enhanced capability of stimulating the secretion of proinflammatory cytokines which play a role at all stages of the RA. Their signalling pathways are displayed amongst genes encoded at disease risk location; they modulate the immunological 'prodrome' including autoantibody pathogenicity and joint pain; they mediate stromal dysregulation within the joint as well as they characterize and keep the inflammation [5]. In addition, this inflammatory response may contribute to the development of cross-reactive antibodies and antigen-antibody complexes resulting in the damage to other organs [6]. Indeed, this infectious agent not solely causes or amplifies the symptoms of RA, or any chronic inflammation, but its total burden upon a given immune environment is important [7]. Moreover, there is a highly increased occurrence of acute myocardial infarction (AMI) among RA patients. It is indicated that same molecular mechanisms are involved in causing AMI, RA, and cancer. In addition to inflammation, *H. pylori* (and other infectious agents) amplify coagulative mechanisms, and therefore are risk factors for AMI and cerebral ischemic events, in particular for young and middle aged patients [8]. Also, *H. pylori* infection causes large increases in oxygen and nitrogen oxidative species which may aggravate RA [9]. A study conducted by Zentilin et al. [10] showed that patients with *H. pylori* positive had a tendency for severe clinical manifestations than *H. pylori* negative patients, which was indicated by increased number of painful joints and functional disability. In addition, the laboratory indices of activity including Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) were higher in *H. pylori* positive than in *H. pylori* negative patients [10]. In another study, no significant difference was found either clinically or laboratory between *H. pylori* positive and *H. pylori* negative patients in rheumatoid activity except in CRP and the authors concluded that there was no relation between *H. pylori* infection and RA activity [11]. El-Hewala et al. [12] and Wen et al. [13] found that *H. pylori* positive RA group had significantly higher DAS-28 than the negative group.

Considering conflicting results regarding *H. pylori* infection and RA and due to incidence of various disabilities and prolonged duration of RA in infected subjects as well as in quest for better identification of the disease and its triggering and aggravating causes, we were encouraged to take a step toward knowing it. The aim of present study was to investigate the relationship between *H. pylori* infection and clinical outcomes in RA patients.

2. Materials and methods

2.1. Subjects

In a case-control study conducted in the rheumatology clinic of Imam Reza medical educational center and Sina Hospital affiliated to Rheumatology Section, Department of Internal Medicine, Tabriz University of Medical Sciences, the role of *H. pylori* in patients with RA was examined. After presenting adequate and understandable language, written informed consent was obtained from all patients. No additional expenses were imposed to the patients for conducting the examinations associated with this research. As well, all information were confidential.

2.2. Clinical and biochemical measurements

The study population consisted of RA patients, *H. pylori* positive and *H. pylori* negative based on the incidence rate of the disease and financial and time constraints according to the statistical advisor's opinion and considering confidence level of 95% and the second error of 0.20 and prevalence of 25% sample size was calculated 47 subjects which increased to 50 after rounding up. A total of 50 patients and 50 controls were selected and enrolled into the study.

In this study, 100 RA patients (20–65 years) were selected via simple sampling and according to the new RA diagnostic criteria (ACR/EULAR) [14,15] and enrolled into the study after obtaining their written informed consent. After exact and complete physical examinations and filling the questionnaire containing personal information, clinical and laboratory data were obtained and recorded. Patients who received only H2 blocker or PPI were eligible to be included in the study. Patients who had received *H. pylori* eradication treatment in the last three months, or were taking *H. pylori* eradication treatment were not included in the study.

Blood samples were taken from the patients and their serum was kept below −70 °C until the experimentation time. Anti-*H. pylori* IgG antibodies was measured using enzyme-linked immunosorbent (ELISA) kit (Padtan-elm, Iran). Samples with Anti-*H. pylori* IgG values more than 30 Iu/ml were considered positive. The second part of this study was to determine the status of cytotoxin-associated gene A (CagA) protein strains in patients with erosive esophagitis and in the control group. The status of IgG antibody against CagA protein was measured by ELISA using CagA-IgG EIA well kit. The antibody concentration was obtained based on specific standards curve against CagA protein and in terms of Arb/ml unit. The positive samples were those with more than 20 Arb/ml of antibodies against CagA protein.

