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Review Article

Helicobacter Pylori infection in rheumatic and autoimmune diseases

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ABSTRACT

Helicobacter pylori (*H. pylori*) infection is responsible for affecting almost 50% to 80% of people worldwide thus making it quite a prevalent bacterial infection. The relationship between infection and autoimmune disease have grown more obvious over the past 20 years. Although the exact cause of autoimmune diseases is unknown, it has long been hypothesized that genetically susceptible individuals may be more likely to develop autoimmune processes as a result of exposure to specific environmental agents, such as bacterial and viral infections or chemical exposures. One important factor in the development of autoimmune disorders is *H. pylori* infection. Clinically, *H. pylori* infection is frequently linked to peptic ulcer disease, while many infected people exhibit no symptoms. Atrophic gastritis, immunological thrombocytopenic purpura, and mucosa associated lymphoid tissue lymphoma are just a few of the illnesses that immune dysregulation has been linked to and reduced by *H. pylori*. Rheumatoid arthritis, systemic lupus erythematosus, and Sjogren's syndrome are examples of autoimmune diseases caused by an immune system that is malfunctioning in the body and invading healthy tissues. The purpose of this research is to review the available information about *H. pylori* infection in rheumatic and autoimmune disease. Numerous researchers have proposed that *H. pylori* may have a role in the emergence of autoimmune diseases due to its frequency and capability to alter human immune function. Although the results from majority of the present study findings in literature are contrasting. Further clinical research is needed to elaborately explain the association between autoimmune diseases and *H. pylori* infection.

Keywords: *H. pylori*, Infection, Autoimmune, Diseases

INTRODUCTION

More than half of the world's population is thought to be affected by the common gastric infection *Helicobacter pylori* (*H. pylori*), which is linked to a number of gastropathies such as chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and gastric cancer. Appropriate assessment and effective treatment are critical in preventing further complications due to its incidence and potential for serious comorbidity.

In year 1983, *H. pylori* was first described in association with chronic gastritis.[1] Between 30% and 50% of people in developed nations and 85% to 95% of people in impoverished countries have *H. pylori*. With advancements in sanitation and eradication techniques, the epidemiology of *H. pylori* infection has changed. However, *H. pylori* infections are still widely prevalent.[2]

The primary cause of chronic gastritis and a significant risk factor for stomach cancer is *H. pylori*. This bacterium has also been thought to be a possible cause of autoimmune gastritis and other forms of stomach autoimmunity. *H. pylori* infection is associated with the emergence of extra-gastrointestinal autoimmune diseases that damage organs unrelated to the stomach in the short term. The interplay of genetic predisposition and environmental exposures results in autoimmune disorders. Infectious triggers are among the environmental exposures that have been mentioned. Bacteria, viruses, and parasites are examples of infectious agents. They can also include other species found in the natural flora. *H. pylori* has drawn the most attention among the infectious organisms involved since it has been linked to both organ-specific and non-organ-specific autoimmune diseases.[3]

Over the past 20 years, the correlation between infection and autoimmunity has become clearer. Loss of tolerance to self-antigen as a result of immune system dysregulation characterizes systemic rheumatic illnesses. Although the precise cause of the majority of these diseases is unknown, it is thought that a complex interaction of host and environmental factors is a key contributor. One of the most extensively researched infectious pathogens identified as initiating an autoimmune response is *H. pylori*. The chronic immune system activation caused by *H. pylori*'s continued presence in the mucosa of stomach includes ongoing cytokine signalling, neutrophil, macrophage, and lymphocyte infiltration, as well as antibody and effector T-cell generation. In an effort to explain the extra-intestinal symptoms of *H. pylori* infections, numerous explanations have been put forth.[4] Chronic *H. pylori* infection may contribute to the etiopathogenesis and persistence of inflammatory activity in various autoimmune diseases. Chronic infections continuously excite the immune system, which may create an autoimmune condition in people with a genetic susceptibility. Several research studies have reported an association between autoimmune illness and *H. pylori* infection. *H. pylori* infections are problematic for people with autoimmune illnesses for a variety of reasons. First, *H. pylori* infection risk is increased because autoimmune diseases are associated with poor immunological competence as a result of disease symptoms or pharmacological treatment. Second, non-steroidal anti-inflammatory drug adverse effects may exacerbate existing harm. Third, suppressing the immune system raises the chance of neoplasm, such as gastric cancer.[5]

A single organ or a number of organs and systems may be affected by an autoimmune disease, which is a chronic disease that typically results from the loss of immunological tolerance to autoantigens. Since the time *H. pylori* has been originally discovered in the stomach and then its harmful effect was recognized, modern gastroenterology has advanced significantly. This bacterium has been linked to the natural history of numerous upper gastrointestinal illnesses, according to the studies undertaken over the past 40 years. As per the epidemiological data, autoimmune illnesses are more common when certain bacteria are infected or afterward. *H. pylori* may be a factor in the development of gastric autoimmunity and may also be linked to other innate and acquired autoimmune illnesses. *H. pylori* infection is among the significant trigger of autoimmune diseases.[6] The purpose of this research is to review the available information about *H. pylori* infection in rheumatic and autoimmune disease.

