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Helicobacter pylori and its association with autoimmune diseases: systemic lupus erythematosus, rheumatoid arthritis and Sjögren syndrome

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ABSTRACT

Helicobacter pylori (H. pylori) is a gram-negative bacterium that adapts to the gastric mucosa and provokes symptoms associated with gastritis. Chronic *H. pylori* infection in patients with a genetic predisposition can trigger autoimmune diseases due to the immune interaction of cellular and humoral responses. Infections are a triggering factor for systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren syndrome (SS), although the association between *H. pylori* and these diseases is unclear. Therefore, we reviewed this interaction and its clinical importance.

1. Introduction

Helicobacter pylori (H.pylori) is a spiral-shaped gram-negative bacterium that can adapt to the acidic conditions of the human gastric mucosa. Currently, more than 4.4 billion individuals are infected, and the prevalence by country fluctuates from 18.9% to 87.7% [1].

Colonization of the gastric mucosa by *H. pylori* is associated with chronic active gastritis, chronic atrophic gastritis, peptic ulceration, gastric adenocarcinoma, and mucosa-associated lymphoid tissue (MALT) gastric lymphoma [2,3]. Recent studies suggest that some systemic diseases are related to *H. pylori* infection; these include iron deficiency anemia [4], vitamin B12 deficiency [5], non-alcoholic fatty liver disease [6], subclinical coronary atherosclerosis [7], insulin resistance, and metabolic syndrome [8]. Several studies describe a link between *H. pylori* infection and autoimmune disease [9].

H. pylori infections are of concern for patients with autoimmune diseases for several reasons. First, autoimmune diseases are related to low immune competence due to disease manifestations or pharmacologic treatment; thus, *H. pylori* infection risk increases [10]. Secondly, the side effects of non-steroidal anti-inflammatory drugs (NSAID) may cause additive damage [11]. Third, immune suppression increases the risk of neoplasm, including gastric cancer [12].

This paper reviews the evidence on these crucial pathogenic aspects related to systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren syndrome (SS).

2. *Helicobater pylori* and autoimmunity

Chronic infections constantly stimulate the immune system, which may generate an autoimmune environment in patients with a genetic predisposition [13]; chronic *H. pylori* infection could participate in the etiopathogenesis and maintenance of inflammatory activity in some autoimmune diseases [14,15].

One of the first trials of *H. pylori* in systemic autoimmune diseases was published in 1995 by Showji et al. [16]. They reported that patients with SS had a higher prevalence of serum antibodies against *H. pylori*

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than people without autoimmune diseases. Ram et al. [17] found that serum levels of IgG against *H. pylori* were more prevalent in patients with anti-phospholipid syndrome, giant cell arteritis, systemic sclerosis, and primary biliary cirrhosis, and anti-*H. pylori* antibodies were associated with a higher prevalence of anti-dsDNA and anti-Ro/SSA antibodies.

A link between *H. pylori* and autoimmune diseases such as immune thrombocytopenic purpura [18], IgA nephropathy [19], Devic disease [20], autoimmune pancreatitis [21], and autoimmune thyroid disease has been reported [22]. Moreover, *H. pylori*-related lymphomas of the gastrointestinal tract are associated with autoimmune diseases [23].

In contrast, evidence suggests *H. pylori* is a protective agent against disorders like asthma [24], allergic airway inflammation [25], and multiple sclerosis [26].

2.1. Pathways between Helicobacter pylori and autoimmunity

Genetic, epigenetic, and environmental factors such as infections lead to loss of immunological tolerance [27,28]. Molecular mimicry, bystander activation, epitope spreading and polyclonal activation are related to immune dysregulation in the presence of *H. pylori* infection [29]. Amedei et al. [30] showed that molecular mimicry produced by *H. pylori* antigens can activate self-reactive T lymphocytes by cross-immunity, and Yamanishi et al. [31] demonstrated that activation of B-1 cells mediated by *H. pylori* urease leads to the generation of autoreactive antibodies.

