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ORIGINAL ARTICLE

Helicobacter pylori infection and gastroduodenal lesions in patients with systemic lupus erythematosus

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Abstract

Objective The aim of this study was to determine the frequency of *Helicobacter pylori* in SLE patients and to compare clinical characteristics and gastroduodenal lesions in patients with and without *H. pylori* infection.

Methods Adult SLE patients were selected and subjected to endoscopy. Gastroduodenal lesions were examined by endoscopy and biopsy (antrum and corpus). Biopsies were evaluated by hematoxylin and eosin and Giemsa staining. Immunochromatographic membrane-based assay using amplification was used to test for *H. pylori* antigen (coproantigen) in stool samples in all participants. Clinical characteristics and gastroduodenal lesions were compared between patients with and without *H. pylori* infection.

Results A total of 118 SLE patients were included (mean age 44.7 ± 11.7 years, mean disease duration 11.6 ± 6.0 years), of whom 101 (85.6%) were receiving non-steroidal anti-inflammatory drugs (NSAIDs). The coproantigen test was positive in 32 (27.1%) patients. *H. pylori* was present in twenty six patients (22.0%) in the gastric biopsy. The frequency of gastric erosions and gastric ulcers were 55.1% and 0.8%, respectively. Gastric erosions were less frequent in SLE patients with *H. pylori* infection than those without H. *pylori* (43.5.7% vs. 62.5%; $p = 0.04$). The age, disease duration, disease activity, chronic damage, gastroprotective drugs, and immunosuppressive therapy did not differ between the two groups.

Conclusions We found a high frequency of *H. pylori* infection in SLE patients. The severity of SLE and reception of gastroprotective therapy do not seem to be related to *H. pylori i*nfection. Immunosuppressive therapy may not be protective against *H. pylori* infection in SLE patients.

Key Points
- *In patients with systemic lupus erythematosus (SLE), the frequency of Helicobacter pylori infection was 39% and gastric erosions were frequent.*
- *Disease activity, chronic damage, gastroprotective drugs, and immunosuppressive therapy may not affect the prevalence of H. pylori infection in SLE patients.*

Keywords Endoscopy · Gastroduodenal lesions · Helicobacter pylori · Systemic lupus erythematosus

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Introduction

Helicobacter pylori (*H. pylori*) is a causative factor in the development of gastroduodenal mucosal lesions [1]. The role of *H. pylori* in the pathogenesis of gastroduodenal lesions induced by non-steroidal anti-inflammatory drugs (NSAID) remains unclear [2–4]. Although some reports have implied a synergistic influence of *H. pylori* on NSAID-induced gastropathies, other studies have shown no correlation between NSAIDs and *H. pylori* in the etiopathogenesis of gastroduodenal lesions. Invasive and noninvasive tests [5] are available for the diagnosis of *H. pylori* infection. Currently, stool antigen assays offer an alternative noninvasive method for the diagnosis of infection [6].

Several manifestations of systemic lupus erythematosus (SLE), such as serositis and musculoskeletal symptoms, are often treated with NSAIDs. A survey of rheumatologists showed treatment with NSAIDs in 84% of lupus patients. Naproxen, salicylates, sulindac, and ibuprofen were the most frequently used agents [7]. In hospital settings, studies have found that 25 ± 76% of SLE patients were treated with NSAIDs [8]. Consequently, SLE patients could be at high risk of gastroduodenal mucosal injury, which has been little studied [9], while the correlation between *H. pylori* and gastroduodenal lesions in SLE patients has been less analyzed [10]. Therefore, we investigated the frequency of *H. pylori* in SLE patients and compared clinical characteristics and gastroduodenal lesions in patients with and without *H. pylori* infection treated with NSAIDs.

