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**Research Article** 

# Evaluating the Effects of *Helicobacter pylori* Eradication on Clinical Course of Rheumatoid Arthritis

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**Background:** Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease which is recognized by symmetric inflammation of joints. Many factors have been proposed as its etiology including microbial infections. *H. pylori* has been considered as one of the infectious agents linked to RA; however, the data regarding this relation is controversial.

**Objectives:** To determine the effects of *H. pylori* on clinical course of disease, we compared the clinical course and laboratory findings of two groups of RA patients, with and without *H. pylori* infection, during one year follow up after *H. pylori* eradication.

**Patients and Methods:** One hundred adult RA patients (diagnosed according to the 2010 Revised ACR/EULAR Criteria) who referred to Rheumatology Clinic of Imam Reza Hospital were evaluated for *H. pylori* infection. Thirty-nine patients were positive for *H. pylori*; from them 30 patients underwent *H. pylori* standard treatment with three drugs including Amoxicillin (1 g/Bid), Clarithromycin (500 mg/Bid) and omeprazole (20 mg/Bid), for 10 days and PPI for one month. Seven *H. pylori* positive patients were excluded from the study because of inappropriate drug compliance and drug resistance and three patients did not refer for follow up. Overall, frothy RA patients, 20 with *H. pylori* infection, and 20 without *H. pylori* infection, were evaluated in the study. Patients' clinical findings and laboratory tests were evaluated in 5 consecutive visits; at the beginning of the study and every 3 months up to one year. *H. pylori* infection and its eradication were evaluated by fecal antigen test performed with Eliza method.

**Results:** Patients of *H. pylori* positive group had a higher number of joints inflammation and tenderness during 5 evaluation visits and the difference in number of joints involvement between two groups was statistically significant. The difference between two groups for pain based on visual analog scale (VAS), DAS-ESR and DAS-CRP was also significant and higher in *H. pylori* positive group. The other clinical and laboratory tests including ESR, CRP, RF and anti-CCP were not significantly different between two groups. *H. pylori* eradication did not improve clinical course of disease and laboratory tests.

**Conclusions:** Considering the results of this study, although having *H. pylori* infection in RA patients was accompanied with higher number of inflamed and tender joints, but *H. pylori* eradication did not improve patients' clinical symptoms and laboratory tests. It seems that the effect of *H. pylori* infection eradication over disease activity in RA patients is not remarkable, if it does exist at all.

Keywords: Eradication; Rheumatoid Arthritis; Helicobacter pylori

## 1. Background

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder distinguished by symmetric polyarthritis affecting all joints. RA affects 0.5%-2% of the population (1), and usually starts at the middle age with symmetric inflammation of synovial joints (2). The disease usually starts from peripheral joints and gradually progresses to more proximal joints causing significant disability for patients, who do not respond to treatment, during 10 - 20 years (3). While modern treatments remission can be induced in many patients, diagnosis in early stages is still important for preventing irreversible damage to the synovial tissue and cartilage of affected joints, and for preventing progression into later disease stages (4, 5).

RA is considered as one of the autoimmune diseases but its exact etiology is unknown (6). The autoimmune disorders are the result of interaction between individual genetic background and harmful environmental factors (7-9). Many factors have been proposed as RA etiology and in fact a combination of genetic, immunologic, neuroendocrine, environmental and psycho-social factors is considered effective in its etiology (10). It has been shown that a number of genetic and harmful environmental factors like smoking play a role in disease onset and severity (11). Microbial infection was also proposed to have a role in disease pathogenesis (12) and a number of bacterial pathogens had been suggested but neither was confirmed as an effective factor (13).

*Helicobacter pylori* (*H. pylori*) is a widely prevalent microbe, and 50 to 80% of the adult population are infected with it worldwide (14). *H. pylori* affects the host immune response in different ways and has been implicated in many diseases caused by immune dysregulation (14).

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Since it is a highly prevalent pathogen and is able to affect human immune function, many researchers have hypothesized that *H. pylori* might contribute to the development of autoimmune diseases (14).

