Research Article

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The autoimmune disorders systemic lupus erythematosus, rheumatoid arthritis, and Sjogren syndrome are linked to Helicobacter pylori.

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ABSTRACT

A gram-negative bacteria called Helicobacter pylori, or H. pylori, attaches itself to the stomach mucosa and causes symptoms similar to gastritis. Due to the immunological interplay of cellular and humoral responses, chronic H. pylori infection can cause autoimmune disorders in persons with a hereditary susceptibility. A common infection is trigger for rheumatoid arthritis (RA), Sjogren syndrome (SS), and systemic lupus erythematosus (SLE), while it's unclear if H. pylori causes these conditions. As a result, we discussed the therapeutic significance of this relationship.

Keywords : Helicobacter pylori, Systemic lupus erythematosus,Rheumatoid arthritis, Sj¨ogren, Syndrome, Infection

INTRODUCTION

The spiral-shaped, gram-negative bacteria Helicobacter pylori, or H.pylori, is able to adjust to the acidic environment of the human stomach mucosa. At now, around 4.4 billion people worldwide carry the virus, with varying country-specific prevalence rates ranging from 18.9% to 87.7% [1].

H. pylori colonization of the stomach mucosa is linked to mucosa-associated lymphoid tissue (MALT) gastric lymphoma, peptic ulceration, chronic active gastritis, and chronic atrophic gastritis [2,3]. A number of systemic illnesses, such as iron deficiency anemia [4], vitamin B12 insufficiency [5], non-alcoholic fatty liver disease [6], subclinical coronary atherosclerosis [7], insulin resistance, and metabolic syndrome [8], have been linked in recent research to H. pylori infection. Numerous researches have reported a connection between autoimmune diseases and H. pylori infection [9]. H. Patients with autoimmune illnesses should be concerned about pylori infections for a number of reasons. Firstly, reduced immune competence associated with autoimmune disorders is a result of disease symptoms or medication therapy; as a result, the likelihood of contracting H. pylori infection rises [10].

Second, non-steroidal anti-inflammatory drug (NSAID) side effects have the potential to inflict more harm [11]. Third, immune suppression raises the possibility of neoplasms, such as stomach cancer [12].

In order to better understand these important pathogenic factors connected to SLE, RA, and Sjogren syndrome (SS), this research examines the available data.

THE IMMUNE SYSTEM AND HELICOBACTER PYLORI

Patients with a genetic susceptibility may develop an autoimmune environment due to chronic infections, which continuously excite the immune system [13]; chronic H. pylori infection could contribute to the some autoimmune disorders' etiopathogenesis and persistence of inflammatory activity [14,15].

One of the earliest studies on H. pylori in autoimmune illnesses of the system was released by Showji et al. in 1995 [16]. They found that blood antibodies against H. pylori were more common in SS patients.compared to those without autoimmune conditions. According to Ram et al. [17], individuals with anti-phospholipid syndrome, giant cell arteritis, systemic sclerosis, and anti-pylori antibody levels were more common.

Anti-H. pylori antibodies were linked to a higher prevalence of anti-dsDNA and anti-Ro/SSA antibodies, as well as primary biliary cirrhosis.

It has been shown [22] that H. pylori is associated with autoimmune disorders, including immune thrombocytopenic purpura [18], IgA nephropathy [19], Devic disease [20], autoimmune pancreatitis [21], and autoimmune thyroid disease. Furthermore, autoimmune disorders are linked to

gastrointestinal tract lymphomas caused by H. pylori [23].
On the other hand, research indicates that H. pylori may offer protection against conditions like multiple sclerosis [26], allergic airway inflammation [25], and asthma [24].