Material and methods

Patients

All ambulatory adult patients with SLE meeting ≥ 4 of the revised classification criteria of the American College of Rheumatology (ACR) [11, 12] who regularly attended the Systemic Autoimmune Disease Research Unit, Specialized Hospital, Medical Unit of High Specialty, National Medical Center Manuel Avila Camacho, Mexican Social Security Institute, Puebla, Mexico, and fulfilled the Rome III diagnostic criteria of functional dyspepsia symptoms [13] were invited to participate in this cross-sectional study from April 2017 to June 2018. The inclusion criteria for patients with dyspepsia symptoms were symptoms of postprandial fullness, bloating, epigastric pain, nausea, or vomiting of at least moderate severity for ≥ 3 months. Patients with a history of abdominal trauma, previous abdominal surgery, coronary artery diseases, and hospital admission to evaluate abdominal pain suspected to be related to SLE activity or pregnancy were excluded. Written informed consent to participate was obtained from all participants. The local ethics committee approved the study (R-2017-2106-1).

Assessment of clinical features

In each patient, age, sex, duration of SLE, and therapies were evaluated at study inclusion. At the first visit, all patients were asked to complete a structured sociodemographic and clinical interview and the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) to determine lupus disease activity [14]. Cumulated organ damage was measured using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) [15]. Gastroduodenal symptoms, such as dyspepsia, were assessed. Current drug administration, such as NSAIDs and glucocorticoids, was also collected. NSAIDs were taken at study inclusion study (Table 1) and the median and interquartile range (IQR) of any NSAID duration was 15 (10–35) days. Diclofenac, naproxen sodium, sulindac and celecoxib doses were 100 mg (100–150), 500 mg (250–500), 200 mg

Table 1 Sociodemographic, clinical, and treatment characteristics in SLE patients

	SLE patients (n = 118)
Age, years; median IRQ	46.5 (35.7–46.5)
Smoking, %	10 (8.4)
Disease duration, mean ± SD	11.6 ± 6.0
SLEDAI-2K score, mean ± SD	1.2 ± 1.7
SLICC ACR DI, mean ± SD	0.3 ± 0.7
Endoscopic findings, n (%)	
Hiatus hernia	22 (18.6)
Reflux disease	30 (24.5)
Gastritis	79 (66.9)
Duodenitis	10 (8.4)
Erosions	65 (55.0)
Gastric ulcers	1 (0.8)
Duodenal ulcers	0 (0)
Multiple abnormalities	35 (29.7)
Prednisone, mg/d, mean ± SD	9.3 ± 7.4
NSAIDs, n (%)	101 (85.6)
Diclofenac	27 (26.7)
Naproxen sodium	12 (11.9)
Sulindac	29 (28.7)
Celecoxib	25 (24.8)
Other	8 (7.9)
Immunosuppressive therapy, n (%)	47 (39.8)
Gastroprotective drugs	
None	17 (14.4)
H2 receptor antagonists	17 (14.4)
PPIs	84 (71.2)

Histamine-2 (H2) receptor antagonists; *NSAIDs*, non-steroidal anti-inflammatory drugs; *PPIs*, proton pump inhibitors; *SLEDAI-2K*, SLE Disease Activity Index 2000; *SLICC*, Systemic Lupus International Collaborating Clinics

(100–300), and 200 mg (200–200), respectively. NSAIDs were prescribed based on expert opinion. One hundred and one (85.6%) patients were receiving non-steroidal anti-inflammatory drugs (NSAIDs). Forty (87.0%) from 46 and sixty-one (84.7%) from 72 patients with and without H. pylori infection were on NSAIDs at the time of the study. The mean cumulative glucocorticoid dose was 29.0±21.8 g. Only two patients had an episode (a month before the study) of antibiotic intake (Ciprofloxacin) for seven and fourteen days, respectively.

Endoscopic and histologic examination

All patients underwent esophagogastroduodenoscopy (EGD) twice using a forward-viewing endoscope (GIFQ20, Q30, Q40 or Q200; Olympus, Tokyo).

During EGD, two biopsy specimens were obtained from the gastric mucosa of normal appearance at the greater curvature of the antrum and upper corpus. Two specimens were taken from each site for histologic assessment. In addition, biopsies were obtained from the margin of gastric ulcers, when found, to rule out malignancy.

