

DR. JIN YOUNG CHOI (Orcid ID : 0000-0002-3641-2504)

PROF. DONG SOO YU (Orcid ID : 0000-0002-2196-949X)

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**Atopic dermatitis is inversely associated with hepatitis B antigen positivity:
a population-based cohort study**

HY Kim, M.D., Ph.D.,¹ CW Kim, M.D., Ph.D.,¹ JY Choi, M.D.,² DS Yu, M.D., Ph.D.,² JW Kim, M.D., Ph.D.,² KD Han, Ph.D.,³ YG Park, Ph.D.,³ YB Lee, M.D., Ph.D.²

¹ Department of Internal Medicine, College of Medicine, The Catholic University of Korea

² Department of Dermatology, College of Medicine, The Catholic University of Korea

³ Department of Medical Statistics, College of Medicine, The Catholic University of Korea

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Corresponding author: Young Bok Lee, M.D., Ph.D.

Correspondence and reprint requests should be addressed to: Department of Dermatology, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Gyeonggi-Do, Korea. 271, Cheon Bo-ro, Uijeongbu, Gyeonggi-Do, 07345, Republic of Korea. Tel +82-31-820-5025, Fax: 82-31-846-4799, e-mail: lyb80@catholic.ac.kr

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First author ORCID ID: orcid.org/0000-0002-8642-2479

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Abstract

Background: No clear association between hepatitis B virus (HBV) infection and atopic dermatitis (AD) has been established. Some studies have reported that subjects with HBV had an increased risk of atopy; other studies reported an inverse association between HBV seropositivity and allergic diseases.

Objective: We evaluated the association between AD and hepatitis B antigen (HBsAg) positivity using Korean National Health and Nutrition Examination Survey data.

Methods: In total, 14,776 participants aged > 19 years were included in the analysis. Multiple logistic regression analyses were used to evaluate the odds ratio of HBsAg positivity in association with AD and asthma.

Results: The prevalence of HBsAg positivity was lower in individuals with AD than in those without AD (mean [SE], 0.7% [0.4] vs. 3.7% [0.2]; $P < 0.001$). However, HBsAg positivity was not significantly associated with asthma (3.7% [0.2] vs. 2.8% [0.8]; $P < 0.001$). HBsAg positivity decreased the risk of AD significantly (OR = 0.223; 95% CI = 0.069–0.72).

Conclusions: This study demonstrates an inverse association between AD and HBsAg positivity using a nationwide, population-based, cross-sectional health examination and survey.

Key words: atopic dermatitis, asthma, cohort study, epidemiology, hepatitis B virus

Introduction

Atopic dermatitis (AD) is a common inflammatory skin disease characterized by pruritic symptoms that is often accompanied by other allergic diseases, including asthma. AD is a multifactorial disease; genetic, environmental, and immunological factors have been suggested. Regarding its immunological pathogenesis, T cells play a key role in AD. In the acute phase, there is a predominantly Th2 response, whereas the chronic phase is characterized by a predominantly Th1 response. The balance between two subsets of CD4⁺ T cells, Th1 and Th2, affects the immune response towards one pathway or the other. Some infections during early infancy such as measles,¹ hepatitis A,² and tuberculosis³ may inhibit allergic disease by stimulating a Th1 response. However, some infections, including respiratory syncytial virus, have been reported to promote allergic disease by preventing a Th1 response.

The association between hepatitis B virus (HBV) infection and AD is controversial. Some studies reported that subjects with HBV had an increased risk of atopy. Kocabas⁴ asserted that the Th2 response, including allergic diseases, may develop in HBV carriers. Kocabas⁴ suggested this hypothesis because HBV carriers showed Th1 insufficiency and decreased levels of interleukin-12 and interferon- γ . Cakir *et al.* supported previous findings showing that symptoms of asthma, eczema, and atopy were found more commonly in HBV carrier children than those with type 1 diabetes mellitus and healthy controls.^{5, 6} However, other studies showed an inverse association between HBV seropositivity and allergic diseases. For example, Koh *et al.*⁷ reported the presence of anti-HBV antibodies was associated with a lower risk of atopy in South Korea. A Turkish study presented that the prevalence of atopy was significantly lower in the HBV-seropositive group (7.1%) than in the HBV-seronegative group (32.2%).⁸

In this study, we evaluated the association between HBV seropositivity and atopic diseases in a Korean population.

Materials and Methods

Study Population and Data Collection

This study analyzed data from the 6th Korean National Health and Nutrition Examination Survey (KNHANES V-3, VI-1, and 2), which was conducted from January 2012 to December 2014 by the Korea Centers for Disease Control and Prevention. The survey was conducted after approval from the institutional review board of the Korea Centers for Disease Control and Prevention (IRB Nos. 2012-01EXP-01-2C, 2013-07CON-03-4C, and 2013-12EXP-03-5C). The study design followed the tenets of the Declaration of Helsinki for biomedical research.

The study was conducted using a rolling sampling design that involved a complex, stratified, multistage, probability cluster survey of a representative sample of the civilian population of South Korea. The Korea Centers for Disease Control and Prevention obtained consent from the participants.

Among 23,625 potential participants, those younger than 19 years ($n = 5,277$) who had not undergone a hepatitis B surface antigen (HBsAg) serological test were excluded.

Additionally, 3,572 individuals were eliminated due to missing data. The final study population consisted of 14,776 participants with complete data sets (Fig. 1).

Questionnaires and laboratory measurements

The surveys included questions on age, sex, smoking and drinking status, and exercise.