H. pylori may generate immune complexes [32] due to activation of cellular and humoral immune responses [33] since it increases the production of INF-gamma (Th1-mediated cellular response) [30,34], and the production of IgM and IgG3 antibodies. In vitro studies showed that B cells chronically stimulated with urease produced by *H. pylori* had the potential to generate autoantibodies such as IgM rheumatoid factor [35,36]. These mechanisms may cause loss of cell tolerance and the generation of more autoantibodies, such as anti-dsDNA and anti-phospholipids [37].

H. pylori strain coding for cytotoxin-associated gene A (CagA) has an enhanced capability to stimulate the secretion of pro-inflammatory cytokines, generating tissue injury, polarity, and host cell proliferation, leading to modulation of host immune responses [38] (Fig. 1).

In contrast, there is evidence of a symbiotic relationship between humans and *H. pylori* as a protective factor against chronic immune-mediated disorders [39]. *H. pylori* can induce a tolerogenic state in dendritic cells and stimulate the generation of regulatory T lymphocytes [40–42].

3. *Helicobacter pylori* and systemic lupus erythematosus

Systemic lupus erythematosus is a chronic disease characterized by the production of autoantibodies that generate tissue damage [43]. Infections are a trigger for SLE, and disease activity is linked to Mycoplasma spp. [44], human papillomavirus [45] and *H. pylori* [46]. The main microorganisms associated with SLE development are Epstein-Barr virus, parvovirus B 19, human T-lymphotropic virus-1, and endogenous retroviruses [47]. Bacteria are also probable causal microorganisms of SLE; the most studied are *Vibrio cholerae* and *H. pylori* [48].

3.1. Epidemiological relationship between Helicobacter pylori and SLE

Studies of the epidemiological relationship between SLE and *H. pylori* have yielded contradictory results. For example, Sawalha et al. [49] showed that African-American women with SLE are less frequently seropositive for *H. pylori* than controls, and *H. pylori* infection was associated with a later SLE onset. However, Showji et al. [16] reported that anti-*H. pylori* antibody concentrations in SLE Japanese patients are similar to those in healthy controls and even lower than in other connective tissue diseases such as SS.