Detection of H. pylori infection

All patients were tested for *H. pylori* using a stool antigen detection kit (CerTest *H. pylori* one step card test, Certest Biotec S.L. Zaragoza, Spain), as it is noninvasive and is not influenced by antibiotics or proton pump inhibitors (PPI). The kit has a sensitivity of 96%, a specificity of 86%, a positive predictive value (PPV) of 98%, and a negative predictive value (NPV) of 96% [16]. CerTest is an immunochromatographic membrane-based assay using amplification technology for the determination of *H. pylori* antibodies. Using the applicator stick, a pea-sized sample (approximately 125 mg) of thoroughly mixed stool was transferred into the predisposed sample diluent vials and homogenized for 15 s in a vortex mixer. One hundred and twenty fine microliters of the stool suspension were added to the test strip vial using the Pasteur pipette supplied. According to the manufacturer's guidelines, stool samples can be stored at 2–8 °C for up to 2 days or indefinitely at – 20 °C before the test. The test strip was immersed in the sample and was left to stand vertically at room temperature for 10 min. The appearance of one green band (control line) indicated a correct test. Another red band (test line) also appears in the site marked with the letter T (result line) as a positive test. All stool tests were performed without knowledge of the other test results.

Biopsy specimens taken for histology were fixed in standard formalin embedded in paraffin and stained with hematoxylin-eosin and modified Giemsa staining for *H. pylori* identification. Local pathologists, who were blinded to the results of the other test, viewed the specimens for *H. pylori* using the updated Sydney System [17]. Since the sensitivity of histology may decrease in patients taking PPI [18], a positive result for *H. pylori* was defined as at least one examination with a positive stool-specific test or histopathological findings.

Statistical analysis

Descriptive statistics were used to describe the prevalence of the type and locations of gastroduodenal endoscopic lesions, the types of biopsy lesions, and the prevalence of *H. pylori* infection. The results were expressed as the number of patients (%), mean ± SD or median, and IQR for categorical, normally distributed and non-normally distributed data, respectively. Comparisons between any two groups (patients with and without *H. pylori* infection; groups based on gastroduodenal lesions in the endoscopy or biopsy) were made using the χ^2 test or Fisher's exact probability test. All statistical analyses were performed using SPSS for Mac version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 118 participants with SLE were enrolled. Demographic and disease-related characteristics are shown in Table 1. The patients were 99% female with a mean age of 44.7 ± 11.7 years. No patient received pulses of methylprednisolone therapy before the gastroduodenal endoscopy examination.

Prevalence of H. pylori infection and gastroduodenal lesions in patients with SLE

Thirty-two patients were positive (27.1%) for *H. pylori* according to the *H. pylori* stool-specific antigen. *H. pylori* was present in 26 (22%) patients in the histopathological diagnosis, and 46 patients had at least one positive test (stool antigen or histopathological examination). Therefore, the prevalence of *H. pylori* was 39%. Using gastroduodenal endoscopy, erosions and gastric ulcers were detected in 55.1% and 0.8%, respectively. Table 1 shows the endoscopic findings. Chronic gastritis was reported in 64.4% of gastric biopsies and no biopsy found malignancy.

Comparison of clinical features between SLE patients with and without H. pylori infection

Tables 2 and 3 compare the clinical and endoscopic findings in patients with and without *H. pylori* infection. Age, smoking, SLE characteristics, and gastroduodenal symptoms did not differ between groups. The prevalence of gastric ulcer did not significantly differ between groups, but the prevalence of

Table 2 Comparison of sociodemographic, clinical, and endoscopic findings between *H. pylori*–positive and negative groups