LITERATURE SEARCH

This study is based on a comprehensive literature search conducted on September 19, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about *H. pylori* infection in rheumatic and autoimmune diseases**.** There were no restrictions on date, language, participant age, or type of publication.

DISCUSSION

H. pylori is a likely infectious agent for initiating autoimmunity because of the prolonged interaction between the bacteria and host immune systems. Cross-reactive T cells were discovered to be activated by molecular mimicry of *H. pylori* antigens, which may result in autoimmune gastritis. It has been shown that B cells make autoantibodies like IgM rheumatoid factor, anti-single stranded DNA antibodies, and anti-phosphotidyl choline antibodies after being activated by *H. pylori* components, particularly urease. Due to the great degree of sequence homology between microbial and human heat shock proteins it has been hypothesized that these proteins have a role in the etiology of autoimmune disorders. It is suggested that heat shock protein 60, which is produced by *H. pylori*, may play a role in the etiology of Sjögren's disease. Almost 50% of the time, immune thrombocytopenic purpura patients with *H. pylori* infection should expect to see an improvement in platelet counts. Regarding the connection between *H. pylori* infection and other autoimmune illnesses, there are inconsistent and disputed evidence. The research suggests that an infection with *H. pylori* may have a protective effect in specific circumstances, such as inflammatory bowel disease.[7] Association of *H. pylori* infection with autoimmune diseases is illustrated in (Figure 1).[5]

