Helicobacter pylori infection in systemic sclerosis: a systematic review and meta-analysis of observational studies

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ABSTRACT

Objective. *It has been proposed that Helicobacter pylori (H.pylori) infection causes several extra-gastrointestinal disorders. However, the role of H.pylori infection in the pathogenesis of systemic sclerosis (SSc) is still debatable. This meta-analysis is aimed at exploring the association between SSc and H.pylori infection.*

Methods. *A comprehensive search of the MEDLINE and EMBASE databases was performed from inception through February 2018. The inclusion criterion was observational studies evaluating H.pylori infection in SSc. The pooled odds ratio (OR) of H.pylori infection and their 95% confidence interval (CI) were calculated using a random-effects meta-analysis to compare risk between SSc patients and healthy controls. The between-study heterogeneity of effect-size was quantified using the Q statistic and I^2.*

Results. *Data were extracted from 8 observational studies involving 1,446 subjects. The pooled results demonstrated an increased H.pylori infection in SSc compared with healthy controls (OR=2.10; 95% CI: 1.57-2.82, p-value<0.01, I^2=13%). Subgroup analysis showed an increased risk of H.pylori infection measured with H.pylori ELISA test (OR=2.49; 95% CI: 1.82-3.40, p-value<0.01, I^2=0%).*

Conclusion. *Our study has shown that patients with SSc have an increased prior existence of H.pylori infection. This finding implies that the role of previous infection may cause an abnormal immunological cascade in the pathogenesis of SSc. Further studies that could elucidate the inflammatory response in the pathogenesis of SSc are warranted.*

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterised by progressive fibrosis of the connective tissue of the skin, lungs, gastrointestinal tract, heart, and kidneys secondary to excessive deposition of extracellular matrix (1). There are three different pathophysiologic processes in SSc that might be triggered by an unknown event. First of all, the generation of autoantibodies such as anti-topoisomerase, anti-centromere, anti-fibrillin-1, anti-RNA polymerases I and III, and anti-endothelin antibodies is a feature of an abnormal humoral immune response in SSc; while an increase of CD4+ T-helper and TCR+ lymphocytes and decreased levels of CD8 lymphocytes are the abnormalities of cellular immunity in SSc. Both of these defects can cause microvascular damage and overproduction of collagen by fibroblasts (1, 2). Moreover, endothelial dysfunction is similar to the vasculopathy in allograft rejection, graft-*versus*-host disease, haemolytic uraemic syndrome, and thrombotic thrombocytopenic purpura. Microvascular endothelial cell activation causing increased expression of adhesion molecules such as E-selectin, P-selectin and intracellular adhesion molecule-1 (ICAM-1), and injury-inducing apoptosis of endothelial cell are the characteristic findings of endothelial dysfunction (1, 2). Lastly, the imitation of chronic graft-*versus*-host reaction, porphyrias, and other unregulated scar tissue formation through fibroblast activation and proliferation contributes to the extracellular matrix proteins deposition.

It has been proposed that numerous infectious pathogens play a role in the pathogenesis of SSc through the mechanisms above (1, 2), triggering the inflammatory cascade which leads to dysregulation of the immune system (3). Other diseases that may be linked to infection, and that stimulate the autoimmune cascade include pericarditis,

primary biliary cirrhosis, atherosclerosis, fibromyalgia syndrome, and fever of unknown origin (4). These pathogens include bacteria (Porphyromonas gingivalis, Helicobacter pylori, and Chlamydia), viruses (parvovirus, CMV, EBV, hepatitis B), and toxoplasmosis (1, 2, 4). Among all of the infectious agents, Helicobacter pylori (H.pylori) is the most extensively studied microbial due to its common infection worldwide, especially in the developing and underdeveloped countries. The prevalence of H.pylori infection is strongly correlated with age and socioeconomic status. It is linked to the development of gastric and duodenal ulcers, gastric adenocarcinomas and lymphomas (5).

It has been suggested that H.pylori infection is related to various autoimmune disorders other than SSc, such as primary Sjögren's syndrome (PSS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), Behçet's disease, alopecia areata, and psoriasis (3). The proposed mechanism of H.pylori infection causing extra-gastrointestinal conditions is due to a significant local inflammatory response to the gastric mucosa, which could potentially produce a systemic effect because of the alteration of systemic inflammatory mediators (3, 5). Despite that, there is no clear agreement on this reported association in studies. Thus, we performed this systematic review and meta-analysis to explore the correlation between SSc and H.pylori infection.