Fresh fecal samples were also taken observing the conditions to avoid taking antibiotics for 7 days as well as red meat for three days, and the fecal *H. pylori* antigen was extracted by the special buffer and was measured by ELISA at the same day. And eventually, clinical condition as well as severity and type of RA symptoms in both groups of *H. pylori* positive and *H. pylori* negative were compared.

2.3. Statistical analysis

Statistical analyses were performed by SPSS software version 16.0 (SPSS, Inc., USA). Normality of variables distribution was evaluated using the Kolmogorov–Smirnov test. Categorical and normally distributed quantitative variables were displayed as numbers (percentages) and means ± SD, respectively. Between group comparisons were made by chi-square test and independent sample t-test, as appropriate. $P < 0.05$ was considered statistically significant.

3. Results

In this study, 24 patients were males and 76 were females. The mean ± SD age was 57.46 ± 12.11 years in males and 51.05 ± 13.18 years in females ($P = 0.035$). Mean duration of disease was 8.92 ± 7.12 years in males and 9.51 ± 7.76 years in females ($P = 0.737$). Furthermore, all our study patients were treated with prednisolone and DMARDs including methotrexate and hydroxychloroquine.

Table 1 presents laboratory parameters based on serum *H. pylori* antibody levels in studied patients. According to Table 1, serum levels of rheumatoid factor (RF), ESR, CRP, anti-cyclic citrullinated peptide (Anti−CCP), and anti-mutated citrullinated vimentin (Anti-MCV) were significantly higher in *H. pylori* positive patients than in *H. pylori* negative patients ($P < 0.05$).

Table 2 presents laboratory parameters based on serum CagA protein in studied patients. As indicated in Table 2, RF, ESR, CRP and Anti-MCV levels were significantly higher in CagA positive patients than in

Table 1
Laboratory findings of RA patients based on *H. pylori* IgG.

	H. pylori IgG (Iu/ml)		P*
	< 30	> 30	
RF	15.51 ± 19.87	27.61 ± 14.07	< 0.001
ESR	14.78 ± 15.96	31.29 ± 17.06	< 0.001
CRP	12.47 ± 8.01	22.85 ± 11.26	< 0.001
Hemoglobin	12.75 ± 1.55	12.52 ± 1.33	0.410
Anti-CCP	68.93 ± 357.39	62.11 ± 123.84	0.889
Anti-MCV	19.67 ± 16.64	36.07 ± 17.46	0.002

RA: rheumatoid arthritis; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Anti−CCP: anti-cyclic citrullinated peptide antibody; Anti-MCV: anti-mutated citrullinated vimentin.
Values are means ± SD.
P < 0.05 was considered significant.
**P*-values indicate comparison between groups (independent sample t-test).

Table 2
Laboratory findings of RA patients based on CagA protein.

	CagA protein (Arb/ml)		P*
	< 25	> 25	
RF	12.65 ± 9.99	32.96 ± 18.19	< 0.001
ESR	15.45 ± 15.76	33.75 ± 16.39	< 0.001
CRP	12.95 ± 8.56	24.33 ± 10.80	< 0.001
Hemoglobin	12.79 ± 1.43	12.43 ± 1.40	0.232
Anti-CCP	24.11 ± 25.16	108.21 ± 352.40	0.078
Anti-MCV	18.08 ± 16.04	40.28 ± 14.45	< 0.001

RA: rheumatoid arthritis; CagA: cytotoxin-associated gene A; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Anti−CCP: anti-cyclic citrullinated peptide antibody; Anti-MCV: anti-mutated citrullinated vimentin.
Values are means ± SD.
P < 0.05 was considered significant.
**P*-values indicate comparison between groups (independent sample t-test).

CagA negative patients (P < 0.05).

As presented in Table 3, there were no significant differences in DAS-28 scores between *H. pylori* positive and *H. pylori* negative patients (P = 0.064) as well as between patients with positive and negative fecal *H. pylori* antigen (P = 0.237). However, DAS-28 score was significantly higher in CagA positive patients than in CagA negative patients (P < 0.001). Furthermore, mean VAS score was significantly higher in *H. pylori* positive patients (P = 0.031) and CagA positive patients (P = 0.004); however, there were no significant differences in VAS scores between patients with positive and negative fecal *H. pylori* antigen (P = 0.310).

