Korean J Gastroenterol Vol. 82 No. 3, 122-126
https://doi.org/10.4166/kjg.2023.037
pISSN 1598-9992 eISSN 2233-6869

ORIGINAL ARTICLE

헬리코박터 파일로리 감염과 호산구성 식도염의 연관성

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Association between *Helicobacter pylori* Infection and Eosinophilic Esophagitis

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Background/Aims: This study examined the association between eosinophilic esophagitis (EoE) and *Helicobacter pylori* (*H. pylori*) infection.
Methods: A single tertiary referral center case-control study was performed. EoE patients diagnosed at Seoul National University Bundang Hospital from July 2003 to March 2022 were reviewed retrospectively. Forty-five EoE patients were included in the analysis. For each EoE patient, two age and sex-matched normal controls were selected randomly from an outpatient population who received upper gastrointestinal endoscopy.
Results: Although 17 out of 90 (18.9%) controls had a *H. pylori* infection, only two out of 45 (4.4%) EoE patients showed evidence of a *H. pylori* infection. EoE was inversely associated with a *H. pylori* infection (odds ratio 0.20, 95% confidence interval 0.04–0.91, p=0.044).
Conclusions: An inverse association was observed between *H. pylori* infection and EoE. Further prospective studies will be needed to validate the protective effects of *H. pylori* infection for EoE. **(Korean J Gastroenterol 2023;82:122-126)**

Key Words: Eosinophilic esophagitis; *Helicobacter pylori*; Hygiene hypothesis

INTRODUCTION

Although the incidence of eosinophilic esophagitis (EoE) is increasing worldwide, the etiology and risk factors of EoE are not completely understood.[1] Both genetic and environmental factors are involved in the pathogenesis of EoE.

The hygiene theory of EoE development has attracted attention in the medical field because allergic conditions are common in EoE patients, and EoE is a T helper 2 (Th2)-mediated chronic inflammation. *Helicobacter pylori* (*H. pylori*), which infects half of the world's population,[2] involves T helper 1 (Th1)-mediated immune response. The rapid decrease in *H. pylori* prevalence and the coincident increase in EoE in Westernized countries have supported the inverse correlation between *H. pylori* infections and EoE reported through various observational studies over the past two decades.[3]

As Western society experiences an increasing incidence of EoE with a decreasing prevalence of *H. pylori*, South Korea

Received April 3, 2023. **Revised** June 15, 2023. **Accepted** July 18, 2023.

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Financial support: None. Conflict of interest: None.

may follow the same path with ongoing *H. pylori* eradication efforts and the improving hygiene environment over the last decades.[4] On the other hand, studies on the actual prevalence of EoE and its association with *H. pylori* in South Korea are scarce.[5,6] Therefore, the present study evaluated the relationship between *H. pylori* infection and EoE patients diagnosed at the authors' tertiary referral university hospital, Seoul National University Bundang Hospital.

SUBJECTS AND METHODS

1. Study design and data source

A 1:2 age and sex-matched case-control study was performed. Patients diagnosed with EoE at Seoul National University Bundang Hospital from July 2003 to March 2022 were reviewed retrospectively. The study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (X-2206-765-902).

2. Data collection

EoE patients were selected according to the updated consensus recommendation from Proceedings of the AGREE Conference.[7] EoE patients were defined as those with symptoms of esophageal dysfunction and at least 15 eosinophils per high power field on esophageal biopsy specimens without evidence of secondary eosinophilia.[7] The electronic medical records of the EoE patients, including demographic, outpatients' notes, histologic, and endoscopic data, were collected. The controls were recruited from patients who underwent upper gastrointestinal endoscopic procedures for routine checkups or were not diagnosed with any significant gastrointestinal disease from endoscopic evaluation from July 2003 to March 2022 at Seoul National University Bundang Hospital.

3. Study population

Initially, 56 patients were diagnosed with eosinophilic esophagitis in the authors' institution from July 2003 to March 2022. Nine patients who did not have the status of *H. pylori* were excluded. Two patients with secondary eosinophilic esophagitis were also excluded. Finally, 45 patients were diagnosed with eosinophilic esophagitis. For the controls, each EoE case was matched with two controls by age and sex (Fig. 1).

4. *H. pylori* status

All included study participants (cases and controls) were required to have diagnostic tests for the *H. pylori* status. For diagnosis of a *H. pylori* infection, the medical records of rapid urease test, urea breath test, and endoscopic biopsy results were evaluated. The participant was classified as *H. pylori*-positive if any of the diagnostic tests were positive.

5. Statistical analysis

Continuous variables were described as the means and standard deviations, while categorical variables were described with numbers and percentages. For each EoE patient, two age and sex-matched normal controls were selected using the propensity score-matching package installed in R. All statistical analyses were conducted using R software version 4.1.3.