Therefore, *H. pylori* has been considered as one of the infectious agents linked to RA; however, the data regarding this relation is controversial. Janssen et al. (15) in their study reported that an increased incidence of peptic ulcer disease in RA patients is probably caused by the higher use of non-steroidal anti-inflammatory drugs in these patients. Yamanishi et al. (16) in their study found an increase in IgM rheumatoid factor in B cells chronically stimulated by *H. pylori* urease. A few studies reported improvement in RA symptoms in patients after *H. pylori* lori infection eradication (13, 17); however, others did not find any changes in RA symptoms after *H. pylori* eradication (18-20). Hence, a few other studies reported that the *H. pylori* prevalence in people with RA is less than others or equal to healthy population (21-23).

# 2. Objectives

Since the early diagnosis and treatment of RA is important in controlling disease activity and with considering the controversial relation between RA and *H. pylori*, in this study we aimed to compare the clinical course and laboratory findings of two groups of RA patients, with and without *H. pylori* infection, during one year follow up after *H. pylori* eradication.

## 3. Patients and Methods

This was a clinical trial study including two groups of RA patients with *H. pylori* positive and negative condition. The study sample size was calculated based on Zentilin et al. (13) considering the mean difference test, patients ESR and  $\alpha = 0.05$ ,  $\beta = 0.2$ , x2 = 30 - SD2 = 11, x1 = 20 - SD1 = 6, which was equal to 13 patients in each group. We included 20 patients in each group for increasing the confidence.

One hundred patients, who had been diagnosed with RA based on the 2010 revised ACR/EULAR criteria (An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative), were selected initially. The study population was selected from RA patients over 18 years old who referred to Rheumatology Clinic of Imam Reza Hospital. The inclusion criteria were age > 18 years, and receiving treatment with NSAID, DMARD (methotrexate 10 - 25, hydroxychloroquine) and prednisolone 7.5 mg/day during last 6 months. All the participants signed an informed consent form before participating in the study.

Participants of both groups were evaluated regarding RA related clinical symptoms and laboratory tests in five consecutive visits; at the beginning of the study and every 3 months during one-year follow up. Patients' information including demographic, past medical history, physical examination and laboratory tests including CRP, ESR, RF, Anti CCP, CRP DAS, and ESR DAS were recorded in a specific checklist. Patients were examined regarding *H. pylori* infection by *H. pylori* fecal antigen test performed by Eliza method (24). Although the endoscopy and biopsy are the standard method for detecting *H. pylori*, but because biopsy is invasive, it is not accepted by all the patients and it is not applicable for all the patients. Fecal antigen test is a good alternative for biopsy, its sensitivity and specificity was reported 96% and 97% in some researches (25).

Among 100 RA patients, 39 were *H. pylori* positive, from which 30 patients were eligible and accepted to participate in the study. These 30 patients underwent H. pylori eradication treatment that was included 10-day treatment with amoxicillin (1 g/Bid), clarithromycin (500 mg/ Bid) and omeprazole 20 mg/Bid), followed by 4-week treatment with PPI. Four weeks after end of eradication treatment, patients were examined for H. pylori infection again by H. pylori fecal antigen. Seven H. pylori positive patients were excluded from the study because of inappropriate drug compliance and drug resistance and three patients did not refer for follow up. Therefore, 20 H. pylori positive patients were finally entered the study. Twenty RA patients from H. pylori negative group who were matched with H. pylori positive group regarding age, gender, and duration of RA and demographic information were selected as the control group. To evaluate patients' health status, the short form 36 (SF 36), a general health questionnaire, was used (26). In each visit, 28 joints were examined based on ACR20 and improvement in pain, tenderness and inflammation (20% or more) was documented. The number of inflamed and tender joints was calculated in each visit. Patients evaluation of pain and general evaluation of disease activity, and physician evaluation of disease activity were all performed using visual analog scale (VAS); scoring from 1 to 10. The disease activity score 28 (DAS28) was used to calculate disease activity. DAS28 provides a number on a scale from 0 to 10 indicating the current activity of the rheumatoid arthritis of patient. A DAS28 above 5.1 means high disease activity; whereas, a DAS28 below 3.2 indicates low disease activity. Remission is achieved by a DAS28 lower than 2.6. To calculate disease activity index, the severity of pain and tenderness in each joint was scored from 1 to 3 (slight: 1, medium: 2 and sever: 3), and was added together as follow:

DAS28-ESR =  $0.56\sqrt{\text{Tender28} + 0.28}\sqrt{\text{Swollen28} + 0.7 \text{ Ln}}$ (ESR) + 0.014GH

