

Correlation Between *Helicobacter pylori* Infection, IgE Hypersensitivity, and Allergic Disease in Korean Adults

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Keywords

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Abstract

Background: The correlation between allergic disease and *Helicobacter pylori* infection is still controversial in endemic areas. The aim of this study was to determine whether *H. pylori* infection is related to allergic disease and/or immunoglobulin E (IgE) hypersensitivity in Korean adults.

Materials and Methods: Consecutive Korean adults who visited our center for a routine checkup were enrolled. All subjects completed a questionnaire that was designed to ascertain their medical history pertaining to physician-diagnosed allergic disease, allergy treatments, and *H. pylori* eradication therapy. Blood was sampled for serum anti-*H. pylori* IgG antibody. IgE hypersensitivity was measured using a commercially available ImmunoCAP® Phadiatop (Phadia AB, Uppsala, Sweden).

Results: Of the 3376 Korean adults who were enrolled, 62 did not answer to the questionnaires adequately and were thus excluded. The proportion of noninfected subjects ($p < .001$) and the prevalence of IgE-related allergic disease ($p < .001$) were both highest among those aged <40 years, while the prevalence of non-IgE-related allergic disease was highest among those aged ≥ 70 years ($p < .001$). Logistic regression analysis revealed that being younger than 40 years was significantly related to the absence of *H. pylori* infection (OR = 2.507, 95% CI = 1.621–3.878, $p < .001$).

Conclusions: The statuses of *H. pylori* infection, IgE hypersensitivity, and allergic diseases differ with age group, there being a higher prevalence of IgE-related allergic disease and a lower *H. pylori* infection rate among young adults. The hygiene hypothesis might explain these findings in young Koreans, due to the rapid development and improvements in sanitation in Korea.

Helicobacter pylori infection is one of the most common bacterial diseases worldwide. *H. pylori* mediates an inflammatory response with a chronic persistent infection not only inside the stomach, but also causing extraintestinal diseases that require eradication [1]. Previous studies have shown that *H. pylori* infection is related to allergic diseases [2–5], with the presumed pathogenesis that *H. pylori* infection can provoke histamine release from basophils [6,7]. Conversely, an inverse association between *H. pylori* infection and allergic diseases has also been reported [8–13]. Although the theoretical background remains uncertain and hypothetical, *H. pylori* seems to suppress the allergic reaction through an immune response via helper T cells [14,15]. The findings are thus contradictory,

suggesting that *H. pylori* infection is both associated with a decreased risk for allergy and is a protective factor against allergy.

Allergic reactions are immediate hypersensitivity (type I) reactions against common environmental allergens that have a tendency to produce excessive amounts of immunoglobulin E (IgE) antibodies [16]. Phadiatop is a valuable tool for the diagnosis of allergic sensitization that detects IgEs to common aeroallergens from a mixture of weed, grass, tree pollen, cat, dog, dust mite, and mold allergens [17]. It is a multi-allergen screening test that is useful for detecting the presence of respiratory allergies such as asthma and allergic rhinitis and can be used for the diagnosis of skin allergies to pneumoallergens. Previous studies have shown

that the specificity of Phadiatop is similar to that of other methods such as the total IgE test and skin-prick test and that it exhibits relatively high sensitivity [18]. Moreover, the Phadiatop assay is relatively cheap and simple and is not affected by the prior use of steroids or antihistamines [17]. With the ImmunoCAP® Phadiatop assay, a positive result demonstrates the presence of an atopic allergy, and thus, the physician may proceed with more specific testing to confirm the causative allergen; a negative result indicates that the symptoms are not caused by common environmental allergens. Although it is not sufficient for allergic disease manifestation, it can be considered an indicator of a predisposition toward a hypersensitivity reaction.

While the prevalence of allergic diseases has increased over the past decades, that of *H. pylori* infection has decreased in Korea [19,20]. The association between allergic disease and *H. pylori* infection remains controversial in endemic area of *H. pylori* infection, and there have been no large-scale studies in this field involving Koreans. Therefore, this study investigated the relationship between *H. pylori* infection and allergic diseases in Korean adults using a Phadiatop assay as an indicator of a predisposition to IgE hypersensitivity. In addition, the status of *H. pylori* infection, IgE hypersensitivity, and allergic disease was analyzed to test the hypothesis that exposure to *H. pylori* reduces the risk of allergic disease.