The connections between autoimmune and Helicobacter pylori

Immunological tolerance declines as a result of environmental, genetic, and epigenetic variables, including infections [27, 28]. Molecular emulation, Immune dysregulation in the context of H. pylori infection is linked to bystander activation, epitope dissemination, and polyclonal activation [29]. Cross-immunity generated by H. pylori antigens can activate self-reactive T lymphocytes by molecular mimicry, as proven by Amedei et al. [30] and Yamanishi et al. [31], who showed that H. pylori urease-mediated B-1 cell activation results in the production of autoreactive antibodies.
Because H. pylori promotes the synthesis of INF-gamma (a Th1-mediated cellular response), it can activate both cellular and humoral immune responses, leading to the generation of immunological complexes [32, 33]. and the generation of antibodies IgM and IgG3. Studies conducted in vitro demonstrated that B cells that were continuously stimulated with H. pylori-produced urease had the capacity to develop autoantibodies such IgM rheumatoid factor.
[35, 36]. Loss of cell tolerance and an increase in autoantibodies like those against phospholipids and dsDNA may result from these processes [37].
The strain of H. pylori that codes for cytotoxin-associated gene A (CagA) is more effective at inducing tissue damage, polarity, and host cell proliferation through the release of pro-inflammatory cytokines, which in turn modulates host immunological responses [38] (Fig. 1).
The symbiotic interaction between humans and H. pylori, on the other hand, appears to be protective against chronic immune-mediated diseases [39]. In dendritic cells, H. pylori can cause a tolerogenic condition. cells and promote the production of T lymphocytes that are regulatory [40–42].

The disease systemic lupus erythematosus and Helicobacter pylori

Autoantibodies that cause tissue destruction are the hallmark of the chronic illness known as systemic lupus erythematosus [43]. SLE is brought on by infections, and Mycoplasma species [44], the human papillomavirus [45], and H. pylori [46] are associated with disease activity. The primary microbes linked to the development of SLE are endogenous retroviruses, human T-lymphotropic virus-1, parvovirus B 19, and Epstein-Barr virus [47]. The most researched bacteria that are thought to be the cause of SLE are H. pylori and Vibrio cholerae [48].

The epidemiological connection between SLE and Helicobacter pylori

Research on the epidemiological connection between H. pylori and SLE has produced conflicting findings. Sawalha et al. [49], for instance, demonstrated that Seropositive African-American women with SLE are less likely than controls to be H. pylori positive, and H. pylori infection has been linked to a delayed onset of SLE. Showji et al. [16], however, reported revealed the levels of anti-H. pylori antibodies in Japanese patients with SLE are comparable to those in healthy controls and even lower than those in patients with other connective tissue illnesses like SS.The findings of a statewide cohort research conducted in Taiwan by Wu et al. [50] show that the incidence of SLE is higher in the population infected with H. pylori than in the controls (1.17 vs. 0.72 per 100,000 person-months) and H. pylori infection, particularly in women under 30 years of age, raise the risk of SLE 1.63 times.
In the first three years of follow-up, eradication of H. pylori within three months of diagnosis reduced the incidence of SLE (aHR = 0.16, p = 0.0013), according to a follow-up research by Wu et al. [51]. This implies that a longer duration of H. pylori exposure raises the risk of SLE. However, the duration until the eradication therapy began had no discernible effect on the long-term risk of SLE [51]. In an attempt to address this, Youssefi et al. [52] recently performed a meta-analysis and discovered no evidence of a connection between H. pylori infection and SLE (OR: 0.97; 95%CI: 0.76–1.23; p-value: 0.82). But there is autoimmune illnesses such autoimmune gastritis and SLE have been linked to H. pylori CagA positive strains (ORs: 2.65 with 95% CI, p-value: 0.001) [52].

Markers associated with SLE and Helicobacter pylori

H. pylori infection was linked to higher levels of anti-H. pylori and anti-dsDNA antibodies, increased generation of splenic autoimmune cells, and increased SLE severity in FcγRIIb− /− mice, a polymorphism linked to the development of SLE [53]. In animal models, urease stimulated the development of anti-ssDNA antibodies [31].
Furthermore, Ram et al. [17] discovered that anti-dsDNA antibodies were more common in a group of people seropositive for H. pylori and with various autoimmune diseases (21 vs. 16.2%, $p < 0.05$). Simultaneously, there was a correlation between the concentration of anti-H. pylori antibodies (1.9 vs. 1.7, $p < 0.05$) and the existence of anti-dsDNA. Nevertheless, no meaningful correlation was observed between anti-H. pylori antibodies and SLE. But even among those in good health, there was a favorable correlation found, independent of other variables including age, sex, and race, to be associated with higher amounts of anti-ANA antibodies and H. pylori seropositivity [54].