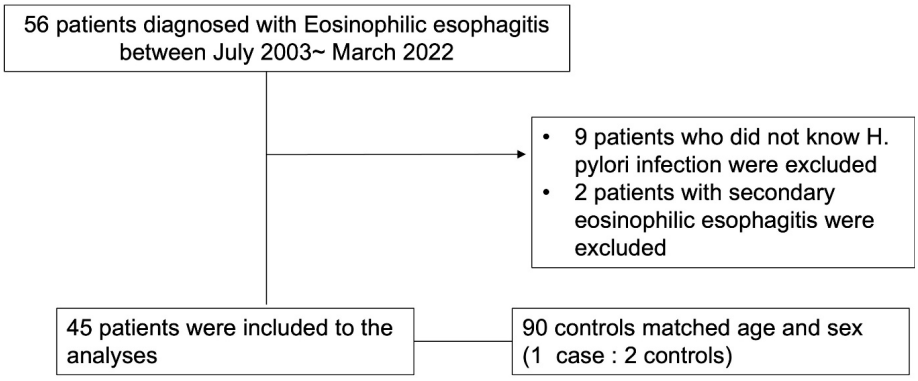

Fig. 1. Flowchart of the study.

RESULTS

1. Baseline characteristics of the enrolled subjects

Table 1 lists the baseline characteristics of study participants. The mean age of EoE patients and controls were 19.3±23.9 years and 20.3±21.9 years, respectively. The proportion of males was 66.7% for both groups. The gastrointestinal symptoms of EoE patients included 19 patients (42.2%) with epigastric pain, 19 patients with vomiting (42.2%), and 15 patients with dysphagia (33.3%). Concomitant allergic conditions were common in EoE patients because 31 EoE patients (68.9%) had allergic diseases, such as food allergies (57.8%), allergic rhinitis (26.7%), atopic dermatitis (11.1%), asthma (8.9%), chronic urticaria (6.7%), drug allergy (4.4%), and dermatographism (2.2%). Peripheral eosinophilia (eosinophil count in the peripheral blood of ≥500/μL) was found in 21 EoE patients (46.7%). Table 2 lists the endoscopic grading of EoE patients according to the proposed endoscopic reference score classification.[8]

2. *H. pylori* status and EoE

Although 17 out of 90 (18.9%) controls had a *H. pylori* infection, only two (4.4 %) EoE patients showed evidence of a *H. pylori* infection (odds ratio 0.20, 95% confidence interval 0.04–0.91, p=0.044) (Fig. 2).

Table 2. Endoscopic Findings According to EoE Endoscopic Reference Score (EREFS) in 45 Patients with EoE

Endoscopic findings	Value (n=45)
Fixed rings	
Grade 0: none	30 (66.7)
Grade 1: mild	15 (33.3)
Grade 2: moderate	0 (0.0)
Grade 3: severe	0 (0.0)
Exudates	
Grade 0: none	23 (51.1)
Grade 1: mild	18 (40.0)
Grade 2: severe	4 (8.9)
Furrows	
Grade 0: none	24 (53.3)
Grade 1: mild	15 (33.3)
Grade 2: severe	6 (13.3)
Edema	
Grade 0: absent	10 (22.2)
Grade 1: present	35 (77.8)
Stricture	
Grade 0: absent	43 (95.6)
Grade 1: present	2 (4.4)

Values are the number of patients (%).
EoE, eosinophilic esophagitis.

Table 1. Baseline Characteristics of the Enrolled Subjects

Clinical characteristics		EoE (n=45)	Control (n=90)	p-value
Sex (male)		30 (66.7)	60 (66.7)	0.183
Age at diagnosis		19.3±23.9	20.3±21.9	0.809
Gastrointestinal symptoms				<0.001
	Epigastric pain	19 (42.2)	0 (0.0)	
	Vomiting	19 (42.2)	0 (0.0)	
	Dysphagia	15 (33.3)	0 (0.0)	
Allergic conditions				
	Total	31 (68.9)	2 (2.2)	<0.001
	Food allergy	26 (57.8)	0 (0.0)	
	Allergic rhinitis	12 (26.7)	0 (0.0)	
	Atopic dermatitis	5 (11.1)	0 (0.0)	
	Asthma	4 (8.9)	2 (2.2)	
	Chronic urticarial	3 (6.7)	0 (0.0)	
	Drug allergy	2 (4.4)	0 (0.0)	
	Dermatographisim	1 (2.2)	0 (0.0)	
Peripheral eosinophilia		21 (46.7)	0 (0.0)	<0.001

Values are presented as number (%) or mean±standard deviation.
EoE, eosinophilic esophagitis.