Materials and methods

This systematic review and meta-analysis were conducted and reported according to the Meta-analysis Of Observational Studies in Epidemiology statement (6). This review was registered in PROSPERO (registration number: CRD42017080015).

Search strategy

Three authors (WCY, AS, SU) independently searched published studies indexed in MEDLINE and EMBASE from date of inception to February 2018. References of all selected studies were also examined. The following primary search terms were used: systemic sclerosis, scleroderma, Helicobacter pylori. The full search terms used are detailed in the Supplementary Material and Methods.

Inclusion and exclusion criteria

This review included all published observational studies inclusive of cross-sectional, prospective cohort, retrospective cohort and case-control studies in which the association between SSc and H.pylori infection was assessed. Reviews, case reports, and abstracts were excluded because the quality of the studies they contained could not be determined.

We included studies that recruited participants from the general population and used data from medical records of healthcare facilities. Participants were adults age 18 years and older, both SSc and healthy individuals. The primary outcome, in deference to the diagnosis of H.pylori infection, resulted from the comparison between patients diagnosed with SSc and participants without SSc. SSc was diagnosed by fulfilling the 1980 or 2013 American College of Rheumatology diagnostic criteria, or the 1988 classification system proposed by LeRoy *et al*. (7). The outcomes were extracted through the implementation of odds ratios (OR), relative risks (RR), hazard ratios (HR), and the number of participants. The H.pylori infection was diagnosed by anti-H.pylori enzyme-linked immunosorbent assay (ELISA) test, urea breath test, stool antigen test, rapid urease test or gastric mucosa biopsy.

Data extraction

All authors independently reviewed titles and abstracts of all citations previously identified. After the abstracts were reviewed, data comparisons between the three investigators were conducted to ensure completeness and reliability. The inclusion criteria were independently applied to all identified studies. Differing decisions were resolved by consensus.

Full-text versions of potentially relevant papers identified in the initial screening were retrieved. Data concerning study design, source of information, participant characteristics, assessment of SSc and H.pylori infection were independently extracted. We contacted the authors of the original reports to request any unpublished data. If the authors did not reply, we used the available data for our analyses.

Assessment of bias risk

A subjective evaluation of the methodological quality of observational studies was performed by all three authors using the Newcastle-Ottawa Scale (NOS) (8), a quality assessment tool for non-randomised studies. It uses a "star system" based on three major perspectives: the selection of the study groups (0–4 stars, or 0–5 stars for cross-sectional studies), the comparability of the groups by controlling for essential and additional relevant factors (0–2 stars), and the ascertainment of outcome of interest and/or exposure (0–3 stars). A total score of 3 or less was considered poor, 4–6 was considered moderate, and 7–10 was deemed high quality. We excluded studies from our meta-analysis if they were of poor quality. Discrepant opinions between authors were resolved by consensus.

Statistical analysis

Meta-analyses of the included studies were performed using Review Manager 5.3 software from The Cochrane Collaboration to generate forest plot and Comprehensive Meta-Analysis 3.3 software from Biostat, Inc. to create funnel plot and perform Egger's regression test. Pooled effect estimate of incidence of H.pylori infection was calculated with 95% confidence interval (CI) comparing SSc and control groups using a random-effects model. We used effect size (OR, HR, RR) from univariate or, if available, multivariate models with confounding factors adjusted in each study. We excluded studies from meta-analyses and only presented the results with narrative description (qualitative analysis) when there were not sufficient data available to calculate pooled effect size. The heterogeneity of effect estimates across these studies was quantified using the Q statistic and I^2 ($p<0.10$ was considered statistically significant). The Q statistic compared the observed between-study dispersion and expected