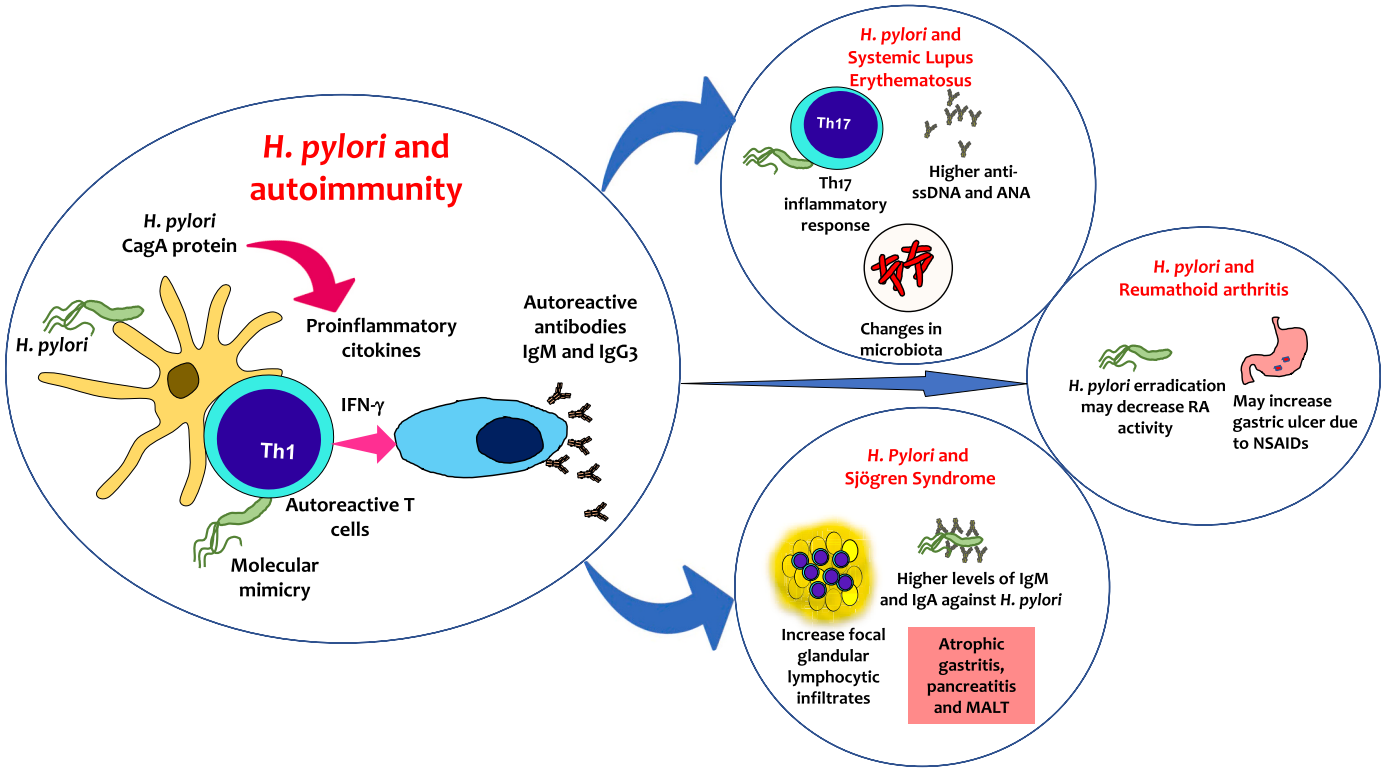

Fig. 1. Potential association of *Helicobacter pylori* and autoimmune diseases. *H. pylori* stimulates the secretion of pro-inflammatory cytokines and may generate immune complexes since it increases the production of INF-γ. These mechanisms may cause loss of cell tolerance and the generation of autoantibodies, such as anti-single-stranded DNA (ssDNA) and anti-nuclear antibodies (ANA).

These results contrast with a nationwide cohort study in Taiwan by Wu et al. [50], who reported that the incidence of SLE is higher in the *H. pylori*-infected population compared with controls (1.17 vs. 0.72 per 100,000 person-months) and *H. pylori* infection increases 1.63 times the risk of SLE, especially in women aged <30 years.

A subsequent study conducted by Wu et al. [51] showed that eradication of *H. pylori* within three months of diagnosis decreased the risk of SLE (aHR = 0.16, p = 0.0013) in the first three years of follow-up. This suggests that more prolonged exposure to *H. pylori* confers an increased risk of SLE. Nevertheless, the time to the start of eradication therapy did not significantly influence the long-term SLE risk [51].

Youssefi et al. [52] conducted a recent meta-analysis to resolve this issue; they found no significant relationship between SLE and *H. pylori* infection (OR: 0.97; 95%CI: 0.76–1.23; p-value: 0.82). However, there is an association between *H. pylori* CagA positive strains and autoimmune diseases such as autoimmune gastritis and SLE (ORs: 2.65 with 95% CI, p-value: 0.001) [52].

3.2. Helicobacter pylori and SLE-related markers

In FcγRIIb−/− mice, a polymorphism associated with SLE development, *H. pylori* infection was associated with increased SLE severity, higher levels of anti-*H. pylori* and anti-dsDNA antibodies, and increased production of splenic autoimmune cells compared with wild-type mice [53]. Urease induced the production of anti-ssDNA antibodies in animal models [31].

Additionally, Ram et al. [17] found a higher prevalence of anti-dsDNA antibodies in a population with different autoimmune diseases and seropositive for *H. pylori* (21 vs. 16.2%, p < 0.05). At the same time, the presence of anti-dsDNA was related to a higher concentration of anti-*H. pylori* antibodies (1.9 vs. 1.7, p < 0.05). Despite this, no significant relationship was found between SLE and anti-*H. pylori* antibodies. However, even in healthy adults, a positive association was found between higher concentrations of anti-ANA antibodies and *H. pylori* seropositivity, despite other factors such as age, sex, and race [54].