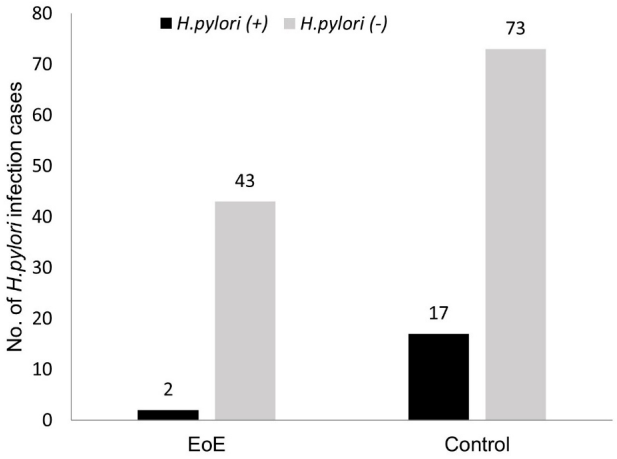

Fig. 2. Number of *H. pylori* infection cases in the EoE and Control group. EoE, eosinophilic esophagitis; *H. pylori*, *Helicobacter pylori*.

DISCUSSION

The role of *H. pylori* in the pathogenesis of EoE is controversial. In response to previous studies, this study investigated retrospectively the association between the *H. pylori* status and EoE in a tertiary referral university hospital in South Korea. With 45 EoE patients and 90 age and sex-matched controls, *H. pylori* infection and EoE were inversely associated.

The underlying biological mechanism between *H. pylori* and EoE is not completely understood.[1] According to the hygiene hypothesis, an imbalance between Th1 and Th2 mediated immune response causes a particular bias towards the Th2 type immune response, which is related to allergic conditions.[9] A *H. pylori* infection is associated with a Th1-mediated immune response.[10] Therefore, Th2 mediated response may be hyperactivated when *H. pylori* is absent. The decreasing prevalence of a *H. pylori* infection because of the improved sanitation and aggressive eradication efforts over the last few decades may have resulted in a stronger Th2 response leading to EoE pathogenesis. Thus, a "protective" effect of *H. pylori* infection in allergic diseases, such as EoE, has been suggested together with the hygiene hypothesis.[11]

These findings confirm the inverse association between a *H. pylori* infection and EoE shown in previous studies. The recent meta-analysis of 11 studies by Shat et al. has shown that exposure to *H. pylori* was associated with a lower risk of EoE.[12] Since Cheung et al.[13] first described an inverse association between *H. pylori* and EoE, the following studies attempted to reveal this relationship. In 2011, Dellon et al.[14] reported an inverse relationship between EoE and *H. pylori* infection in esophageal biopsy specimens from a US pathology database. Two years later, Furuta et al.[15] reported lower rates of *H. pylori* infections in both EoE and eosinophilic gastroenteritis (EGE) patients compared to their normal control subjects in Japan. In 2014, Elitsur et al.[16] reported a significant inverse association between a *H. pylori* infection and EoE in their first retrospective review of EoE children. In 2016, Arnim et al.[17] contributed to the hypothesis from their large *H. pylori* serology database in Germany. Although all these observational studies differed in the study designs and diagnostic methods for *H. pylori* and EoE, their results are consistent with the present findings.

In contrast to earlier studies, Molina-Infante et al.[18] negated the association between *H. pylori* infection and EoE. This first large multicenter prospective study states that previous observational studies are methodologically limited. The protocol for taking biopsies and information on previous proton pump inhibitor (PPI) use were not provided. Furthermore, the author questioned the inverse association between *H. pylori* infection and atopic disorders because the increasing incidence of allergic disorders may be influenced by complex changes in the human microecology related to improved hygiene, frequent antibiotics use, and changes in diet.[18] In addition to Molina-Infante et al.[18], Doulberis et al.[11] claimed that the so-called protective hypothesis of *H. pylori* infection against EoE is incomplete because of a lack of esophageal biopsies in the control groups and the prevalence of *H. pylori* was too low in these case-control studies.

In line with previous observational studies, this study had some limitations. First, the small sample size was insufficient to generalize the protective hypothesis. Second, the primary data source was retrospective, with inadequate clinical information. Third, there was no accurate history of previous PPI prescriptions before the diagnosis of EoE. The negative states of *H. pylori* from the present study participants may not be accurate because PPI use can suppress the detection of *H. pylori*. On the other hand, all the EoE patients in the present study had at least one biopsy result from EGD. Therefore, the presence of biopsy results increases the accuracy of *H. pylori* states. Fourth, this study could not determine if the study patients had received *H. pylori* eradication therapy before the diagnosis of EoE. Fifth, the short and long-term

effects of *H. pylori* infection on EoE development could not be evaluated because of limited information on the timing and duration of *H. pylori* infection. Lastly, this study could not confirm that the control participants were non-EoE patients because not all the control group participants had biopsies during routine EGD checkups. To the best of the authors' knowledge, this study is the first to primarily investigate the association between the *H. pylori* status and EoE in South Korea. The diagnostic limitations of earlier studies were overcome by confirming the EoE diagnosis according to the latest EoE consensus and evaluating the *H. pylori* infection status with histopathology, rapid urease test, and urea breath test.

In conclusion, this study found a strong inverse association between EoE and *H. pylori* from retrospective data obtained at a tertiary university hospital in South Korea. Multicenter and multiethnic prospective studies will be needed to find the underlying mechanism behind this association.

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