Methods

Subjects

This cross-sectional study was based on the medical records of the health examinee at our center who visited between January 2010 and July 2013. Subjects who underwent serum anti-*H. pylori* immunoglobulin G (IgG) antibody and Phadiatop assay on the same day were enrolled. This study was approved by the Institutional Review Board (IRB) of Konkuk University School of Medicine which confirmed that the study was in accordance with the ethical guidelines of the Helsinki Declaration (KUH1010509). After the IRB approval, this study was registered as ClinicalTrials.gov ID: KCT0000828 (<https://cris.nih.go.kr/cris/en>).

Questionnaires

Each of the subjects completed a questionnaire in which they were asked whether they have ever been diagnosed by a physician with allergic rhinitis, atopy, drug or food allergy, or asthma, and whether they were currently under treatment for an allergic disease. In

addition, they were asked whether they had ever undergone successful *H. pylori* eradication therapy. Subjects who provided inadequate answers to this questionnaire were excluded from the study.

Serum *H. pylori* Antibody Test

After 12 hours of fasting, blood sampling was performed for serum anti-*H. pylori* IgG antibodies and their levels were measured using an ELISA that detects human serum antibodies to *H. pylori* (Platelia™ *H. pylori* ELISA; Bio-Rad, Marnes-la-Coquette, France or Chorus *Helicobacter pylori* IgG, DIESSE Diagnostica Senese, Moteriggioni, Italy). The results of serum anti-*H. pylori* IgG antibody assay were expressed as either negative or positive.

The subjects were classified into three groups according to their *H. pylori* infection status: (i) past infection (*H. pylori*-eradicated group) if the subject had a history of *H. pylori* eradication and the serum was negative for anti-*H. pylori* antibody, (ii) current infection (*H. pylori*-persistent group) if the subject's serum was positive for anti-*H. pylori* antibody, and (iii) no infection (noninfected control group) if the subject had no history of *H. pylori* infection and the serum was negative for anti-*H. pylori* antibody.

Phadiatop Assay

Specific IgE to common inhalant allergens was measured using a commercially available ImmunoCAP® Phadiatop (Phadia AB). For qualitative evaluation, results were expressed as positive or negative. The 0.35 kU/L specific IgE calibrator was used as a cutoff level. Level of the positive results was subdivided into weak, moderate, and strongly positive (weak 0.35–0.99 kU/L, moderate 1.00–9.99, and strong ≥ 10.00).

The subjects were also classified into four groups based on the results of a Phadiatop assay:

- 1 IgE-related allergic disease – if the Phadiatop assay was positive in a subject with self-reported physician-diagnosed allergic disease on current medication.
- 2 Non-IgE-related allergic disease – if the Phadiatop assay was negative in a subject with allergic disease on current medication.
- 3 Subclinical IgE hypersensitivity – if the Phadiatop assay was positive in a subject without allergic disease that requires current medication, because elevated IgE is not synonymous with allergic disease.
- 4 No allergy (normal control) – if the Phadiatop assay was negative in a subject without allergic disease that requires current medication.

Statistical Analysis

Continuous variables were summarized as mean $\pm$ standard deviation (SD) using Student's *t*-test. Categorical variables were summarized as frequency (%) using chi-square test. Logistic regression analysis was performed to verify the significance of allergic disease according to the status of *H. pylori* infection using odds ratio (OR) and 95% of CI (confidence interval). All analyses were conducted using SPSS for Windows (versions 19.0, Chicago, USA.), and a *p*-value of $<.05$ was considered statistically significant.