3.3. Medication and gastric lesions in SLE patients

Reshetnyak et al. [55] found significant differences in the detection rate of *H. pylori* with respect to the drugs used to treat SLE; the rate is higher with anticoagulant therapy (P = 0.038; OR = 2.96; 95% CI, 1.01–8.68) and low-dose acetylsalicylic acid (P = 0.031; OR = 3.58; 95% CI, 1.05–12.17) than for glucocorticoid and NSAID users. Nevertheless, Mendoza-Pinto et al. [46] reported that immunosuppressive or glucocorticoid therapy did not increase the prevalence of *H. pylori* infection in patients with SLE.

Furthermore, there is no higher prevalence of gastroduodenal mucosal lesions or reflux disease in SLE patients with *H. pylori* infection than in the general population [46,55].

3.4. Potential links between Helicobacter pylori and SLE

Multiple studies have been conducted on the relationship between the alteration of the intestinal microbiota and autoimmune diseases such as SLE [56,57] through ways such as the stimulation of regulatory B cells [58], enhanced exposure to extracellular nuclear autoantigens, molecular mimetism [59], and the translocation of gut pathobiont to systemic organs in SLE-prone hosts [60]. *H. pylori* may play a role in this because it produces changes in the gut microbiota through hypochlorhydria, hypergastrinemia, and by the action of the CagA factor [61]; in addition, *H. pylori* eradication treatment affects bacterial diversity [62]. However, to the best of our knowledge, there are no studies on the relationship between *H. pylori,* dysbiosis, and SLE.

H. pylori infection induces a systemic Th-17 inflammatory response, which plays an essential role in the pathophysiology of SLE [63,64]. Moreover, *H. pylori* can increase the expression of ETS1, through the CagA-activated NF-κB pathway [65], a negative regulatory transcription factor for Th17 cell and B cell differentiation involved in the pathogenesis of SLE [66]. Therefore, further investigations are required to comprehend the role of *H. pylori* in these pathways and the risk of SLE.

In sum, the few reports on the relationships between *H. pylori* and SLE have contradictory results. However, there is evidence that *H. pylori* is a dynamic factor with two possible roles: a triggering and protective factor; depending on race, age and the organs affected. It is necessary to consider *H. pylori* in the comprehensive approach to patients with SLE, mainly because the clinical and immunological implications are yet to be elucidated.

4. *Helicobacter pylori* and rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic synovial membrane inflammation damage to articular cartilage and juxta-articular bone [67]. Microorganisms such as *Porphyromonas gingivalis*, gut microbiota, and the herpes simplex virus are associated with the etiopathogenesis of RA [68]; in addition, there are antecedents that *H. pylori* eradication worsens RA activity [69]. However, the association between *H. pylori* infection and RA is not well-understood [35,70].

4.1. Epidemiological relationship between Helicobacter pylori and RA

Recently, Bartels et al. [27] studied 56,000 patients diagnosed as *H. pylori*-positive or *H. pylori*-negative for a median of 8 years, both groups with similar comorbidities. No relationship between *H. pylori* and RA was found, and there was no difference in the prevalence of RA.

Youssefi et al. [29] found no significant association between *H. pylori* infection and RA (OR 1.18; 95% CI: 0.91–1.52, p-value: 0.19), and the authors concluded that *H. pylori* infection had no significant effect on RA pathogenesis [29]. Meron et al. [71] found no significant differences in the rates of antibodies against *H. pylori* between RA patients and healthy controls.

4.2. Helicobacter pylori and RA-related markers

Zentilin et al. [72] evaluated the effects of *H. pylori* eradication on disease activity in RA patients after four months of follow-up. They found that the resolution of *H. pylori* infection reduced the chronic inflammatory stimulus, improving both serological and clinical abnormalities. Similarly, Seriolo et al. [73] found that patients with eradicated *H. pylori* infection significantly improved clinical and laboratory findings compared with *H. pylori*-negative and positive (unresponsive) patients. The authors suggested that *H. pylori* infection was associated with the pathogenesis of RA, and *H. pylori* eradication may induce a significant improvement in disease activity over 24 months [74].