In individuals with SLE, medication and gastric lesions

Significant variations were observed between the H. pylori detection rate and the medications used to treat SLE by Reshetnyak et al. [55]. Anticoagulant therapy had a higher rate (P = 0.038; OR = 2.96; 95%). lower-dose acetylsalicylic acid (P = 0.031; OR = 3.58; 95% CI, 1.05–12.17) and glucocorticoid users (CI, 1.01–8.68). However, Mendoza-Pinto et al. [46] noted that individuals with immunosuppressive or In patients with SLE, glucocorticoid medication did not raise the prevalence of H. pylori infection.

Furthermore, SLE patients with H. pylori infection do not have a higher prevalence of reflux disease or gastroduodenal mucosal lesions than the general population [46,55].

Possible connections between SLE and Helicobacter pylori

The connection between changes in the gut microbiota and autoimmune disorders like SLE has been the subject of numerous studies [56,57]. These studies have looked at the activation of regulatory B cells [58], increased exposure to extracellular nuclear autoantigens [59], molecular mimicry [59], and the translocation of gut pathobionts. to systemic organs in hosts susceptible to SLE [60]. Due to its ability to create hypochlorhydria, which alters the gut flora, H. pylori may be involved in this.

hypergastrinemia, as well as by the CagA factor's action [61]; additionally, bacterial diversity is impacted by H. pylori eradication treatment [62]. To the best of our knowledge, however, no research has been done on the connection between dysbiosis, SLE, and H. pylori.

An important part of the pathophysiology of SLE is the systemic Th-17 inflammatory response that is triggered by H. pylori infection [63, 64].

Furthermore, via activating the CagA-activated NF-κB pathway [65], H. pylori can upregulate the expression of ETS1, a transcription factor that negatively regulates Th17 cell and B cell development and is implicated in the pathophysiology of SLE [66]. Thus, additional research is necessary to recognize the risk of SLE and the part H. pylori plays in these pathways.

All things considered, the scant research on the connections between H. pylori and SLE has produced inconsistent findings. Nonetheless, there is proof that H. pylori is a dynamic component that, depending on ethnicity, age, and the organs afflicted, can play either a triggering or protecting role. H. pylori must be taken into account in a comprehensive approach to patients with SLE, primarily due to the unclear clinical and immunological implications.

Rheumatoid arthritis and Helicobacter pylori

Rheumatoid arthritis (RA) is an inflammatory disease that damages articular cartilage and juxta-articular bone due to persistent inflammation of the synovial membrane [67]. Microbes such the herpes simplex virus, Porphyromonas gingivalis, and gut microbiome are linked to the etiopathogenesis of RA [68]; additionally, there are indications that the removal of H. pylori exacerbates RA symptoms [69]. It is unclear, therefore, how H. pylori infection and RA are related [35,70].

The epidemiological connection between RA and Helicobacter pylori

For a median of eight years, Bartels et al. [27] examined 56,000 individuals with identical comorbidities who were classified as H. pylori-positive or H. pylori-negative. No correlation between H. pylori and RA was discovered, and the prevalence of RA did not vary.

Youssefi et al. [29] concluded that H. pylori infection had no significant effect on RA etiology after finding no significant connection between H. pylori infection and RA (OR 1.18; 95% CI: 0.91–1.52, p-value: 0.19). Meron and others [71] did not discover any appreciable variations in H. pylori antibody frequencies between RA patients and healthy controls.

Markers associated with RA and Helicobacter pylori

After four months of follow-up, Zentilin et al. [72] assessed the impact of H. pylori eradication on disease activity in individuals with RA. They discovered that the elimination of the H. pylori infection improved both serological and clinical abnormalities by lowering the chronic inflammatory stimulation. Similarly, compared to H. pylori-negative and positive (unresponsive) individuals, patients with eradicated H. pylori infection dramatically improved clinical and laboratory findings (Seriolo et al., 73). The authors proposed that the pathophysiology of RA was linked to H. pylori infection, and that eliminating H. pylori over a 24-month period may result in a significant improvement in disease activity [74].

