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

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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 autoimmunity [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. *Helicobacter 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*...
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 more autoantibodies, such as anti-dsDNA 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 autoimmunity gastritis and SLE (ORs: 2.65 with 95% CI, p-value: 0.001) [52].

3.2. *Helicobacter pylori* and SLE-related markers

In FcγR IIb−/− 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 autoimmunity 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 [38], 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 hyperchlorhydria, 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, Serafino 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 (1.97–62.87)), 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 gastrointestinal 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 + HPx), patients with PUD without treatment against *H. pylori* (PUD–HPx), and patients without PUD (controls), and compared the effects of treatment for *H. pylori* infection on the risk of autoimmunity. They found that PUD + HPx 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* titters 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, lymphoblastic infiltration, and activation of CD8 cells [101,102].

Irani et al. [88] demonstrated through immunohistochemical tissue studies 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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