Results

Characteristics of the Subjects

Of the 3376 Korean adults in whom blood test were performed, 62 did not answer the questionnaires adequately and were thus excluded from the study (Fig. 1). The remaining 3314 subjects were then classified into three groups according to their *H. pylori* infection status: (i) noninfected and without a history of *H. pylori* infection (noninfected control group, $n = 1128$), (ii) current *H. pylori* infection (*H. pylori*-persistent group, $n = 1973$), and (iii) noninfected after *H. pylori* eradication (*H. pylori*-eradicated group, $n = 213$). The baseline characteristics of these subjects are summarized in Table 1.

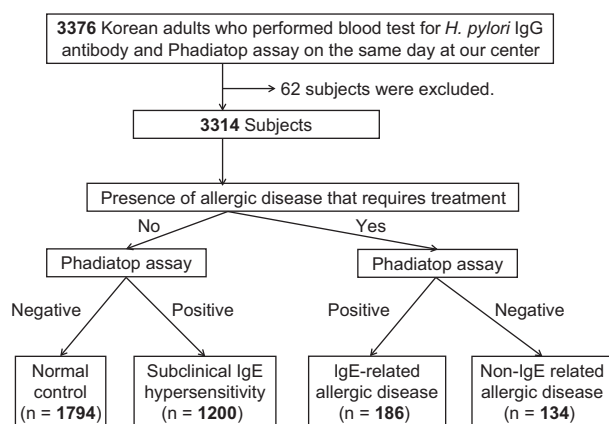


Figure 1 Study flow of the subjects based on their classification according to the presence of allergic disease and Phadiatop assay results. Allergic disease includes physician-diagnosed allergic rhinitis, atopy, drug or food allergy, and asthma that requires treatment. In the presence of allergic disease, IgE-related and non-IgE-related allergic diseases were diagnosed by a positive and negative Phadiatop assay result, respectively. A positive Phadiatop assay result without physician-diagnosed allergic disease was classified as subclinical IgE hypersensitivity.

Table 1 Baseline characteristics of the subjects

All subjects (n = 3314)	
Age (years old, mean $\pm$ SD)	55.4 $\pm$ 9.9
Age group	
≤ 39 years old	123 (3.7%)
40–49 years old	8214 (24.6%)
50–59 years old	1322 (39.9%)
60–69 years old	776 (23.4%)
≥ 70	279 (8.4%)
Gender (male/female, % of male)	2016/1298 (60.8%)
Positive anti- <i>H. pylori</i> IgG antibody	1971 (59.5%)
Low bacterial load (<100 AU/mL)	350
Moderate bacterial load (100–200 AU/mL)	1000
High bacterial load (>200 AU/mL)	621
Positive Phadiatop assay	1386 (41.8%)
Weakly positive (0.35–0.99 kU/L)	467
Moderately positive (1.00–9.99 kU/L)	686
Strongly positive (≥ 10.00 kU/L)	233
Presence of allergic disease	512 (15.4%)
Allergic disease requiring current medication	320
Past history only	192

SD, Standard deviation.

Prevalence According to Age Group

The *H. pylori* infection status differed significantly according to the age group (Fig. 2). The proportion of noninfected subjects was highest among those aged <40 years, and conversely, the proportion of infected subjects was higher in those aged ≥ 40 years ($p < .001$). The prevalence of IgE hypersensitivity was higher among the younger subjects than the older subjects

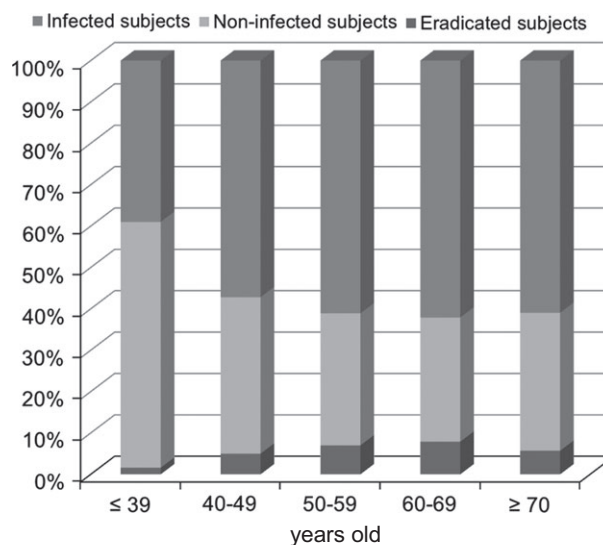


Figure 2 *H. pylori* infection status according to age group. The status of *H. pylori* infection differed according to the age group. Subjects aged <40 years had the lowest rate of *H. pylori* infection ($p < .001$).