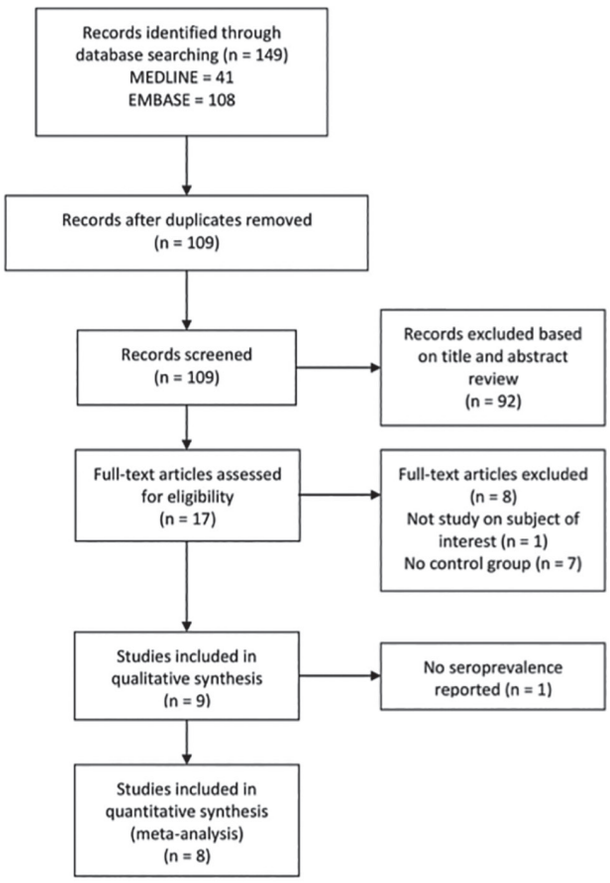

Fig. 1. Flow of search methodology and selection process.

dispersion of the effect size, and was expressed in *p*-value for statistical significance. An I^2 is the ratio of actual heterogeneity to total observed variation. An I^2 of 0–40% was considered to exclude heterogeneity, 30–60% was considered to represent moderate heterogeneity, 50–90% was considered to represent substantial heterogeneity, and 75–100% was considered to represent considerable heterogeneity (9). Publication bias was assessed using funnel plot and Egger's regression test (10).

Results

Description of included studies

The initial search yielded 109 articles (Fig. 1); 92 articles were excluded based on the title and abstract review. A total of 17 articles underwent full-length review. Eight articles were excluded (7 articles had no control group; 1 article was not studied on the subject of interest). Nine studies were included in qualitative synthesis and meta-analysis. One study (11) was included in the qualitative analysis only because it compared serum anti-H.pylori titre in SSc subjects with the mean serum anti-H.pylori titre of all participants (no seroprevalence of H.pylori infection). Data was extracted from 8 studies involving a total of 1,446 participants. The included studies varied in study location, sample size, and source of data. Five studies used H.pylori ELISA test (12-16); 1 study performed the rapid urease test on gastric biopsy specimens (17), and two studies used the ^{13}C urea breath test as H.pylori diagnostic method (18, 19). The characteristics of the nine extracted studies included in this review are outlined in Table I.

Meta-analysis results

The pooled result depicted an increased H.pylori infection in SSc compared with controls (OR=2.10; 95% CI: 1.57-2.82, *p*-value<0.01, I^2 =13%, $P_{heterogeneity}$=0.33) (Fig. 2). Subgroup analysis showed a statistically significant increase of H.pylori infection that was mainly driven by using ELISA test for H.pylori detection in SSc (OR=2.49; 95% CI: 1.82–3.40, *p*-value<0.01, I^2 =0%, $P_{heterogeneity}$=0.58) compared with controls.

Publication bias

To investigate potential publication bias, we examined the funnel plot of the included studies in the meta-analysis of the H.pylori infection (Fig. 3). The vertical axis represents study size (standard error) while the horizontal axis represents the log odds ratio. From this plot, publication bias does not exist due to its symmetric distribution of studies with the Egger's test result (*p*=0.84) that was not significant.

Discussion

To the best of our knowledge, this is the first meta-analysis of exploring the association between SSc and H.pylori infection. Our study has shown an increased H.pylori infection in patients with SSc that was mainly driven by the infection detected with H.pylori ELISA test. Although there was an increased of H.pylori infection detected with urea breath test, the result was insignificant. Since the ELISA test only detects host exposure to the bacterium regardless of current or previous infection while urea breath test or rapid urease test detect ongoing infection, our result implies that H.pylori infection in the past could be the culprit of the abnormal immunological cascade in the pathogenesis of SSc. Showji *et al*. (11) reported the average H.pylori IgG serum titres from patients with SSc were not significantly higher than the average titre of all serum samples of patients with SLE, RA, PSS, polymyositis/dermatomyositis, mixed connective tissue disease, SSc, chronic pulmonary diseases and healthy volunteers.