Ebrahimi et al. [38] investigated the relationship between *H. pylori* infection and clinical outcomes in RA patients. They measured anti-*H. pylori* IgG antibodies, fecal *H. pylori* antigen, and CagA protein, and found that several serum inflammatory biomarkers were significantly higher in *H. pylori*-positive patients than in negative patients, and in CagA positive patients than in CagA negative patients. However, they found no differences in the DAS-28 score regarding *H. pylori* status, although the DAS-28 score and VAS were significantly higher in CagA positive patients than in CagA negative patients.

In contrast, Steen et al. [75] demonstrated a limited and transient effect of *H. pylori* eradication therapy on the lipid profile and no impact on C-reactive protein concentrations in patients with rheumatic diseases on chronic NSAID treatment.

4.3. Medication and gastric lesions in RA patients

Almost three decades ago, Janssen et al. [76] reported that RA

patients receiving intramuscular gold had decreased *H. pylori* seropositivity and hypothesized that intramuscular gold could be a protective factor against peptic ulcer disease (PUD). However, Wolde et al. [77] and Paimela et al. [78] showed that gold therapy in RA patients does not influence the serological parameters of *H. pylori* infection.

Later, Grigoriadou et al. [79] studied a possible role of NSAIDs and colonization of the gastric antrum with *H. pylori* in the development of PUD in RA patients and found that NSAID increased the relative risk (RR) of ulceration (RR 8.67 (1.19–62.87)), while the presence of *H. pylori* is associated with ulcers in RA patients (RR 3.71 (0.37–37.35)). The RR for the combination of NSAID consumption and *H. pylori* colonization was 14.44 (2.05–101). The authors concluded that *H. pylori* infection increased the risk of NSAID-induced ulceration [79].

Moriyama et al. [80] showed that *H. pylori* infection was not associated with gastroduodenal lesions or disease activity in RA patients under long-term NSAID treatment. In addition, spontaneous remission of *H. pylori* infection in RA patients was documented. The authors concluded that routine *H. pylori* eradication might not be necessary for RA patients under long-term NSAID treatment.

Lin et al. [39] conducted a study based on 79,181 patients classified as having PUD and treatment against *H. pylori* infection (PUD + HPRx), patients with PUD without treatment against *H. pylori* (PUD–HPRx), and patients without PUD (controls), and compared the effects of treatment for *H. pylori* infection on the risk of autoimmunity. They found that PUD + HPRx had the highest adjusted hazard risk (aHR) for autoimmunity, including RA (aHR, 2.44; 95% CI, 2.01–2.95; $P < 0.001$). The authors hypothesized that resident gut microbes play a role in modulating self-susceptibility to systemic immune-mediated disorders, but more research is needed.

In conclusion, *H. pylori* is considered one of the infectious agents linked to RA, but the association remains unclear.

5. *Helicobacter pylori* infection and Sjögren's syndrome

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by sicca syndrome due to lymphoplasmacytic infiltration of the exocrine glands [81]. Infections are considered a risk factor for SS, especially viral infections, such as those caused by the Epstein-Barr virus (EBV), cytomegalovirus (CMV), hepatitis C (HCV), coxsackievirus and human T-lymphocyte virus type I (HTLV-1) [82]. Additionally, bacteria have been proposed to be involved in the pathogenesis of SS, including commensal bacteria, mycobacteria, and *H. pylori* [87].

5.1. Epidemiological relationship between Helicobacter pylori and SS

H. pylori infection triggers an immune response against bacterial antigens, including the heat-shock protein of 60 kDa (HSP60), which has homology to a human protein, partially explaining the relationship between *H. pylori* and autoimmune diseases [83].

In a study that included 118 persons divided into four groups (primary SS, secondary SS, other autoimmune diseases, and healthy controls), an increase in the prevalence of serum antibodies against *H. pylori* and HSP60 was in primary SS patients compared with the rest of the groups [83].

Showji et al. [84] found that SS patients had much higher serum IgG anti-*H. pylori* titers than patients with chronic lung disease, age-matched controls, and those with other connective tissue diseases.