Table 3
Correlation between DAS-28 and VAS with *H. pylori* IgG, Stool antigen and CagA protein in RA patients.

		DAS-28		VAS	
		Mean ± SD	P*	Mean ± SD	P*
H. pylori IgG (Iu/ml)	< 30	4.89 ± 0.98	0.064	39.33 ± 11.90	0.031
	> 30	5.24 ± 0.92		44.61 ± 12.61	
Stool antigen (Iu/ml)	< 23	5.20 ± 0.91	0.237	43.57 ± 11.23	0.310
	> 23	4.97 ± 1.01		41.10 ± 13.82	
CagA protein (Arb/ml)	< 25	4.71 ± 0.84	< 0.001	39.27 ± 11.36	0.004
	> 25	5.50 ± 0.91		45.69 ± 12.97	

RA: rheumatoid arthritis; DAS-28: Disease Activity Score-28; VAS: visual analog scale; CagA: cytotoxin-associated gene A.
Values are means ± SD.
P < 0.05 was considered significant.
**P*-values indicate comparison between groups (independent sample t-test).

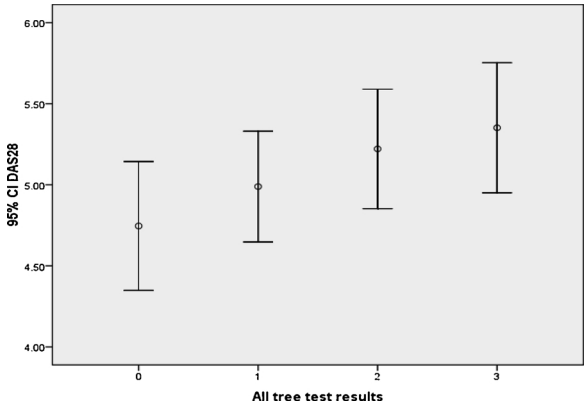

Fig. 1. Distribution of DAS-28 score based on frequency of positive test in RA patients.

Considering all three tests altogether, 85 patients had at least one positive test and all tests were negative only in 22 patients. Furthermore, 29 patients had one, 32 patients had two and 24 patients had three positive tests. The DAS-28 score range in patients based on the number of positive tests is shown in Fig. 1. Mean DAS-28 scores were 4.74 ± 0.89 in patients with three negative tests, 4.0 ± 98.89 in patients with one positive test, 5.22 ± 1.02 in patients with two positive tests and 5.0 ± 35.94 in patients with three positive tests; although the mean DAS-28 score in patients increases with an increase in the number of positive tests, this difference was not statistically significant (P = 0.136).

4. Discussion

The relationship between infection and autoimmunity has been intensely investigated over the last years. *H. pylori* infection in autoimmune diseases causes aggravated symptoms and inflammation of these diseases. In present study, there were *H. pylori* antigen in 57.9%, fecal *H. pylori* antigen in 47.7% and CagA antigen in 48.6% of the patients. Jones et al. [16] examined the frequency of *H. pylori* infection in RA patients and reported that 43–68% of RA patients had *H. pylori* infection which was consistent with our study.

Based on our study, serum levels of RF, ESR, CRP, Anti−CCP, and Anti-MCV were significantly higher in *H. pylori* positive patients than in *H. pylori* negative patients. Moreover, RF, ESR, CRP and Anti-MCV levels were significantly higher in CagA positive patients than in CagA negative patients. Similar to our study, Zentilin et al. [10] showed that laboratory indices of activity including ESR and CRP were higher in *H. pylori* positive than in *H. pylori* negative patients [10]. In another study, no significant difference was found either in clinical or laboratory parameters between *H. pylori* positive and *H. pylori* negative patients in rheumatoid activity except in CRP and therefore the authors concluded that there was no relationship between *H. pylori* infection and RA activity [11].

