Study of the Effect of Treatment of Helicobacter pylori Infection in Rheumatoid Arthritis Patients

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ABSTRACT

Objective: To assess the disease activity after treatment of *Helicobacter pylori* infection in rheumatoid arthritis patients at a tertiary care hospital of Rawalpindi.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: Department of Rheumatology, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Jun to Nov 2021.

Methodology: A total of 197 adult patients diagnosed with rheumatoid arthritis and with symptoms of dyspepsia were inducted into this study. First, the disease activity was measured considering parameters such as clinical swollen and tender joints count, disease activity scores 28(DAS-28), visual analogue scale (VAS) and laboratory parameters like erythrocyte sedimentation rate at the start as the baseline. Then, these were repeated after six months, and the differences between the two groups were compared.

Results: At the start of the study, patients who were positive for *H. pylori* had markedly more swollen and tender joint counts and raised ESR values than those in the negative group. In addition, the disease activity score of 28 and pain scores was markedly raised in the positive group. After *H. pylori* eradication, the *H. pylori*-positive patients differed significantly ($p<0.001$) from patients group negative for *H. pylori* infection in terms of improvement in DAS-28 score, visual analogue score and clinically. Laboratory indices like ESR showed significantly decreased values ($p<0.001$) in the *H. pylori*-treated group compared to those not infected with *H. pylori*.

Conclusion: From our results, it is suggested that *H. pylori* infection has a role in the pathogenesis of rheumatoid arthritis.

Keywords: Disease activity score 28, *Helicobacter pylori*, Rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a disease of autoimmune origin. It can cause irreversible joint damage. Autoimmune reaction to unknown stimuli is to be involved in pathogenesis along with infection with as yet unidentified microorganisms; however.[1]

Warren and Marshall have been the first to explain the presence of *Helicobacter pylori*, a gram-negative curved and motile microorganism, in biopsy specimens from patients with gastritis. *H. pylori* may be recognized in 70-90% of all incidences of gastritis and gastroduodenal ulcers.[2] *H-pylori* infection may also be associated with extra-gastric diseases or manifestations.[3]

Serving as a source of continuous antigenic stimulation, chronic *H. pylori* infection underlies the pathogenic ability to induce a generalized inflammatory response.[4] Furthermore, b cells were shown to autoantibodies, such as IgM rheumatoid factor (RF),

antinuclear antibody, anti-single-stranded DNA antibody and anti-histone antibodies after their activation by urease component of H. pylori in particular.[5] *H. pylori* infection leading to the pathogenesis of RA is not yet confirmed. Although in-vitro studies suggest a role for the bacterium in developing autoimmunity, the correlation between *H. pylori* infection and RA on clinical grounds has been less convincing.[6] Our study aims to assess the disease activity after treatment of *Helicobacter pylori* infection in rheumatoid arthritis patients at a tertiary care hospital of Rawalpindi.

METHODOLOGY

The comparative cross-sectional study was conducted at the Rheumatology Department Outpatient Clinic, Pak Emirates Military Hospital, Rawalindi Pakistan, from June and November 2021. The Ethical Committee of the hospital (via letter number A/28/2021) approved the study. Non-probability consecutive sampling technique was used to gather the sample for this study. The sample size was calculated using the WHO sample size calculator by using the population prevalence of *H-pylori* infection in patients of RA as 30%.[7]

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Inclusion Criteria: Patients with dyspeptic symptoms aged 26 to 52 years were included in the study.

Exclusion Criteria: Patients with the presence of another rheumatological disease or history of an active peptic ulcer or previous gastrointestinal surgery and pregnant women were excluded from the study.

Patients were divided into two groups based on the presence or absence of *H. pylori* faecal antigen; *H. pylori*-positive and *H. pylori*-negative groups. The *H. pylori*-positive group received medical treatment for two weeks on Omeprazole 20mg, twice daily, Amoxicillin 1000mg, twice daily, and Macrolide Clarithromycin 500mg, twice a day and were assessed for the elimination of the bacterium. Clinical and lab assessments of RA disease activity were done at the start of the study and six months later for both groups.

All participating patients were diagnosed as RA patients based on the 2010 revised criteria of the American College of Rheumatology for the classification of RA.[7] For classification purposes, a patient has to satisfy at least four of the seven criteria to be considered to have RA. Six weeks is the minimum duration for symptoms of criteria. Patients with two clinical diagnoses are excluded. The patients were questioned about the current age and duration of RA. The inquiry was made about several swollen, tender joints and symptoms of dyspepsia.

Clinical examination was performed for all patients, including general and locomotor examination. Locomotor system assessment included joints like the right and left shoulder, elbow, wrist, metacarpophalangeal (MCP), and proximal interphalangeal (PIP) and knee joints. First, joints were examined for swelling and tenderness then Disease Activity Score 28(DAS-28) was calculated for each patient.[8,9] A DAS score of less than 2.6 was taken as in remission. The following laboratory investigations were performed ESR (by Westergren method) and *H. pylori* faecal antigen titer (FAT) by ELISA.[10]

VAS (visual analogue scale) was used to evaluate pain severity. 'No pain' and 'extreme pain' were scored between 0 and 100. For estimating pain, patients were asked to mark the line at a point, and the severity of pain was represented by the distance from zero.[11,12]

Statistical calculations were done using Statistical Package for the social sciences (SPSS) version 23:00. Quantitative variables were expressed as mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test was applied to find out the association. Independent sample t-test was applied to find the mean differences among the groups. The *p*-value lower than or up to 0.05 was considered as significant.