DAS28-CRP = 0.56√Tender28 + 0.28√Swollen28 + 0.36 Ln (CRP + 1) + 0.014GH + 0.98

Tender 28 = number of painful joints from 28 joints, Swollen 28 = number of inflamed joints from 28 joints Ln (ESR) = natural logarithm of ESR (first hour/mm) Ln (CRP) = natural logarithm of CRP (mg/L)

GH = patient general health or his global evaluation of disease activity (measures by a 100 mm VAS)

#### 4. Results

Forty patients with RA participated in this study; 20 *H. pylori* positive, 20 *H. pylori* negative. Thirty seven patients

were women, three men. The mean age of patients was  $46.28 \pm 11.06$  years (range from 24 to 67 seven). The mean weight was  $71.37 \pm 12.93$  kg (50 - 110), the mean height of patients was  $161.85 \pm 6.39$  cm (150 - 180). The mean duration of RA involvement was  $6.98 \pm 7.66$  years (0.2-35).

The mean number of inflamed joints in all five visits was significantly higher in *H. pylori* positive group compared with negative group. The number of tender joints was also significantly higher in *H. pylori* positive group in all visits except forth visit (Table 1).

The mean of disease activity score and duration of morning stiffness in five visits did not show significant difference between two groups. Analysis of variance with repeated measures for CRP showed that the difference between CRP means that there is no significant difference between two groups during five stages of evaluation (P = 0.245). The CRP changes during study period were similar in both groups (P = 0.981). The ESR of patients in both groups significantly decreased during first two evaluations (P = 0.019). The difference between mean of ESR in two groups, was not significant (P = 0.101), the changes in ESR values also did not show significant difference between two groups (P = 0.057).

The difference for RF means between two groups was not significant difference (p = 0.752), and both groups showed similar behavior during study (P = 0.647). The anti-CCP showed significant decrease in both groups in first stage (P = 0.035), but the difference between means of two groups was not significant (P = 0.532) and course of variable change was similar between two groups (P = 0.690).

Regarding the patients' pain, the decrease between first two visits was significant in both groups (P = 0.00), the behavior of two groups during study period was similar (P = 0.168) and the difference between means of two groups was not significant (P = 0.246).

The decrease in DAS-ESR and DAS-CRP during study in both groups was significant (P = 0.00 for both variables), the trend of decrease or increase in pain in both groups was similar (P = 0.282 and P = 0.413 respectfully). However, the slope of decrease in *H. pylori* positive group was higher for both variables, and the mean of pain showed significant difference between two groups (P = 0.007, and P = 0.008 respectfully) (Figures 1 and 2). Table 2 shows the p-value for comparing the mean of each variable changes during study period between two groups.

#### 5. Discussion

RA is a chronic systemic autoimmune disease which is characterized by symmetric inflammation of almost all joints. Although, its exact etiology is unknown, a combination of immune, genetic, neuroendocrine, environmental and psycho-social factors is proposed as its etiology (10). Microbial infections are also proposed to have a role in RA, among them *H. pylori*, because of its ability to induce chronic immune response in host (14), has received lots of attention.

The aim of this study was to compare the clinical course and laboratory findings of two groups of RA patients; with and without *H. pylori* infection, during one year follow up after *H. pylori* eradication. The results of our study showed that the number of tender and inflamed joints were higher in *H. pylori* positive group in all five visits. The mean of pain duration, morning stiffness, and functional class of disease in 5 visits were not significantly different between two groups.