(Fig. 3). The prevalence rates of subclinical IgE hypersensitivity and IgE-related allergic disease were also highest among subjects aged <40 years, while the prevalence of non-IgE-related allergic disease was highest among those aged ≥70 years ($p < .001$).

Link Between Allergic Disease and *H. pylori* Infection

Subjects with either IgE-related allergic disease or subclinical IgE hypersensitivity were younger and

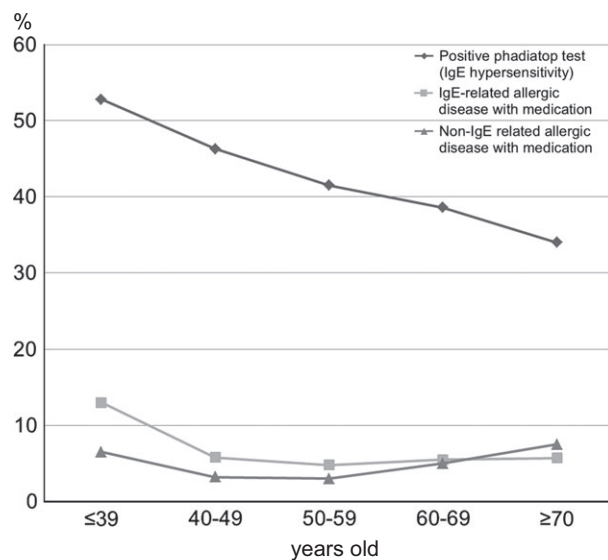


Figure 3 Prevalence of allergic disease according to age group. The prevalence of IgE hypersensitivity and IgE-related allergic disease decreased with age ($p < .001$). Conversely, the prevalence of non-IgE-related allergic disease increased with age.

predominantly male compared to those with non-IgE-related allergic disease and normal controls (Table 2). Subjects with past infection had the highest rate of current allergic disease, regardless of the IgE hypersensitivity status ($p = .002$). Logistic regression analysis revealed that allergic disease was more common in subjects with a past *H. pylori* infection (OR = 2.093, 95% CI = 1.439–3.046, $p < .001$). However, the bacterial load of *H. pylori* did not appear to be affected by the presence of either allergic disease or IgE hypersensitivity (Table 2).

Logistic regression analysis revealed that the absence of *H. pylori* infection was significantly associated with age ≤40 years (OR = 2.507, 95% CI = 1.621–3.878, $p < .001$). The presence of neither IgE hypersensitivity ($p = .100$) nor allergic disease ($p = .652$) was related to the absence of *H. pylori* infection itself (Table 3). With regard to the absence of IgE hypersensitivity, female gender and being older were significantly related to a negative Phadiatop assay result (Table 4). However, IgE hypersensitivity was not directly correlated with *H. pylori* infection (OR = 1.132, 95% CI = 0.977–1.311, $p = .100$).

Discussion

This study yielded contradictory findings regarding *H. pylori* infection and allergic disease according to age group in Korean adults. Subjects younger than 40 years had a lower *H. pylori* infection rate and higher prevalence of IgE-related allergic disease, whereas older subjects had a higher infection rate and a higher prevalence of non-IgE-related allergic disease. Due to the rapid development and improved sanitation in Korea, this inverse correlation between IgE-related

Table 2 Characteristics of the subjects according to the presence of allergic disease

