

HELICOBACTER PYLORI ERADICATION EFFECTS ON RHEUMATIC DISEASES: A SYSTEMATIC REVIEW

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Abstract – Objective: *Helicobacter pylori* (HP) eradication treats peptic ulcers, gastric lymphoma, or adenocarcinoma. Although, there are effects on the rheumatic disease activity. The aim of the study was to systematically review the HP eradication effects on rheumatic diseases.

Materials and Methods: We systematically search PubMed for articles on HP eradication effects in rheumatic diseases between 1966 and August 2022. No language limitation was used. Scielo, PubMed, and Web of Science were the database analyzed.

Results: 13 articles were published in this field, with 42,327 patients. We found studies on the following rheumatic diseases: rheumatoid arthritis (n=4), antiphospholipid syndrome (n=1), Behçet's disease (n=1), Henoch-Schönlein purpura (n=1), systemic lupus erythematosus (n=1), Rowell syndrome (n=1), Sjögren's syndrome (n=1), and fibromyalgia (n=1). One study included patients with systemic sclerosis, rheumatoid arthritis, polymyositis, dermatomyositis, vasculitis, pemphigus, Sicca syndrome, Crohn's disease, and ulcerative colitis. The range of the age in the studies varied from 33 to 62 years old; 37% to 100% were females. Follow-up trials ranged from 2 months to 31 years. Regarding HP eradication effects, 10/13 (77%) of the studies observed an improvement in the rheumatic diseases, 2 studies verified a decrease in the incidence of lupus and Henoch-Schönlein purpura, and 3 studies confirmed a worsening of the rheumatic condition. Side effects were mild, and no patient stopped the treatment.

Conclusions: This systematic review demonstrates that HP eradication positively affects rheumatic disease activity and may reduce the risk of lupus and Henoch-Schönlein purpura. Nonetheless, more prospective studies are desired to confirm the present data.

Keywords: *Helicobacter pylori*, H. pylori, Helicobacter pylori eradication, Rheumatic diseases, Rheumatoid arthritis, Systemic lupus erythematosus, Fibromyalgia, Vasculitis.

INTRODUCTION

Autoimmune diseases are based on genetic susceptibility and environmental exposure¹. Among environmental exposures, infectious triggers were associated with and studied extensively². Infectious agents include bacteria, viruses, and parasites linked to autoimmune disorders. Several mechanisms by which infectious agents may cause autoimmune disease are studied, including molecular mimicry, epitope spreading, bystander effect, microbial super-antigens,



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immune complex formation, and others³. Among infectious agents implicated in several diseases, *Helicobacter pylori* (*H. pylori* or *HP*) has received particular attention as it has been responsible for both organ-specific and non-organ autoimmune diseases⁴. Similarly, multiple other autoimmune conditions have been associated with *H. pylori*. In fact, among the autoimmune or autoimmune-related diseases, 95 of them have been studied sporadically or systematically regarding their connection with *H. pylori*⁵.

Interestingly, HP eradication is linked with the cure or improvement of some diseases, such as idiopathic thrombocytopenic purpura⁶.

There are some articles on the role of HP eradication in a few rheumatic diseases. In light of this, the objective of this article is to perform a systematic review of the studies that evaluated *Helicobacter pylori* eradication effects on rheumatic diseases.

MATERIALS AND METHODS

Literature Review

We performed a systematic search of articles published in PubMed/MEDLINE, Web of Sciences, LILACS, and Scielo from 1966 to August 2022 using the following MeSH entry terms: “*Helicobacter pylori*” OR “*H. pylori*” AND “eradication” OR “treatment” AND “autoimmune disease” OR “rheumatologic” OR “systemic lupus erythematosus” OR “lupus” OR “fibromyalgia” OR “rheumatoid arthritis” OR “spondyloarthritis” OR “Sjögren’s syndrome” OR “myositis” OR “systemic sclerosis” OR “vasculitis” OR “Takayasu disease” OR “Wegener’s disease” OR “granulomatosis with polyangiitis” OR “Kawasaki’s disease” OR “polyarteritis nodosa” OR “Livedoid vasculitis” OR Churg-Strauss” OR “eosinophilic granulomatosis with polyangiitis” OR “osteoarthritis” OR “gout”. We used equivalent strategies in other databases. All related articles were searched without language restriction. The reference lists in the selected articles were analyzed to identify other publications. Initially, two authors (JFC and VMF) performed the literature search and independently selected the study abstracts. In the second stage, the same reviewers independently read the full-text articles selected by abstracts. Finally, a third reviewer resolved disagreements arising in consensus meetings. The authors followed PRISMA guidelines⁷. We designed a standardized form to extract the following information from relevant articles regarding authors, year of publication, the number of patients studied, demographic data, disease duration, study follow-up, lactation duration, and rheumatic disease risk.