			- 1			
Variable	HP Condition	First V	Second V	Third V	Forth V	Fifth V
Inflamed joint						
	HP negative	$1.85 \pm 1.78$	$1.75\pm1.55$	$1.00\pm1.25$	$1.05\pm1.43$	$1.00\pm1.26$
	HP positive	$3.3 \pm 2.13$	$3.20\pm1.54$	$2.70\pm\!169$	$2.10\pm1.65$	$2.40\pm1.50$
	P value	0.038	0.009	0.002	0.046	0.004
Tender joint						
	HP negative	$2.00\pm1.83$	$1.85 \pm 1.93$	$1.70\pm1.26$	$1.40\pm1.14$	$1.00\pm0.92$
	HP positive	$3.80\pm2.76$	$3.45\pm2.01$	$3.00\pm1.97$	$2.20\pm\!1.54$	$2.40\pm1.46$
	P value	0.033	0.010	0.040	0.102	0.003
Morning stiffness, min						
	HP negative	$15 \pm 14.42$	$16.75\pm14.62$	$16.50\pm11.37$	$16.25\pm10.24$	$16.50\pm10.40$
	HP positive	$17.90\pm20.10$	$19.75\pm17.20$	$19.65 \pm 16.88$	$17.50\pm13.33$	$19.50 \pm 17.16$
	P value	0.820	0.602	0.698	0.497	0.820
Disease activity score						
	HP negative	$1.60 \pm 0.68$	$1.60 \pm 0.68$	$1.55 \pm 0.69$	$1.55\pm0.69$	$1.55\pm0.69$
	HP positive	$1.60 \pm 0.60$	$1.60 \pm 0.60$	$1.60 \pm 0.60$	$1.60 \pm 0.60$	$1.60 \pm 0.60$
	P value	0.925	0.925	0.710	0.718	0.718

<sup>a</sup> Abbreviation: V, visit.

<sup>b</sup> Values are presented as mean  $\pm$  SD.



Figure 1. The Trend of DAS-ESR Changes During Study Time





**Table 2.** The P Value for Comparing the Mean of Each VariableChanges During Study Period Between Two Groups

Variable	P Value
Anti-CCP	0.690
RF	0.752
CRP	0.245
ESR	0.101
Pain	0.246
DAS-ESR	0.007
Das-CRP	0.008

The mean of laboratory tests including CRP, ESR, RF and anti-CCP in 5 visits did not show significant difference between two groups (P = 0.245, P = 0.101, P = 0.752, and P = 0.690 respectively). The manner of changes of these variables during study period did not also differ significantly between two groups.

Our results indicated that although patients in *H. pylori* positive group had higher number of inflamed and tender joints, the *H. pylori* eradication did not improve their symptoms and did not affect clinical course of disease.

Wen et al. (27) in a study explore the relation between *H. pylori* infection and rheumatic diseases. They found that 88% of RA patients were *H. pylori* positive. Their result demonstrated that RA patients with *H. pylori* infection have a higher prevalence of the value of CRP associated with the DAS28 (r = 0.287, P = 0.034). Zentilin et al. in two studies which were published in 2000 (28) and 2002 (13) compared clinical course of disease in two groups of RA patients; one group *H. pylori* positive and one group negative after *H. pylori* eradication. The results of these studies showed significant improvement in all clinical indices of *H. pylori* positive group after eradication. The results of Zentilin studies (13, 28) and Wen et al.(27) study which show *H. pylori* eradication improve patients outcome, disagree with our findings.

Graff et al. (29) studied the level of inflammatory disease activity before eradication and during a 42-week follow-up period. Their results showed a non-significant decrease in ESR after *H. pylori* eradication, and a significantly reduced number of tender joints in patients unaffected by *H. pylori*. They concluded that their results indicate the role of *H. pylori* on the inflammatory state of rheumatoid arthritis, but for final conclusions, further studies are required. The result of our study is somehow similar to this study, we found higher number of inflamed and tender joints in *H. pylori* positive patients.

On the other hand, there are studies questioning the relation of *H. pylori* and RA. Steen et al. (20) assessed the effects of *H. pylori* eradication on patients CRP and lipid profiles in RA. Their results indicated that the effect of eradication on CRP and lipid profiles is very limited and temporary. Saad and Rashad (30) study also declared no significant clinical and laboratory difference, except CRP level, between RA patients with and without *H. pylori* infection. These results are also in agreement with our results that showed *H. pylori* eradication does not improve clinical course of disease.

Furthermore, two published reviews about the relation between RA and *H. pylori* by Hasni et al. (14) and Smyk et al. (31), both declared that the current data about the relation between RA and *H. pylori* are mixed and unclear.

Regarding the results of this study although having *H. pylori* infection in RA patients was accompanied with higher number of inflamed and tender joints, *H. pylori* eradication did not improve patients' clinical symptoms and laboratory tests. The etiological relation be-

tween *H. pylori* and RA does not seem a strong relation, if it does exist at all. Further studies with more participants and longer follow up period are required to clear this relation.

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## **Authors' Contributions**

Zhale Shariaty reported receiving research grants and consulting fees for speaking from Qhaem hospital

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