Saghafi et al. [85] compared serum IgM and IgA anti-*H. pylori* antibodies levels in 43 SS patients and 95 healthy controls, these antibodies were found to be significantly higher in SS patients (34.9% vs. 10.5 %, $p = 0.001$). El Miedany et al. [86] also showed that the prevalence of *H. pylori* is higher in groups with SS than other connective tissue diseases and healthy controls. Caporali R et al. [87] evaluated the presence of *H. pylori* antibodies in Italian patients with anti-Ro positivity antibodies. They found a higher prevalence of *H. pylori* antibodies in confirmed SS patients compared with those without SS (Odds ratio OR- 15.67, 95% CI:4.5–54.8, P-value < 0.001).

Chen et al. [88] in a meta-analysis of nine studies with 1958 participants, including 619 patients with SS, found that patients with primary SS had a small but significantly-higher rate (63.6% vs. 49.3%) of *H. pylori* infection than controls (OR = 1.19, 95% CI: 1.01–1.41, P = 0.033), and a significantly-higher *H. pylori* infection rate in patients with primary SS than controls (OR = 1.24, 95% CI: 1.03–1.50, P = 0.026). Of the nine studies included, seven evaluated positivity for *H. pylori* through serum and two through tissue specimens [89]. In addition, Banno et al. [90] demonstrated a highly positive association between *H. pylori* infection and SS (OR = 2.33).

Studies have linked *H. pylori* and SS with the development of multiple diseases, such as MALT lymphoma [91–95] and autoimmune pancreatitis [96,97], which could be incidental clinical findings, although they may share pathogenic molecular pathways such as the expression of CXCL13 and its CXCR5 receptor [98,99]. For example, in a study conducted in 9 SS patients with gastric MALT lymphoma, MALT lymphoma translocation 1 gene (MALT1) rearrangement was present in 78% of cases, and MALT1 is associated with resistance to *H. pylori* eradication therapy [100].

5.2. Helicobacter pylori and SS-related markers

H. pylori infection is also associated with SS due to shared histological findings, such as the destruction of exocrine glands, lymphocytic infiltration, and activation of CD8 cells [101,102].

Irani et al. [88] demonstrated through immunohistochemical tissue stuides a higher presence of *H. pylori* in patients with inflammatory oral mucosa lesions than oral mucosa from healthy patients. Moreover, *H. pylori* possibly interacts with surface of epithelial cells, developing direct cell damage or producing pro-inflammatory mediators [103].

Theander et al. [103] found that *H. pylori* seropositivity was not associated with the presence of immunological markers of SS such as circulating autoantibodies or a lip biopsy with abnormal focus score. However, Caporali et al. [87] found a significant association between seropositivity for *H. pylori* and focal glandular lymphocytic infiltrates (OR 14.17, 95% CI 4.1–48.7, P-value < 0.001).

5.3. Medication and gastric lesions in RA patients

Collin et al. [104] evaluated the frequency of gastritis in patients with SS compared with controls, finding a higher rate of atrophic antral gastritis in SS patients but with no difference in the prevalence of *H. pylori.* However, Banno et al. [90] showed that atrophic gastritis in SS patients may occur due to *H. pylori* infection.

In contrast, Sorrentino et al. [105] found no differences in the prevalence of IgG anti-*H. pylori* in patients with dyspepsia with SS (57%) or without SS (62%) or in anti-CagA antibodies among patients with SS and the control group, so SS was not associated with more virulent strains.

Small series and non-randomized trials show conflicting results regarding the benefit of *H. pylori* eradication in autoimmune diseases, including SS [106]. Lin et al. [39] found that patients with PUD and treatment of *H. pylori* infection had an aHR (3.15; 95% CI, 2.57–3.87; $P < 0.001$) for SS compared with patients with PUD without *H. pylori* infection treatment.

6. Conclusion

Although infectious agents are essential triggers in both the induction and perpetuation of autoimmunity, the role of *H. pylori* infection in this process remains unclear, so further research is required to evaluate this association and its clinical significance, with a focus on when *H. pylori* eradication should be recommended in patients with an autoimmune disease or a high risk of developing them.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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