	Subjects with non-IgE-related allergic disease (n = 134)	Subjects with IgE-related allergic disease (n = 186)	Subjects with subclinical IgE hypersensitivity (n = 1200)	Normal controls (n = 1794)	p-Value
Age (years old, mean ± SD)	57.5 ± 11.4	54.2 ± 11.1	54.4 ± 9.5	56.1 ± 9.8	<.001
Gender (male, %)	63 (47.0%)	126 (67.7%)	874 (72.8%)	953 (53.1%)	<.001
Status of <i>H. pylori</i>					.002
Eradicated group	18 (13.4%)	19 (10.2%)	71 (5.9%)	105 (5.8%)	
Persistent group	73 (54.5%)	115 (61.8%)	731 (60.9%)	1054 (58.8%)	
Noninfected group	43 (32.1%)	52 (28.0%)	398 (33.2%)	635 (35.4%)	
Serum anti- <i>H. pylori</i> IgG antibody level					.475
<10 AU/mL	61 (45.5%)	71 (38.2%)	469 (39.1%)	742 (41.4%)	
≥10 and <100 AU/mL	14 (10.4%)	26 (14.0%)	130 (10.8%)	180 (10.0%)	
≥100 and <200 AU/mL	34 (25.4%)	48 (25.8%)	372 (31.0%)	546 (30.4%)	
>200 AU/mL	25 (18.7%)	41 (22.0%)	229 (19.1%)	326 (18.2%)	

Data were analyzed by chi-square test and Student's *t*-test.
SD, Standard deviation.

Table 3 Significant variables related to the absence of *H. pylori* infection

	Odds ratio	95% confidence interval	<i>p</i> -Value
Gender			
Male	1.004	0.868–1.162	.955
Female	1 (reference)		
Age (years old)			
<40	2.507	1.621–3.878	<.001
≥40 and <70	1.039	0.807–1.337	.766
≥70	1 (reference)		
IgE hypersensitivity			
Absent	1.132	0.977–1.311	.100
Present	1 (reference)		
Allergic disease			
Absent	1.047	0.859–1.276	.652
Present	1 (reference)		

Data were analyzed by logistic regression analysis.

Table 4 Factors related to a negative Phadiatop assay result

	Odds ratio	95% confidence interval	<i>p</i> -Value
Gender			
Male	0.406	0.349–0.473	<.001
Female	1 (reference)		
Age (years old)			
<40	0.467	0.296–0.736	.001
≥40 and <70	0.670	0.511–0.878	.004
≥70	1 (reference)		
<i>H. pylori</i> infection			
Absent	1.132	0.977–1.311	.100
Present	1 (reference)		
Allergic disease			
Absent	2.976	2.433–3.641	<.001
Present	1 (reference)		

Data were analyzed by logistic regression analysis.

allergic disease and *H. pylori* infection may be attributable to the so-called “hygiene hypothesis” only for the young Koreans in this study. The higher prevalence of past and current *H. pylori* infection among the elderly indicates that their sanitary conditions were probably poor when they were young; that is, the exposure to microbes may have resulted in polarization of the immune system and a reduction in the risk of IgE-related conditions in these subjects. These opposing findings could alternatively be due to alterations in the gut microbiome, because younger subjects were exposed to antibiotics at a younger age or more frequently than the older subjects. Furthermore, the findings of this study suggest that the pathogenesis of non-IgE allergic disease is different from that of

IgE-related allergic disease, based on the hygiene hypothesis.

The association between *H. pylori* infection and allergic disease has been investigated in many other studies, but confusion has resulted from the strikingly different results obtained [2–16]. The studies have varied with respect to the type of allergy investigated, the study design, and the race and age of the subjects. Moreover, differences between the types of allergy such as IgE- and non-IgE-related allergic disease were overlooked. This point has been clarified in the present study by classifying the condition into IgE-related allergic disease, non-IgE-related allergic disease, and subclinical IgE hypersensitivity. Distinction was also made in this study between those with a past *H. pylori* infection and those who have never had *H. pylori* infection (i.e., the *H. pylori*-eradicated and noninfected groups, respectively), because eradication for *H. pylori* infection is more frequently performed nowadays. As a result, it was found that the statuses of *H. pylori* infection, IgE hypersensitivity, IgE-related allergic disease, and non-IgE-related allergic disease differed between the age groups in adult Korean subjects.