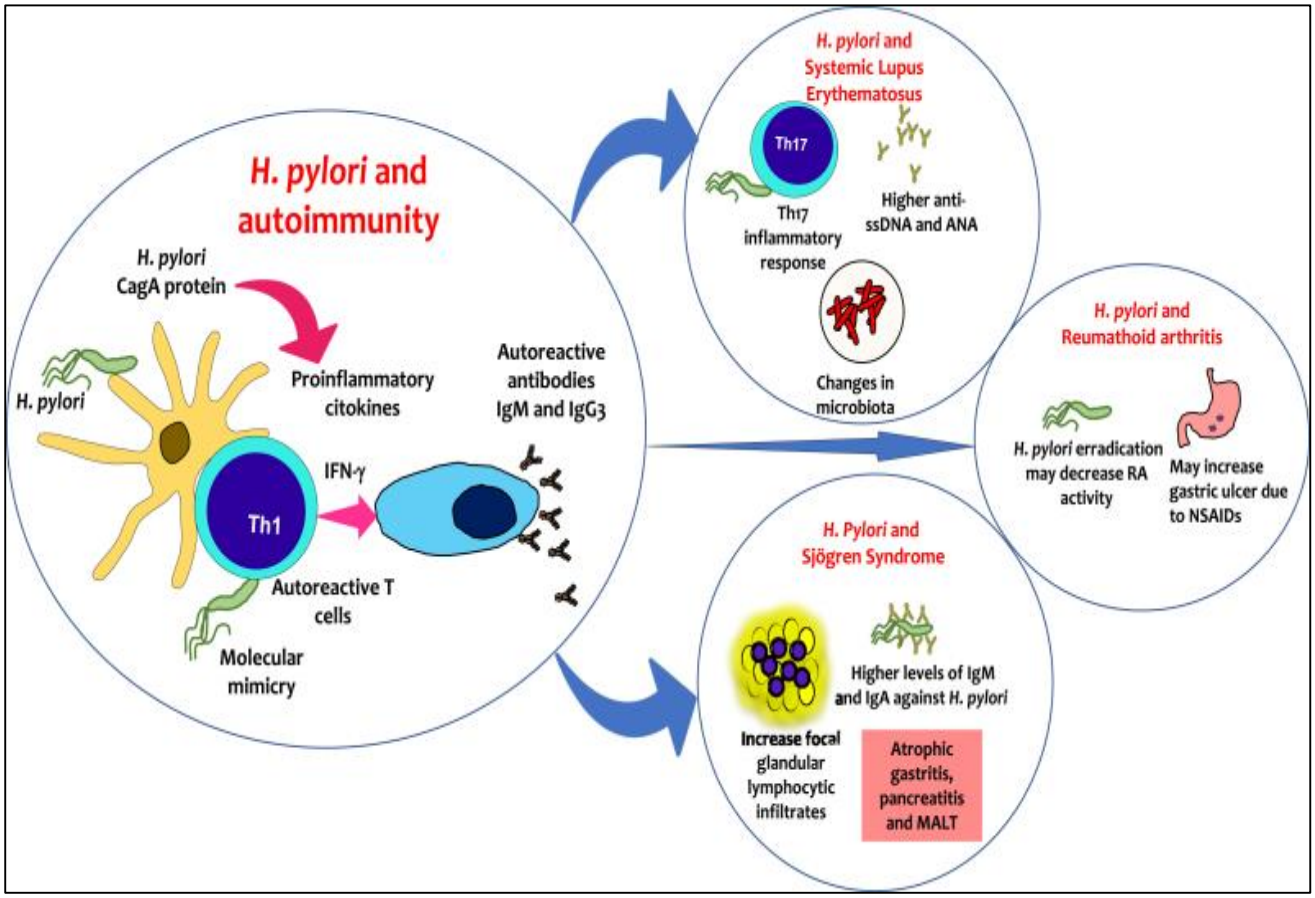

Figure 1: Association of *H. pylori* with autoimmune diseases.[5]

*NSAIDS: non-steroidal anti-inflammatory drugs** MALT: mucosa associated lymphoid tissue.

Role of H. pylori in various rheumatic and autoimmune diseases

H. pylori and rheumatoid arthritis (RA)

RA is an autoimmune disease which is characterized by chronic inflammation of the synovial membrane and damage to the articular cartilage and juxta-articular bone. The etiopathogenesis of RA is linked to microbes such as *Porphyromonas gingivalis*, gut microbiota, and the herpes simplex virus; there are also indications that eliminating *H. pylori* increases RA activity.[8-10] Bartels et al. investigated 56,000 patients with a median follow-up of 8 years who were either *H. pylori* -positive or *H. pylori* -negative and shared similar comorbidities. The prevalence of RA was the same, and no association between *H. pylori* and RA was observed.[11] Results of meta-analysis also showed no evidence of a significant relation between *H. pylori* infection and RA (Odds ratio (OR) 1.18; 95% confidence interval (CI): 0.91-1.52, p=0.19), and the authors came to the conclusion that RA pathogenesis was unaffected by *H. pylori* infection.[12] Ebrahimi et al. reported in his findings that both *H. pylori* positive and CagA positive patients had significantly higher serum inflammatory biomarkers than negative individuals. However, despite the fact that the disease activity score-28 score, and visual analogue scale were relatively high in CagA positive patients than in CagA negative patients, they did not observe any variations in the disease activity score-28 score as per *H. pylori* status.[13]

Grigoriadou et al investigated the relationship among non-steroidal anti-inflammatory drugs and *H. pylori* infection of the gastric antrum in RA patients' with the development of peptic ulcer disease and demonstrated that non-steroidal anti-inflammatory drugs elevated the relative risk (RR) of ulceration (RR 8.67 (1.19-62.87)) while *H. pylori* is linked to ulcers in RA patients (RR 3.71 (0.37-37.35)). The risk ratio for the two factors; non-steroidal anti-inflammatory drugs use and *H. pylori* colonization-was 14.44. (2.05-101). The author further concluded that non-steroidal anti-inflammatory drug induced ulceration risk was increased by *H. pylori* infection.[14] Although these findings are in contrast to the results reported by Moriyama et al who revealed that RA patients receiving long-term non-steroidal anti-inflammatory drugs therapy, *H. pylori* infection was not related to gastroduodenal lesions or disease activity. *H. pylori* infection spontaneous remission in RA patients was also confirmed. Regular *H. pylori* elimination may not be necessary for RA patients receiving long-term non-steroidal anti-inflammatory drugs therapy.[15]