RESULTS

There are 13 articles published in this field, with 42,327 patients⁸⁻²¹. The study designs were: prospective trial (n=4), case report (n=4), placebo-controlled trial (n=3), nationwide population-based cohort (n=1) and database (n=1). The countries in which the studies were performed are Turkey (n=3), Italy (n=2), Japan (n=2), Taiwan (n=2), Netherland (n=1), China (n=1) and Romania (n=1). In addition, we found studies on the following rheumatic diseases: rheumatoid arthritis (n=4), antiphospholipid syndrome (n=1), Behçet’s disease (n=1), Henoch-Schönlein purpura (n=1), systemic lupus erythematosus (n=1), Rowell syndrome (n=1), Sjögren’s syndrome (n=1), and fibromyalgia (n=1). In addition, one study included patients with systemic sclerosis, rheumatoid arthritis, polymyositis, dermatomyositis, vasculitis, pemphigus, *sicca* syndrome, Crohn’s disease, and ulcerative colitis²⁰.

All studies’ ages varied from 33 to 62 years old; 37% to 100% were females. Follow-up trials ranged from 2 months to 31 years. Regarding HP eradication effects, 10/13 (77%) of the studies observed an improvement in the rheumatic diseases, 2 studies verified a decrease in the incidence of lupus¹⁶ and also Henoch-Shönlein purpura¹⁵, and 3 studies^{9,18,20} verified a worsening of the rheumatic condition: the first one was a case report that saw a RA flare as clinical as proinflammatory markers, 8 weeks after HP treatment⁹; the second, a case report of a Rowel syndrome had a flare of this disease after 1 week of HP eradication¹⁸; and the third, a Taiwan database showed an increased risk for several autoimmune diseases²⁰.

Concerning side effects related to HP eradication drugs, only one study described them, and they were mild; the patients did not stop the treatment and included: metallic taste (n=17 patients), nausea (n=6), headache (n=5), fatigue (n=4), and moderate abdominal pain (n=2). Nine out of 13 articles did not write anything about these effects, and 2/13 did not see side effects. All data above is in Table 1.

DISCUSSION

This is the first study to systematically review the effects of HP eradication on rheumatic disease conditions.

The study strengths are: (1) the inclusion of studies with patients with international criteria for rheumatic diseases and (2) all studies that evaluated the relationship between *H. pylori* and autoimmune disorders were included.

H. pylori is a gram-negative, microaerophilic, spiral-shaped, and flagellated bacterium infecting about half the world's population, whose main reservoir is the human stomach. Typically, initial *Helicobacter pylori* (*H. pylori*) infection is acquired by oral ingestion during

TABLE 1. STUDIES ON *H. PYLORI* ERADICATION AND ITS EFFECTS ON RHEUMATIC DISEASES.

Author, reference	Study design	Country	Rheumatic disease	N, age, gender	Follow-up	Outcome	Side effects
Steen et al, 200 ⁹⁸	Placebo-controlled trial	Netherlands	Rheumatoid arthritis	213, 60 yo, 73% females	1 year	ApoA-1 increased (<i>p</i> 0.01) CRP reduced at 3 months, but it was not significant.	NA
Matsukawa et al, 200 ⁵⁹	Case report	Japan	Rheumatoid arthritis	1, 62 yo, female.	1983-2014 (31 years)	RA exacerbated after 8 weeks of HP eradication. Polyarthralgia, knee arthritis, increased ESR, CRP, and RF.	NA
Zentilin et al, 2002 ¹⁰	Open, prospective trial	Italy	Rheumatoid arthritis	58, 56 yo, 80% females	2 years	Improvement in clinical and laboratory features after HP eradication: Improved tender and swollen joints, disease activity, morning stiffness, HAQ, VAS, and grip strength. Reduced CRP, ESR, fibrinogen, and increased hemoglobin.	NA
Zentilin et al, 2000 ¹¹	Open, prospective trial	Italy	Rheumatoid arthritis	31, 55 ± 10.6 yo, NA	16 months	Improvement in clinical and laboratory features after HP eradication.	NA