RESULTS

A total of 197 patients with rheumatoid arthritis with complaints of dyspeptic symptoms were included in the study. Of these, 39(19.8%) were males, and 158(80.2%) were females. The mean age of the study participants was 36.89±7.40years. At the start of the study, there were 77(39.1%) patients with positive *H. pylori* FAT and 120(60.9%) patients with negative *H. pylori* FAT. After 06 months, no patients had positive titer (0%), and all patients had negative titer (100%). There was a highly significant difference (*p*< 0.001) between FAT results at the initiation of the study and after 06 months of treatment and follow-up (Table-I).

Table-I: Difference in Positive Fecal Antigen Test and Titers for H-pylori at Base Line and after 6-Months (n=197)

Fecal antigen test	At baseline	After six months	*p*-value
Positive	77(39.1%)	0(0.0%)	-
Negative	120(60.9%)	197(100%)	-
Titer (Mean±SD)	1.61±0.48	2.0±0.00	<0.001

There was a statistically significant difference between FAT-positive and negative groups regarding DAS (*p*<0.001), VAS (*p*<0.001), ESR (*p*<0.001), and tender joint involvement (*p*<.001) at baseline (Table-II).

Table-II : Difference in Clinical and Laboratory Parameters between Patients with Positive and Negative Stool Antigen Test at Baseline (n=197)

Parameters	Positive Fecal Antigen Test (n=77) (Mean±SD)	Negative Fecal Antigen Test Negative (n=120) (Mean±SD)	*p*-value
Tender joints	19.19±3.30	9.00±1.92	<0.001
Disease activity score 28	6.35±0.38	5.20±0.76	<0.001
Visual analogue scale	76.01±9.68	41.66±8.53	<0.001
Erythrocyte sedimentation rate	66.69±6.08	50.98±3.78	<0.001

DAS (*p*<0.001), VAS (*p*<0.001), ESR (*p*<0.001) and tender joint involvement (*p*<0.001) were statistically significantly different at the baseline and after six months of treatment (Table-III).

DISCUSSION

H. pylori infection implication in the pathogenesis of RA is controversial. Studies have shown a link between *H-pylori* infection and etiopathogenesis of

RA.[13] In this study, and we found that 39.1% of RA patients had positive *H. pylori* FAT. Graff *et al.*[14] reported that the seroprevalence of *H. pylori* in RA patients was 32%. Zentilin *et al.*[15] reported that the seroprevalence of *H. pylori* in RA patients was 48%. Other studies found a higher prevalence (80-88%) of *H. pylori* infection in RA patients than our results.[16-18] In our study regarding sex, positive *H. pylori* antigen test titer was more common in female patients than in male patients, which is in contrast to the studies by Graff *et al.*[14] and Nakamura *et al.*[16] who found that the sex of RA patients did not affect *H. pylori* status.

Table-III: Difference in Clinical and Laboratory Parameters at Baseline and at the End of 6-Months (n=154)

Parameters	Study Groups		*p*-value
	Fecal antigen test +at baseline (n=77) (Mean±SD)	Fecal antigen test +at 6 months (n=77) (Mean±SD)	
Tender joints	19.19±3.30	13.94±2.95	<0.001
DAS 28	6.35±0.38	3.92±0.19	<0.001
VAS	76.01±9.68	56.10±9.68	<0.001
ESR	66.69±6.08	26.23±3.03	<0.001

In this study, another similar,[17] the positive group had higher RA disease activity than the negative group, and the difference was significant. Our study found that the FAT-positive group had significantly more tender joints count than the negative group. In addition, we found a significant difference ($p<0.001$) between *H. pylori* FAT-positive and negative groups regarding the ESR level at baseline. This study found that the FAT-positive group had significantly higher DAS, such as DAS28, than the negative group.

In contrast with the result of Graff *et al.*[14] we found that there was a significant difference between *H. pylori* FAT-positive and negative patients regarding pain scores at baseline. In this study, we found that, after treatment of *H. pylori,* the tender joint count was significantly decreased ($p<0.001$).

In this study, in agreement with the study Zentilin *et al.*[15] we found that after treatment of *H. pylori*, the swollen joint count was significantly decreased. In contrast, Graff *et al.*[14] stated that no appreciable difference ($p=0.12$) existed in the number of tender joints in the *H. pylori*-positive group after *H. pylori* treatment.

In this study, we found that the value of ESR was significantly reduced after the treatment of *H. pylori*. This result agrees with Zentilin *et al.*[15] In contrast, Graff *et al.*[14] found no appreciable difference ($p=0.14$) in the ESR level in the *H. pylori*-infected RA patients at the start of the study and after treatment. In this study, we found that after treatment of *H. pylori*, the value of DAS28 was significantly reduced. In our study, we found a significant difference ($p<0.001$) between the VAS score of *H. pylori* FAT-positive patients at the initiation of the study and after *H. pylori* eradication.

LIMITATIONS OF STUDY

The use of different DMARDs and other medications alongside study protocols may impact on parameters included in the study; therefore, it cannot be inferred that improvement in symptoms was due to *H-pylori* treatment exclusively.

CONCLUSION

This study showed that *H. pylori*-positive RA patients are more prone to developing severe disease. *H. pylori* infection in a RA patient leads to higher disease activity, tender joint involvement and high levels of ESR. Treatment of *H. pylori* infection with triple therapy is associated with a prominent decrease in the activity of RA disease, tender joint involvement and ESR. Complete elimination of h pylori in RA patients may help decrease the use of biological drugs, but further study and research are required.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

UUH & SH: Conception, study design, drafting the manuscript, approval of the final version to be published.

HN & RH: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

FH & QAMUD: Critical review, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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