	H. pylori–positive patients (*n* = 46)	*H. pylori*–negative patients (*n* = 72)	*p* value
Age, years, mean ± SD	45.3 ± 11.4	44.3 ± 12.0	0.64
Smoking, *n* (%)	2 (4.3)	8 (11.1)	0.31
Disease duration, years; mean ± SD	10.9 ± 5.1	12.0 ± 6.5	0.35
SLEDAI-2K score, median IRQ	1.1 ± 1.6	1.2 ± 1.8	0.75
SLICC ACR DI, median IRQ	0 (0–1)	0 (0–1)	0.74
Gastroduodenal symptoms, *n* (%)	7 (15.2)	19 (26.4)	0.17

SLEDAI-2K, SLE Disease Activity Index 2000; *SLICC*, Systemic Lupus International Collaborating Clinics

gastric erosions was lower in *H. pylori*–positive patients than in *H. pylori*–negative patients (43.5.7% vs. 62.5%; $p = 0.04$).

Comparison of medication between patients with and without H. pylori infection

Table 4 shows the medications used for SLE and antacid prescriptions. There was no difference in SLE medications between patients with and without *H. pylori* infection. The daily corticosteroid dose ranged from 2.5 to 30 mg. No patient was treated with NSAID suppositories. The prescription of histamine-2 (H2) receptor antagonists and PPIs did not differ between patients with and without *H. pylori* infection.

Discussion

The results of this study suggest that *H. pylori* infection did not influence gastroduodenal mucosal lesions or the clinical characteristics of SLE patients receiving NSAIDs. The overall frequency of *H. pylori* infection (39%) appears low when compared with the prevalence in the general population in a Japanese study [19] and a Mexican study [20]. Studies have found that the difference in the prevalence of *H. pylori* infection between SLE patients and the general population is insignificant [21, 22]. A possible explanation for the lower frequency of H. *pylori* in our SLE patients is that they were relatively young (mean age 44 years) compared with a Mexican community–based study that included subjects up to 90 years of age [20]. In another Mexican cross-sectional study of persons aged 18–24 years, the overall *H. pylori* seroprevalence was 59.8% [23]. Further studies are necessary to determine whether the prevalence is really lower in subjects with SLE.

Most of our patients were receiving NSAIDs as previously reported in these patients. [8] The possible interaction between NSAIDs and *H. pylori* with respect to the risk of gastroduodenal mucosal lesions is unclear. It has been reported that *H. pylori* infection did not influence the endoscopic grade of gastroduodenal lesions in long-term NSAID users [4]. In contrast, a Taiwanese study that included 67 SLE patients receiving pulse methylprednisolone therapy found that the use of NSAIDs/aspirin increased gastric mucosal injury [10]. In our study, the prevalence of gastric ulcer and dyspeptic symptoms did not differ between patients with and without *H. pylori*. Surprisingly, fewer *H. pylori*–positive patients had gastric erosions than *H. pylori*–negative patients. Similarly, in a recent study evaluating 65 SLE patients, those who were H. pylori positive on polymerase chain reaction had a lower frequency of gastric erosions [9]. The positive or negative interaction between *H. pylori* and NSAIDs use is not clear. A major reason adduced to support a protective effect of *H. pylori* infection is that *H. pylori*–negative patients may have delayed ulcer healing, which is

Table 3 Endoscopic findings in SLE patients with and without *H. pylori*

	H. pylori–positive patients (*n* = 46)	*H. pylori*–negative patients (*n* = 72)	*p* value
Hiatus hernia, *n* (%)	10 (21.7)	12 (16.7)	0.62
Reflux disease, *n* (%)	14 (30.4)	16 (22.2)	0.38
Gastritis, *n* (%)	33 (71.7)	46 (63.9)	0.42
Duodenitis, *n* (%)	2 (4.3)	8 (11.1)	0.31
Erosions, *n* (%)	20 (43.5)	45 (62.5)	0.04
Gastric ulcers, *n* (%)	0 (0.0)	1 (1.4)	1.00
Multiple abnormalities, *n* (%)	13 (28.3)	22 (30.6)	0.83

H. pylori, *Helicobacter pylori*

Table 4 Comparison of SLE therapies and gastroprotective drugs in patients with and without *H. pylori*