According to our study, there were no significant differences in DAS-28 scores between *H. pylori* positive and *H. pylori* negative patients as well as between patients with positive and negative fecal *H. pylori* antigen; however, DAS-28 and VAS scores were significantly higher in CagA positive patients than in CagA negative patients. It was reported that CagA positive strains were associated with more severe inflammatory reactions and an increased risk of adverse clinical outcomes in western countries [17] which was consistent with our study. A study in RA patients with positive *H. pylori* infection under *H. pylori* eradication treatment clearly reported a reduction in disease symptoms within two years; whilst RA patients in the control group with negative *H. pylori* infection had no significant changes in clinical symptoms [10]. In another study, Smyk et al. [18] examined the role of *H. pylori* infection in RA patients and stated that *H. pylori* infection could be a

stimulating and intensifying factor in autoimmune diseases. Magen et al. [19] evaluated the role of *H. pylori* infection in various diseases and showed that there was a cross reactivity between T-cells and production of autoantibodies in these patients, which could cause or aggravate autoimmune diseases in patients with *H. pylori* infection. Jafarzadeh et al. [20] in a study in RA patients with *H. pylori* infection stated that RF and antinuclear antibodies (ANA) levels in patients with peptic ulcer in the field of *H. pylori* infection was significantly higher than the control group. Hasni et al. [21] assessed the role of *H. pylori* infection in autoimmune diseases and indicated that *H. pylori* infection could intensify or trigger autoimmune diseases or in patients predisposed to these diseases caused cross reactivity between the autoantibodies in T-cells. Tanaka et al. [22] showed that *H. pylori* infection in RA patients was significantly lower than the control group. In addition, El-Hewala et al. [12] and Wen et al. [13] found that *H. pylori* positive RA group had significantly higher DAS-28 than the negative group. Furthermore, Zentilin et al. [10] showed that patients with *H. pylori* positive had a tendency for severe clinical manifestations than *H. pylori* negative patients which was indicated by increased number of painful joints and functional disability. They also stated that eradicating *H. pylori* infection reduced the severity of RA [10]. However, in another study, Zentilin et al. [23] showed that *H. pylori* infection intensified the symptoms in RA patients. Furthermore, Voutilainen et al. [24] stated that 30% of RA patients had gastric ulcer which was significantly higher than the control group and 48.8% of patients with gastric ulcer had *H. pylori* infection. Goggin et al. [25] stated that use of NSAIDs along with *H. pylori* infection aggravated gastritis complications in RA patients. Gubbins et al. [26] reported that 41% of RA patients had *H. pylori* infection; however, no relationship was observed between intolerance for NSAIDs and *H. pylori* infection in RA patients. It is indicated that development of systemic rheumatic disease is unlikely to depend exclusively on an infectious agent. Instead, it likely occurs as a consequence of interactions between the infectious agent and a cascade of host-specific factors. In a particular genetic background, *H. pylori* infection may be considered as an etiologic factor for the expression of some autoimmune disease [27]. In other word, infectious agent not solely causes or amplifies RA symptoms, but its total burden upon a given immune environment is important. This is not surprising since immune response to infection is highly individual. In fact, the culprit is when the balance between the proinflammatory and the protective mechanisms including both genetic and environmental factors overcome the threshold for a given individual. The protective mechanisms are both genetic including prevalent interleukins and their receptors, their abundance, as well as their polymorphisms, and environment such as dietary factors; *e.g.* it was reported that over 700 components of the diet interfere with nuclear factor kappa beta (NF-κβ) which is a main regulator of inflammatory cytokines. Furthermore, the genetic polymorphism of both interleukins and receptors was shown very important in determining disease outcome of *H. pylori* infection (*e.g.* in causing gastric adenocarcinoma). In addition, polymorphisms in genes unrelated to immunity may cause an infectious agent to induce disease through molecular mimicry in one person and not another [7,26].

Our study had some limitations including the low number of patients and limited project budget.

Follow up and treatment of RA patients, particularly resistant cases with high DAS-28 score is recommended. Also, examination of those patients in terms of infection with serum and fecal *H. pylori* organism and CagA protein seems necessary that will contribute to better and further control and treatment of the patients.

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