An inverse tendency found in our subjects younger than 40 years could be explained by previous studies showing that *H. pylori* infection can prevent the occurrence of allergic disease [8–13]. There has been an increase in the prevalence of allergic diseases in recent years due to various environmental factors such as air pollution, and a decrease in the prevalence of *H. pylori* infection due to the development of eradication therapies and improvements in hygiene [13,21,22]. Notably, an increase in allergen-specific IgE antibodies was found between 1973 and 1994, with a possible relationship to *H. pylori* infection [13]. In addition, *H. pylori* neutrophil-activating protein was found to be a candidate for novel strategies of prevention and treatment of allergic diseases by reducing eosinophilia, IgE, and Th2 cytokine levels [23]. In line with this, markers of poor hygiene such as hepatitis A virus, *H. pylori*, and *Toxoplasma gondii* infection were associated with a lower prevalence of atopy [14]. These findings suggest that hygiene-related environmental factors have played a role in the increase in allergic sensitization. Hygiene and a Westernized, semi-sterile diet may promote allergic disease by influencing the overall pattern of commensal pathogens that stimulate the lymphoid tissue, thus contributing to the present epidemic of allergic asthma and rhinitis in developed countries [14]. According to this theory, living in an unhygienic environment may prime the immune system and thus protect against the development of allergic diseases [24].

The rapid development and improvements in sanitation that have occurred over the past several decades in Korea have led to a rapid decrease in the prevalence of *H. pylori* infection, as observed in the subjects aged <40 years in the present study. Recent Japanese studies have demonstrated a similar clear inverse association only in men and young subjects [8,12]. This is consistent with our finding that young men had more IgE-related allergic diseases. *H. pylori* infection was not found to be associated with IgE hypersensitivity, especially in older populations. The inverse association found in the previous and the present studies may be attributable to young males having more allergic diseases and a lower prevalence of *H. pylori* infection. These findings suggest that *H. pylori* infection is associated with a reduced risk for IgE-related allergic conditions, and thus be a protective factor. Therefore, it appears that the inverse relationship between the low *H. pylori* infection rate and the high prevalence of allergic disease in young Korean and Japanese subjects may be attributable to the hygiene hypothesis.

Interestingly, only the prevalence of IgE-related conditions was increased in young subjects in the present study, whereas the prevalence of non-IgE-related allergic disease was increased in older subjects. These contradictory findings suggest that the hygiene hypothesis can explain only IgE-related conditions, because non-IgE-related allergic disease was more often noticed in those with current or past *H. pylori* infection. The present findings suggest that *H. pylori* infection plays a role in the complex interplay between hygiene and allergy and may contribute toward our understanding of the allergy epidemic. *H. pylori* infection might provoke the occurrence of non-IgE-related allergic disease rather than preventing it by pathogenesis, because *H. pylori* infection provokes histamine release from basophils [6,7]. In other words, the inverse relationship between *H. pylori* infection and allergic disease is not found for non-IgE-related allergic disease. Rather, *H. pylori* infection might be a risk factor for non-IgE-related allergic disease, but not IgE-related allergic disease. This supports the previous finding that exposure to certain intestinal bacterial pathogens is associated with a higher prevalence of atopy, whereas exposure to markers of poor hygiene is associated with a lower prevalence of atopy [14]. This leads to the hypothesis that different groups of food-borne and orofecal microorganisms exert different effects on the risk of allergic disease.

In conclusion, the statuses of *H. pylori* infection, IgE hypersensitivity, and allergic disease differ according to the age group in Korean adults. The lower *H. pylori* infection rate and higher prevalence of IgE-

related allergic disease found in Korean adults aged <40 years may reflect changes in, for example, hygiene and sanitation that are attributable to Korea's rapid development. Conversely, older subjects exhibit a higher prevalence of *H. pylori* infection and non-IgE-related allergic disease. These contradictory findings suggest that the hygiene hypothesis can be applied only to IgE-related conditions, and not to non-IgE-related allergic diseases, the prevalence of which are increased in subjects with a current or past *H. pylori* infection.

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