	H. pylori–positive patients (n = 46)	*H. pylor*– negative patients (n = 72)	p value
Prednisone, mg/day, mean ± SD	7.9 ± 6.3	10.3 ± 7.7	0.08
NSAIDs, n (%)	40 (87.0)	61 (84.7)	0.98
Immunosuppressive therapy, n (%)	16 (34.8)	31 (43.1)	0.44
Azathioprine	12 (26.3)	19 (26.4)	0.91
Methotrexate	3 (6.5)	10 (13.8)	0.24
Mycophenolate mofetil	1 (2.2)	2 (2.8)	0.79
Gastroprotective drugs n (%)	39 (84.8)	62 (86.1)	0.83
H2 receptor antagonists	4 (8.7)	13 (18.1)	0.18
PPIs	35 (76.1)	49 (68.1)	0.40

Histamine-2 (H2) receptor antagonists, *NSAIDs*, non-steroidal anti-inflammatory drugs; *PPIs*, proton pump inhibitors

biologically plausible since *H. pylori* seems to increase the anti-secretory activity of proton pump inhibitors [24]. However, our exploratory study was not powered to evaluate risk factors for gastroduodenal lesions in SLE patients under NSAIDs therapy.

Evidence from small observational studies supports the role of *H. pylori* eradication in some autoimmune diseases. An improvement in morning stiffness after 4 months of *H. pylori* eradication in rheumatoid arthritis (RA) patients was reported [25]. In contrast, no changes in symptoms were found after this strategy in RA patients in another study [26]. *H. pylori* eradication in Sjogren syndrome may result in a decreased incidence of MALT, as is the case for gastric MALT lymphomas [27]. Moreover, early data have demonstrated that *H. pylori* eradication improves Raynaud's phenomenon in patients with systemic sclerosis [28]. Although the frequency of *H. pylori* in immune thrombocytopenic purpura patients has been found to be similar to that of healthy controls, improvements in platelet counts after *H. pylori* eradication have been described [29, 30]. There is a lack of information about the role of *H. pylori* eradication in changes in SLE manifestations. However, our results showed no relationship between SLE activity and *H. pylori*, although most patients included had mild lupus activity.

The effect of glucocorticoid and immunosuppressive therapies on the prevalence of *H. pylori* has not been widely studied. In RA patients, anti-rheumatic drugs did not affect the prevalence of *H. pylori* [31], although a suppressive effect of glucocorticoids on *H. pylori* in RA patients has been reported [32]. In contrast, we found no relationship between any immunosuppressive or glucocorticoid therapies and the prevalence of *H. pylori* in SLE patients. However, our study was not powered to analyze the influence of any specific SLE therapy on the prevalence of *H. pylori*. Consequently, longitudinal studies with an *a priori* sample size calculation are required to establish causal effects since, in other chronic inflammatory disorders [33], immunosuppressive drugs have been shown to be suppressive of *H. pylori* infection.

Our study has several limitations. First, the cross-sectional design and sample size does not permit causality to be inferred and accurate collection of NSAID and glucocorticoid duration was limited. Secondly, there was no control group that would have enabled the prevalence of *H. pylori* infection to be compared between patients and healthy controls. Thirdly, it has been determined that although the *H. pylori* coproantigen has a high sensitivity, the false-negative rate should not be ignored [16]. Fourthly, in the histological analysis, atrophic changes were not recorded, as they were in studies including RA patients [26, 34]. Finally, most patients were also receiving PPIs, which could have affected the results of the *H. pylori* evaluation, even though the stool antigen should not be influenced by this treatment.

In conclusion, our findings show that *H. pylori* infection does not seem to be associated with disease activity or gastroduodenal lesions in patients with SLE receiving NSAIDs. Immunosuppressive therapy and glucocorticoid use did not affect the prevalence of *H. pylori* infection in SLE and there seems to be no evidence to suggest the necessity for *H. pylori* eradication in patients with SLE receiving NSAIDs.

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Compliance with ethical standards

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