There are several mechanisms of H.pylori-induced autoimmunity. The constant localised inflammatory process induced by H.pylori infection may result in a persistent antigenic stimulation and cause a systemic inflammatory response (3). Molecular mimicry of H.pylori antigens cross-activating T cells in autoimmune gastritis and H.pylori-derived heat shock protein-60 (HSP-60) cross-reacting with human endogenous HSP-60 via Th1-dominant response have been reported (3, 4) as the culprit leading to the development of antigen-antibody complexes or cross-reactive antibodies (2), the

Table I. Characteristics of the nine observational studies included in this review.

Study	Study year and location	Design	Diagnostic criteria	Number		Patient's Demographic			Outcome measurement method	Quality assessment (Newcastle-Ottawa Scale)
				P	C	Mean age ± SD	Female (%)	Disease duration (year)		
Vardar *et al*. 2010 (17)	Izmir, Turkey	Prospective cohort study	Not reported	31	58 with GERD 36 w/o GERD	46 ± 9	84%	4 ± 3 (mean ± SEM)	Rapid urease test of gastric biopsy specimens	Selection = 3 Comparability = 0 Outcome = 3
Ram *et al*. 2013 (14)	Referral centres in Europe and Latin America	Cross-sectional study	"fulfilled the diagnostic criteria for each specific autoimmune disease."	79	385	Not reported	Not reported	Not reported	H. pylori IgG test using "pylori detect" kit	Selection = 4 Comparability = 1 Outcome = 2
Kalabay *et al*. 2004 (13)	2nd Department of Internal Medicine, University Medical School, Pecs, Hungary	Cross-sectional study	Classification system proposed by LeRoy et al. and the 1980 American Rheumatism Association criteria	55	349	49.9 ± 12.1	89.1%	4.46 ± 2.69	H. pylori IgG ELISA test	Selection = 4 Comparability = 0 Outcome = 3
Sulli *et al*. 2000 (19)	Referral to videocapillaroscopic service for diagnosis of CTD, University of Genova, Italy.	Cross-sectional study	Not reported	43	32	51 ± 15	Not reported	8 ± 9	^{13}C urea breath test	Selection = 5 Comparability = 1 Outcome = 3
Danese *et al*. 2000 (18)	Dec 1998 to May 1999. Rheumatology Department, Gemelli Hospital, Catholic University, Rome, Italy.	Cross-sectional study	The 1987 American Rheumatism Association criteria	34	30	Not reported	Not reported	Not reported	^{13}C urea breath test	Selection = 3 Comparability = 1 Outcome = 3
Bilgin *et al*. 2015 (12)	April 2009 to March 2012. Rheumatology unit, Konya Training and Research Hospital, Tampere, Finland.	Cross-sectional study	The 1980 American Rheumatism Association criteria	30	30	35 ± 15.25	63.3%	2.9	H. pylori IgM and IgG ELISA test	Selection = 4 Comparability = 1 Outcome = 3
Yazawa *et al*. 1998 (15)	Department of Dermatology, Tokyo University, Japan.	Cross-sectional study	Classification system proposed by LeRoy et al. and the 1980 American Rheumatism Association criteria	124	50	50.2 ± 12.8	92.7%	7.2 ± 7.0	H. pylori IgG ELISA test	Selection = 5 Comparability = 1 Outcome = 3
Showji *et al*. 1996 (11)	Shizuoka, Japan.	Cross-sectional study	Not reported	11	24	Not reported	Not reported	Not reported	H.pylori ELISA, followed by Western blot	Selection = 2 Comparability = 1 Outcome = 3
Balaji *et al*. 2017 (16)	Jan 2016 to April 2016. Chennai, India.	Cross-sectional study	ACR/EULAR 2013 classification criteria	55	25	38.9 ± 10.6	94.5%	2 [range 0.5 – 5] (median)	H. pylori IgG ELISA test	Selection = 4 Comparability = 1 Outcome = 3

P: patient; C: control; EIA: enzyme immuno assay; H&E: haematoxylin-eosin; ELISA: enzyme-linked immunosorbent assay; SEM: standard error of mean.