Ibrahimi et al. [38] looked at the connection between RA patients' clinical results and H. pylori infection. They examined the levels of CagA protein, fecal H. pylori antigen, and anti-H. pylori IgG antibodies.

They discovered that a number of serum inflammatory indicators were significantly greater in patients with H. pylori infection than in those without it, as well as in patients with CagA infection than in those without it. They could not discover any variations in the DAS-28 score with respect to H. pylori status, despite the fact that CagA positive patients had considerably higher VAS and DAS-28 scores than CagA negative patients.

On the other hand, H. pylori eradication therapy had no effect on C-reactive protein concentrations and only a small and temporary effect on the lipid profile in patients with rheumatic illnesses receiving prolonged NSAID treatment,

according to Steen et al. [75].

RA patients' medication and stomach lesions Janssen et al.

Proposed that intramuscular gold may be a preventive measure against peptic ulcer disease (PUD) after finding that RA patients who received it had lower H. pylori seropositivity nearly thirty years ago. But Wolde and associates [77] and Paimela et al. [78] demonstrated that gold therapy had no effect on the serological indicators of H. pylori infection in individuals with RA.

Subsequently, Grigoriadou et al. [79] investigated the potential interaction between H. pylori colonization of the gastric antrum and NSAIDs in the development of PUD in patients with RA. They discovered that H. pylori is linked to ulcers in RA patients, while NSAID use increased the relative risk (RR) of ulceration (RR 8.67 (1.19–62.87)). 3.71 (RR 0.37–37.35)).

The relative risk (RR) for the co-occurrence of H. pylori colonization and NSAID use was 14.44 (2.05–101). The investigators came to the conclusion that using NSAIDs enhanced the risk of ulceration caused by H. pylori infection [79].

According to research by Moriyama et al. [80], H. pylori infection in RA patients receiving long-term NSAID medication was not linked to gastroduodenal lesions or disease activity. Furthermore, reports of H. pylori infection spontaneously going away in RA patients have been made. The authors came to the conclusion that for RA patients receiving long-term NSAID treatment, routine H. pylori removal might not be required.

A study by Lin et al. [39] used data from 79,181 patients who were categorized as having PUD and receiving treatment for H. pylori infection (PUD + HPRx), PUD patients receiving therapy for H. pylori infection but not receiving treatment (PUD–HPRx), and PUD patients not receiving treatment. (controls), and contrasted how the H. pylori infection therapy affected the likelihood of developing autoimmunity. They discovered that the greatest adjusted hazard risk (aHR) for autoimmunity was associated with PUD + HPRx.

RA (aHR, 2.44; 95% CI, 2.01–2.95; P < 0.001) was among them. Further study is necessary to confirm the authors' hypothesis that resident gut bacteria modulate self-susceptibility to systemic immune-mediated diseases.

In conclusion, although the exact relationship between H. pylori and RA is yet unknown, it is thought to be one of the infectious agents.

The illness caused by Helicobacter pylori and Sjogren's syndrome

A systemic autoimmune condition called Sjogren's syndrome (SS) is characterized by sicca syndrome, which is brought on by lymphoplasmacytic infiltration of the exocrine glands [81]. A known risk factor for SS is an infection, particularly one that is viral, like those that produce by the human T-lymphocyte virus type I (HTLV-1), coxsackievirus, hepatitis C (HCV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) [82]. Furthermore, bacteria have been suggested to play a role in the pathophysiology of SS, including H. pylori, mycobacteria, and commensal bacteria [87].

The epidemiological connection between SS and Helicobacter pylori

The heat-shock protein of 60 kDa (HSP60), which shares homology with a human protein and is involved in the immune response against bacterial antigens, is one of the proteins that H. pylori infection induces [83]. This helps to explain the connection between autoimmune illnesses and H. pylori.

In a research with 118 participants split into four groups (primary SS, secondary SS, other autoimmune disorders, and healthy controls), primary SS patients had higher serum antibody prevalences against H. pylori and HSP60 than the remaining groupings [83].