H. pylori and systemic lupus erythematosus (SLE)

The appearance of SLE, a chronic multisystem autoimmune disease, is extremely diverse. Combinations of genetic, epigenetic, and environmental variables lead to SLE. Pathologically, the condition is principally characterized by aberrant B- and T-cell function and immunological tolerance loss.[16] Sawalha et al described in his results that *H. pylori* seropositivity is less common in African- American women with SLE compared to controls, and *H. pylori* infection has been linked to a later onset of SLE.[17] Findings of a study conducted by Showji et al revealed that Japanese individuals with SLE had anti- *H. pylori* antibody concentrations that are comparable to healthy controls and even less than the patients with other connective tissue diseases as systemic sclerosis.[18] Contradictory to these results, findings of a 13-year-old population-based cohort study proved that there is a high risk of SLE in patients with *H. pylori* infection, especially in female patients under the age of 30 years.[19] Results of subsequent study showed that in the first three years of follow-up, *H. pylori* elimination within three months of diagnosis reduced the incidence of SLE (p=0.0013). This implies that longer-term *H. pylori* exposure increases the chance of developing SLE. However, the delay in beginning elimination medication had no discernible effect on the probability of developing long-term SLE.[20] Pinto et al. reported in his findings that *H. pylori* infection is prevalent in SLE patients. However, there is no evidence connecting *H. pylori* infection to the severity of SLE or receipt of gastroprotective treatment. Also, in SLE patients, immunosuppressive treatment might not be effective at preventing *H. pylori* infection.[21] Ram et al. observed that people who were seropositive for *H. pylori* and had various autoimmune illnesses had a greater prevalence of anti-dsDNA antibodies. Anti- *H. pylori* antibodies were also shown to be more prevalent when anti-dsDNA was present. Despite this, there was no conclusive evidence linking anti- *H. pylori* antibodies to SLE.[22]

H. pylori and Sjögren's syndrome (SS)

Systemic autoimmune disease SS is marked by sicca syndrome which is due to exocrine gland lymphoplasmacytic infiltration.[23] Some studies claimed that SS, a systemic autoimmune illness, had a connection to *H. pylori* infection, which is characterized by lymphocyte infiltration and exocrine gland destruction. *H. pylori* is one of the most well-known infectious agents that causes the autoimmune reactions, therefore this phenomenon may be the outcome of a bacterially driven autoimmune response. However, as per various research, there were no appreciable variations in the prevalence of *H. pylori* infection between the SS and control group. Therefore, it is debatable if *H. pylori* infection is a risk factor for SS.[24] Saghafi et al in comparison of IgM and IgA anti *H. pylori* antibodies reported that in SS patients, antibodies were found to be considerably greater (34.9% versus 10.5%%, p=0.001).[25] El Miedany et al concluded in his study that SS patients are more likely to have *H. pylori* infection than other connective tissue diseases. Age, disease duration, C-reactive protein, and the index for clinical disease manifestations were all linked with serum antibody titer to *H. pylori*.[26] Banno et al reported *H. pylori* infection and SS have a strong correlation (OR=2.33).[27] Theander et al described *H. pylori* seropositivity was not linked to the presence of immunological SS markers like circulating autoantibodies or an aberrant focus score in a lip biopsy.[28] Contradictory to this Caporali et al reported a statistically significant correlation between seropositivity for *H. pylori* and localized glandular lymphocytic infiltrates (OR 14.17, 95% CI 4.1-48.7, p=0.001).[29]

H. pylori and autoimmune skin diseases

Skin self-antigen tolerance is lost as a result of immune system dysregulation, which is the hallmark of autoimmune skin disorders. *H. pylori* is a likely infectious agent for inducing autoimmunity due to the prolonged interaction between the bacteria and host immune systems. An autoimmune condition: psoriasis affects 1% to 3% of the population. Recent immunological research has improved our knowledge of psoriasis pathophysiology. *H. pylori* infection has recently been proposed as a potential trigger for psoriasis. Psoriasis patients had significantly higher rates of *H. pylori* infections than healthy controls. Numerous researchers documented instances when *H. pylori* infections were eliminated, and the psoriatic lesions disappeared.[30] Yu et al stated that as per recent research, *H. pylori* infection is linked to psoriasis, and those who have it may score higher on the psoriasis area and severity Index. Author further suggested that future research should concentrate not just on *H. pylori* infection but additionally on the part that the gut microbiota plays in the development of psoriasis.[31]

Meta-analysis results revealed that patients with Bechet's syndrome had a greater risk of *H. pylori* infection, and after *H. pylori* eradication, clinical symptoms like mouth ulceration, vaginal ulceration, and cutaneous lesions can resolve. The findings suggested that *H. pylori* may play a role in the development of Bechet's syndrome.[32] In contrast to this Ersoy et al concluded that endoscopic results, *H. pylori* prevalence, and eradication rates were indistinguishable in individuals with Bechet's disease and the control group.[33] Clinical research studies conducted to determine the association of *H. pylori* with rheumatic and autoimmune diseases are limited to the past times and contrasting further research is needed to elaborate and understand the relationship between *H. pylori* infection, rheumatic and autoimmune diseases.

CONCLUSION

Infectious agents are significant causal factors in both the initiation and propagation of autoimmunity however, the role of *H. pylori* infection in this process is unclear.

Further research is required to assess this relationship and its clinical significance, with a focus on when *H. pylori* elimination treatment should be advised in patients with an autoimmune disease or who are at an increased risk of its development.

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