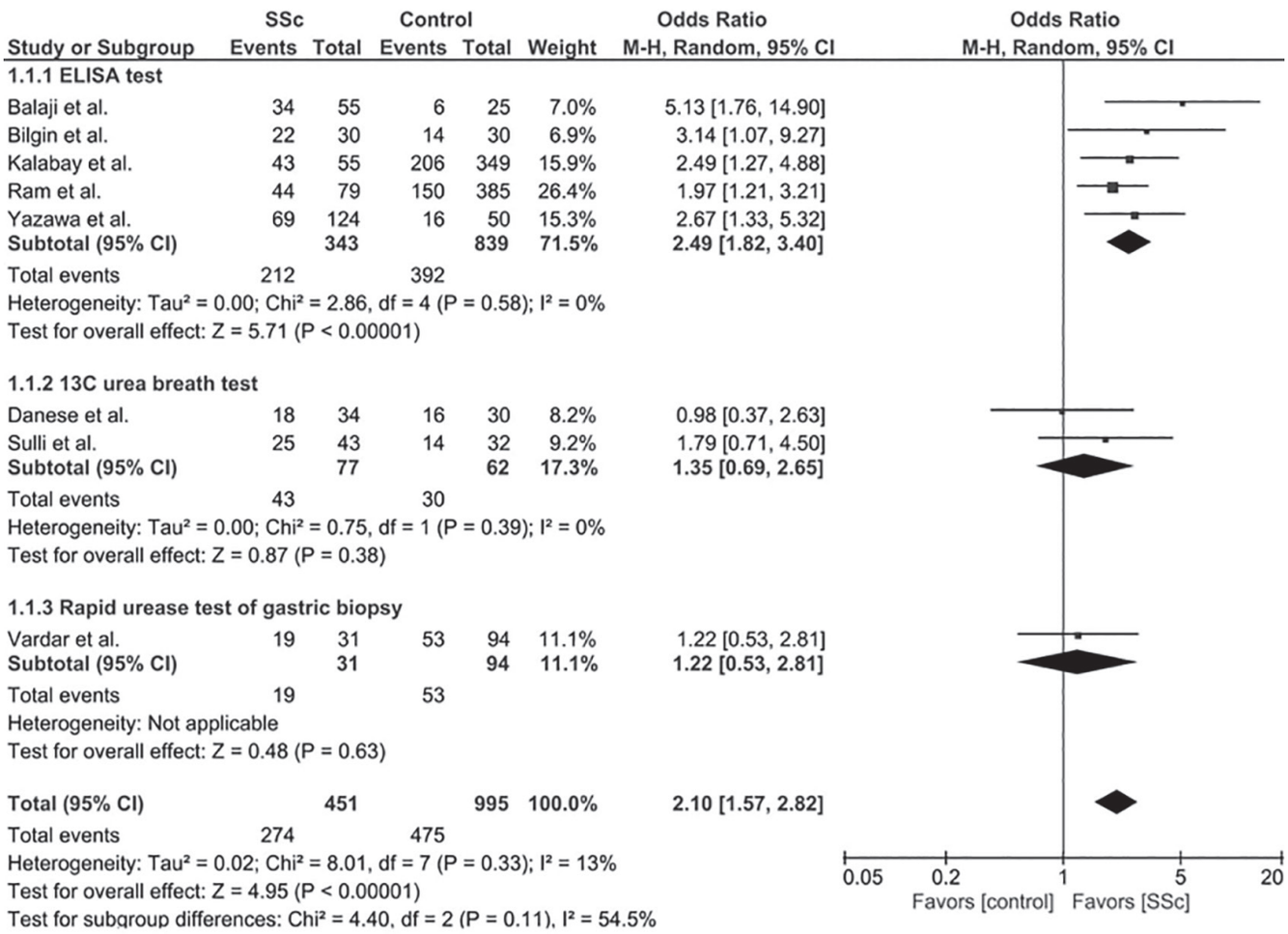

Fig. 2. Forest plot assessing the risk of H.pylori infection in patients with and without SSc. CI: confidence interval.