SS patients showed significantly greater serum IgG levels, according to Showji et al. [84].

anti-H. pylori titers compared to age-matched controls, patients with various connective tissue illnesses, and patients with chronic lung disease.

Serum IgM and IgA anti-H. pylori antibodies were shown to be considerably greater in SS patients (34.9% vs. 10.5% %, p = 0.001) when Saghafi et al. [85] compared the levels of these antibodies in 43 SS patients with 95 healthy controls. Additionally, El Miedany et al. [86] demonstrated that SS patients had a greater prevalence of H. pylori than do patients with other connective tissue diseases or healthy controls. The existence of H. pylori antibodies in Italian patients with anti-Ro positive antibodies was assessed by Caporali R et al. [87]. Compared to individuals without SS, verified SS patients had a greater prevalence of H. pylori antibodies (Odds ratio OR: 15.67, 95% CI: 4.5–54.8, P-value < 0.001).

In their meta-analysis of nine studies involving 1958 participants, including 619 patients with SS, Chen et al. [88] discovered that patients with primary SS had a small but significantly higher rate of H. pylori infection (63.6% vs. 49.3%) than controls (OR = 1.19, 95% CI: 1.01–1.41, P = 0.033), and that patients with primary SS had a significantly higher rate of H. pylori infection than controls (OR = 1.24, 95% CI: 1.03–1.50, P = 0.026). Out of the nine investigations that were included, two used tissue specimens and seven used serum to determine if an individual had H. pylori [89]. Furthermore, a very strong correlation was shown by Bannan et al. [90] between H. SS with H. pylori infection (OR = 2.33).

Research has connected SS and H. pylori to the emergence of several illnesses, including autoimmune pancreatitis [96,97] and MALT lymphoma [91–95]. These findings may be coincidental clinical observations.

notwithstanding the possibility that they share harmful molecular pathways, such as CXCL13 and its CXCR5 receptor expression [98,99]. For instance, MALT lymphoma translocation 1 gene (MALT1) rearrangement was found in 78% of cases in a study involving 9 SS individuals with stomach MALT lymphoma. MALT1 is linked to resistance to H. pylori eradication therapy [100].

Markers associated with SS and Helicobacter pylori

Due to similar histopathological findings, including exocrine gland damage, lymphocyte infiltration, and CD8 cell activation, H. pylori infection is similarly linked to SS [101,102]. Irani et al. [88] used immunohistochemical tissue staining to show that patients with inflammatory oral mucosa lesions had greater levels of H. pylori than did oral mucosa from healthy patients. Additionally,

It's possible that H. pylori interacts with epithelial cell surfaces, causing direct cell injury or releasing mediators that promote inflammation [103].

According to Theander et al. [103], the existence of immunological indicators of SS, such as circulating autoantibodies or a lip biopsy with an aberrant focal score, was not linked to H. pylori seropositivity.

Caporali et al. [87] discovered a noteworthy correlation between focal glandular lymphocytic infiltrates and H. pylori positive (OR 14.17, 95% CI 4.1–48.7, P-value < 0.001).

RA patients' medication and stomach lesions

Collin et al. [104] assessed how frequently patients had gastritis. SS patients had a higher incidence of atrophic antral gastritis than controls, but there was no difference in the prevalence of H. pylori. But Banno et al. [90] demonstrated that SS patients with atrophic gastritis an H. pylori infection may arise in patients.

However, Sorrentino et al. [105] did not find any differences in the anti-CagA antibodies between patients with SS and the control group, nor in the prevalence of IgG anti-H. pylori in patients with dyspepsia with SS (57%) or without SS (62%). Therefore, SS was not linked to more virulent strains.

Results from non-randomized trials and small series are inconsistent when it comes to the advantages of H. pylori removal in autoimmune illnesses like SS [106]. According to Lin et al. [39], PUD patients' outcomes with therapy SS compared to PUD patients without therapy for H. pylori infection exhibited an aHR (3.15; 95% CI, 2.57–3.87; P < 0.001) for H. pylori infection.

CONCLUSION

Further research is needed to assess 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 one. Although infectious agents are crucial triggers in both the induction and perpetuation of autoimmunity, the role of H. pylori infection in this process remains unclear.

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