Continued

TABLE 1 (CONTINUED). STUDIES ON *H. PYLORI* ERADICATION AND ITS EFFECTS ON RHEUMATIC DISEASES.

Author, reference	Study design	Country	Rheumatic disease	N, age, gender	Follow-up	Outcome	Side effects
Cicconi et al, 1999 ¹²	Case report	Italy	Anti-phospholipid syndrome	1, 33 yo, female	9 months	After HP eradication: complete disappearance of dyspeptic symptoms and a gradual resolution of the neurologic symptoms. Her migraines significantly improved and Raynaud's phenomenon disappeared. Interestingly, antiphospholipid antibodies levels became normal (IgG9 U/mL, IgM 7 U/mL)	None
Apan et al, 2007 ¹³	Placebo-controlled trial	Turkey	Behçet's disease	91 BD vs. 83 age- and sex matched control, 33.4 ± 8.3 yo; 58% females	2 months	HP eradication decreased clinical manifestations such as oral and genital ulceration, arthritis/arthralgia, and cutaneous findings	NA
Avci et al, 1999 ¹⁴	Placebo-controlled trial	Turkey	Behçet's disease	13 out of 69 BD, NA, NA	2 months	The size and the number of oral and genital ulcers diminished, the patergia test became negative in 8/13, and skin thrombophlebitis, skin, and ocular manifestations became absent or reduced after the eradication of HP	Metallic taste, (n=17) nausea (n=6), headache (n=5), fatigue (n=4), moderate abdominal pain (n=2)
Cai et al, 2014 ¹⁵	A prospective randomized controlled trial	China	Henoch-Schönlein purpura	153, 6.6 yo, 37% females	6 months	The incidence of Henoch-Schonlein purpura was lower after HP eradication.	NA
Wu et al, 2020 ¹⁶	Nationwide population-based cohort study	Taiwan	Systemic lupus erythematosus	41,653 with HP, NA, 45% females	2000 to 2013 (13 years)	Early eradication (< 3 months) could significantly reduce SLE risk during the 3-year followup (HR: 0.16, 95% I: 0.05-0.53, <i>p</i> = 0.0013)	NA

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TABLE 1 (CONTINUED). STUDIES ON *H. PYLORI* ERADICATION AND ITS EFFECTS ON RHEUMATIC DISEASES.

Author, reference	Study design	Country	Rheumatic disease	N, age, gender	Follow-up	Outcome	Side effects
Branisteanu et al, 2018 ¹⁷	Case report	Romania	Rowell syndrome	1, 45 yo, female	2010 to 2017 (7 years)	1 week after HP eradication, the patient had skin rash and pruritus, fatigue, myalgia, nostalgia, anti-Ro/SS-A, antinuclear antibodies, and rheumatoid factor.	NA
Iwai et al, 2009 ¹⁸	Case report	Japan	Sjogren's syndrome and parotid MALT lymphoma	1, 60 yo, female		The size of the parotid mass gradually decreased, and it disappeared 6 months after HP eradication therapy. Follow-up for 4 years show no evidence of recurrence.	None
Lin et al, 2019 ¹⁹	National Health Insurance Research Database	Taiwan	Autoimmune diseases (lupus, systemic sclerosis, rheumatoid arthritis, polymyositis, dermatomyositis, vasculitis, pemphigus, Sicca syndrome, Crohn's disease, and ulcerative colitis)	79,181 from 1 million, > 18 yo, 48% females	1996 to 2005 (9 years)	Treatment for <i>H. pylori</i> infection is associated with a significant increase in the risk for autoimmune diseases, including IBD.	NA
Gezici et al, 2014 ²¹	Prospective trial	Turkey	Fibromyalgia	32, 38.5±8.6 yo, 88% females	May 2012 to August 2012 (5 months)	After HP eradication: reduction of tender points. No differences in Pittsburgh Sleep Quality Index, the Beck Depression Inventory, and the Beck Anxiety Inventory	NA