systemic effect of endothelial injury, and the obliteration of microvasculature and atherosclerosis (4, 13). The localised inflammatory process in the gastric mucosa may be triggered by the vacuolating cytotoxin VacA and the products of CagA (2). CagA strain of the H.pylori is associated with severe clinical outcome due to its induction of a severe inflammatory reaction through the release of platelet activating factor (PAF), lipopolysaccharides, and neutrophil activating proteins (18) to facilitate the adhesion of neutrophils to the endothelial cells and activation of macrophages. This virulent CagA strain was more prevalent in patients with SSc than healthy controls despite no difference in the prevalence of H.pylori infection between SSc and control groups in Danese's study (18). The interaction between these virulent strains and host signal transduction pathways could mediate cell transformation, cell proliferation, invasion, apoptosis/antiapoptosis, and angiogenesis (2).

Endothelial injury has also been proposed to play a role in the pathogenesis of SSc from the high prevalence of Raynaud's phenomenon and diffuse microangiopathy in patients with SSc. Approximately 78% of the 46 patients (20) infected with the H.pylori in accordance with primary Raynaud's phenomenon were reported. However, it is still unclear whether the collagen overproduction is secondary to the endothelial injury or an abnormality of fibroblasts independent of vasculopathy and immune alteration (2). Furthermore, it has been shown that microbial superantigens could initiate an immediate T cells response after the B cells bind to the microbial superantigens to surface class II MHC molecule and become a target of T-helper lymphocytes (1, 2). Microchimerism was also found more commonly in patients with SSc than controls (82.9% *vs*. 63.6%) in their peripheral blood and skin lesions. This phenomenon is characterised by an individual bearing DNA or cells at a low level that is from another organism (2). The $CD4^+$ microchimeric T cells were found significantly higher in patients with SSc than controls. The vascular endothelium provides an allotypic stimulus to these microchimeric T cells and may trigger a pathway similarly to the process of graft-*versus*-host disease (2). Regarding the gastrointestinal symptoms associated with seropositive H.pylori in SSc patients, heartburn was more common in H.pylori seropositive than seronegative SSc patients (15). Oesophageal involvement (defined as hypomobility shown by radiography) also correlated with H.pylori seropositivity in patients with SSc (15). Despite the fact that the prevalence of heartburn was similar to the healthy controls (17), H.pylori infection may be the cause of

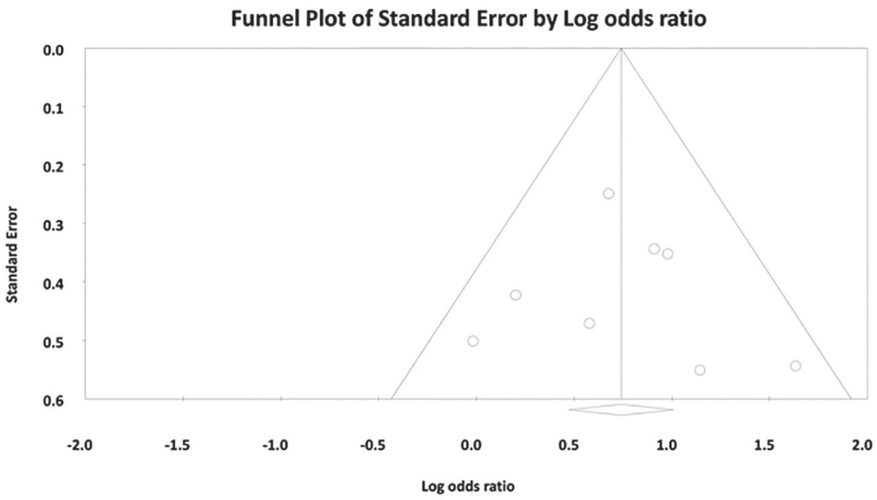

Fig. 3. Funnel plot showing studies reporting H.pylori infection in patients with and without SSc.