HP: *Helicobacter Pylori*; NA: not available; yo: years old.

early childhood, and *H. pylori* will persist for life in untreated cases. The frequency of *H. pylori* infection is approximately 80% in underdeveloped countries compared to 50% in developed parts of the world, correlating the disease prevalence with poor socioeconomic status^{20,21}.

H. pylori possesses microbiological characteristics that allow it to survive in highly adverse conditions such as the gastric acidic environment. Consequently, this bacterium is the leading cause of chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma²².

Several mechanisms of autoimmunity have been described in studies with HP. This bacterial infection is associated with an augmented risk of an elevated C-reactive protein, demonstrating a continuing inflammatory state. This state may result in ongoing antigenic stimulation. It might induce a systemic inflammatory response with extra-gastrointestinal manifestations²³. Another study²⁴ found that molecular mimicry of *H. pylori* antigens activated cross-reactive T cells in autoimmune gastritis. HP components (especially urease) have been shown to activate B-cells to produce autoantibodies, such as IgM rheumatoid factor, anti-ds-DNA, and anti-phosphorylcholine²⁵.

In addition, experimental studies have shown that infection of male C57BL/6 mice with HP can induce a disease that resembles human primary biliary cholangitis²⁶. HP is linked to several autoimmune disorders. Seroprevalence studies²⁷ have shown a link between autoimmune disorders and the presence of HP.

Most autoimmune conditions present a link with HP. In a recent meta-analysis²⁸, the frequency of HP positivity varied from 24 to 77% in SLE, 24 to 65% in RA, 0 to 90% in autoimmune gastritis, and 0 to 86.6% in autoimmune pancreatitis. The only exceptions are inflammatory bowel diseases (IBD), in which epidemiological literature generally supports a negative correlation between *H. pylori* and IBD²⁹.

In specific situations, such as MALT lymphoma, in the case report of Sjogren's syndrome associated with lymphoma, HP eradication could treat the disease³⁰.

Herein we observe that in most situations where HP eradication was studied, a positive response was observed in more than 70% of the situations. In fact, in rheumatoid arthritis, most of the included studies showed a reduction in the disease activity indexes, as clinical features as inflammatory markers^{8,10,11}.

Concerning the cases in which HP eradication brings negative results, there is growing evidence that HP may be a protective factor against some chronic immune-mediated disorders such as asthma and allergy³¹, and inflammatory bowel disease³². It has been hypothesized that this protection includes the induction of intestinal interleukin (IL)-10 and IL-18-mediated regulatory T-cell responses that are immunosuppressive responses to autoimmunity and inflammation³³. Herein, we saw three examples of adverse outcomes after HP. Two case reports (RA and Rowell syndrome) showed a new flare of this disease after HP treatments^{9,17}. Moreover, in a population study from Taiwan with many participants, the rates of several autoimmune diseases increased after HP eradication²⁰.

Finally, some limitations were observed in our study. For instance, no meta-analysis was possible since several autoimmune diseases were included, increasing the heterogeneity.

CONCLUSIONS

This systematic review suggests that the eradication of *H. pylori* might have a beneficial role in the following rheumatic diseases, such as rheumatoid arthritis, Behçet's disease, antiphospholipid syndrome, Henoch-Schönlein purpura, systemic lupus erythematosus, Rowell syndrome, Sjögren's syndrome, and fibromyalgia reduction of clinical and inflammatory parameters was observed in most cases. Although, in a population study, HP eradication was linked to an increase in autoimmune risk. Future studies are needed to confirm the present data and evaluate other autoimmune diseases.

Conflict of Interest

All authors of this work have no conflicts of interest (actual or potential), financial or otherwise, to declare.

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