heartburn and screening of H.pylori infection is needed if SSc patients ever develop heartburn (15). Studies have shown that gastrointestinal dysmotility in SSc patients with coexistence of H.pylori infection has been associated with an increased risk of coronary artery disease and Raynaud's phenomenon (1). After the eradication of H.pylori infection, there was 17% of treated patients with resolution of primary Raynaud's phenomenon, and 72% of treated patients had an improvement of their Raynaud's disease (12). These findings further support the need for H.pylori screening in patients with SSc. Unfortunately, the studies on the role of H.pylori infection in RA, SLE are less extensive with conflicting results. Meron *et al*. reported a comparable prevalence of H.pylori infection in RA to healthy controls by comparing the sera of both groups (20). Meanwhile, Zentilin *et al*. demonstrated that eradication of H.pylori is linked to significant clinical improvement in RA symptoms in H.pylori-infected RA patients compared with non-H.pylori-infected RA patients (21). The studies on RA suggested that H.pylori is less prevalent in RA than in controls, but it may contribute to the severity of RA symptoms in those patients with H.pylori infection. Furthermore, the development of SLE in African-American women is inversely related with H.pylori seropositivity (22). The low prevalence of H.pylori infection in RA and SLE were also supported by Showji *et al*. as the authors have found that the average serum titres of H.pylori in RA and SLE were lower than patients with other connective tissue diseases and similar to healthy controls (11). In contrast, two studies (23, 24) have demonstrated a higher PASI score in psoriasis patients with H.pylori infection, meanwhile two other studies (25, 26) have reported a higher percentage of H.pylori infection among severe psoriasis than those with mild or moderate disease. Onsun *et al*. and Campanati *et al*. (23, 24) also discovered a significant improvement in PASI score after H.pylori treatment with concurrent psoriasis treatment for H.pylori-infected patients than those without H.pylori infection who received only psoriasis treatment. Lastly, the link between primary Sjögren's syndrome (PSS) and H.pylori infection is inconclusive to date. A higher level of anti-H.pylori antibodies titre in patients with PSS, an increased incidence of mucosal-associated lymphoid tissue (MALT) and lymphoma in the lacrimal glands of PSS patients with H.pylori infection, and colonisation of H.pylori in the oral cavity of PSS patients are the supporting evidence of the role of H.pylori infection in PSS (3). There are four studies (27-30) that reported an increased prevalence of H.pylori infection, and four studies (31-34) that reported otherwise. The seroprevalence of H.pylori infection in PSS is positively correlated with advancing age (28, 30, 34), disease duration, disease status and CRP (30).

Nonetheless, a cautious interpretation of our study result is needed because all the included studies are cross-sectional studies. Therefore this result could be an epiphenomenon because SSc patients have gastrointestinal dysmotility and thereby an increased risk of colonisation and infection of H.pylori. We are also unable to factor in the SSc disease activity and organ involvement of SSc that may affect the seropositivity of H.pylori or vice versa. It was also not possible to include in our meta-analysis the prevalence of CagA virulent strain in patients with SSc due to the fact that only one study reported this outcome (18). The relationship between the H.pylori infected time and onset of SSc was challenging to determine. Nor could the impact of environmental factors be determined (12). Although there is no significant increase in H.pylori infection using the urea breath test or rapid urease test of gastric biopsy, the included studies are limited in drawing a definite conclusion.

The prevalence of H.pylori infection generally has a different geographical and chronological distribution. The H.pylori prevalence in the southern European population is known to be higher than Sweden (35, 36), and the prevalence in Asian and Middle East countries are more significant than European countries. Meanwhile, the prevalence of H.pylori infection is declining worldwide, especially in the developed world over time. Moreover, the prevalence of infection in the younger generations is decreasing overall, and population migrations to different countries will change the prevalence and H.pylori strains (37, 38). All these factors could potentially affect the results of each included study in our meta-analysis. Despite that, the studies included in our H.pylori ELISA meta-analysis appear to be conducted and distributed randomly and equally across different geographical locations and years. The studies using urea breath test were both done in the year 2000 in Italy. Thus, the prevalence of H.pylori currently might have changed. Other limitations of our study include the inability to stratify the H.pylori infection prevalence based on the presence of autoantibodies.

Conclusion

In conclusion, our meta-analysis depicted patients with SSc who have had a pre-existing H.plyori infection. This serves to imply that previous H.plyori infection may provoke abnormal immunological cascade in the pathogenesis of SSc.

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