Current smokers and drinkers (more than once per month) were divided into yes or no.

Blood samples were processed appropriately, refrigerated immediately, and transported in cold storage to the Central Testing Institute (Seoul, Korea). HBsAg was measured using an electrochemiluminescence immunoassay (Cobas8000 e602; Roche Diagnostics, Mannheim, Germany). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined using a Hitachi Automatic Analyzer 7600-210 (Hitachi Ltd., Tokyo, Japan).

Metabolic syndrome was defined as same as the previous study.⁹

Definitions of AD and asthma

Participants who answered “Yes” to “Have you ever been diagnosed with AD in your life” were classified in the AD group. Participants who answered “Yes” to the following questions were classified in the asthma group: “Have you ever been diagnosed with asthma by a doctor?”, “Have you experienced wheezing or whistling in your chest at any time in the last 12 months?”, and “Are you currently taking any medicine for asthma?”

Statistical analysis

Continuous variables are presented as means and standard errors (SEs). Categorical variables are presented as percentages (SE). Student’s *t*-test was used to compare mean values for continuous variables; the χ^2 test was used for categorical variables, according to the presence of AD or asthma. To estimate odds ratios (ORs) of AD or asthma according to HBsAg positivity, a logistic regression analysis was performed adjusting for age and sex. A *P*-value

< 0.05 was considered to indicate statistical significance. All analyses were performed using SAS software (ver. 9.3; SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics of the AD and asthma groups

The characteristics of the 14,776 subjects, stratified by the presence of AD or asthma, are shown in Table 1. Among them, 379 (2.6%) subjects had AD and 738 (5.0%) subjects had asthma.

The AD group members were significantly younger (mean age = 32.1 ± 0.7 years) than the control group members (mean age = 45.6 ± 0.2 years). There was no statistically significant difference in sex, smoking status, or alcohol consumption status between the AD and non-AD groups. Subjects with AD were more likely to exercise, have a lower waist circumference, and had a lower percentage of metabolic syndrome than the subjects in the non-AD group.

The AD group had an increased incidence of asthma ($8.2 \pm 1.5\%$) over the non-AD group ($4.9 \pm 0.2\%$). However, the asthma group differed from the AD group. The asthma group was significantly older (49.9 ± 0.9 years) than the non-asthma group (45.1 ± 0.2 years). The asthma group had significantly higher percentages of current smokers, metabolic syndrome, and a large waist circumference than the non-asthma group.

HBsAg positivity in subjects with and without AD or asthma

The prevalence of HBsAg positivity was lower in individuals with AD than in those without AD ($0.7 \pm 0.4\%$ vs. $3.7 \pm 0.2\%$; $P = 0.001$). However, there was no significant difference in the prevalence of HBsAg positivity between subjects with and without asthma ($2.8 \pm 0.8\%$ vs. $3.7 \pm 0.2\%$; $P = 0.2844$; Table 1).

Logistic regression analysis for AD and asthma by the presence of HBsAg

Table 2 shows the ORs of AD and asthma according to HBsAg positivity. A logistic regression analysis, after adjusting for age and sex, showed that HBsAg positivity was a significant negative predictor of AD (adjusted OR = 0.22; 95% confidence interval [CI] = 0.07–0.72). Although the risk of asthma was also lower in the HBsAg-positive group, this was not statistically significant (adjusted OR = 0.75; 95% CI = 0.43–1.29).

Discussion

Korea is in an intermediate HBV endemic area with, 2–7% prevalence, and perinatal transmission is the major route of HBV infection.¹⁰ Children and young adults who acquire a HBV infection perinatally follow distinct clinical phases that are strongly related with patient age; the immune tolerant phase represents the early phase of HBV infection, while the immune active phase is usually associated with adult patients.¹¹

HBV is a non-cytopathic virus; liver damage is mediated mainly by host immune cells targeting virus-infected hepatocytes. The HBV-specific adaptive immune response plays an essential role in the development of immunity to HBV.^{12, 13} In an acute, self-limited HBV infection, the HBV-specific T cell responses, with a Th1 profile of cytokine production is able to clear the HBV infection.¹⁴ However, failure to eradicate HBV leads to the depletion and function impairment of HBV-specific T cells, resulting in viral persistence.¹⁵ It had been reported that HBV-specific Th1 responses are insufficient in HBV carriers.^{16, 17} Contrary to this, a T cell response with Th1-type cytokines is correlated with liver inflammation in chronic HBV infection.¹⁸ Thus, it is believed that children and young adults in the immune tolerant phase lack an adequate HBV-specific Th1 immune response, while HBV-specific immunity is awakened in adults in the immune active phases.

In our study, the prevalence of AD was lower in adult subjects with a chronic HBV infection.

Adults in the immune active phase may have a lower risk of AD because of the predominance of the Th1 response. However, children in the immune tolerant phase of a chronic HBV infection may have an increased tendency for AD because of skewing to a Th2-type immune response. This supposition supports previous studies reporting a positive association between AD and chronic HBV infection, performed in children or young adults.⁴⁻⁶

Although AD and asthma are both considered as allergic diseases, the AD group and asthma group showed several differences. The mean age, life style, and percentage with metabolic syndrome differed between the AD and asthma groups. The asthma group was considered to have more confounding factors that affected HBsAg positivity.

Our study has some limitations. First, we did not investigate immunological profiles. Thus, the immunological mechanisms underlying the relationship between AD and chronic HBV infection remain unclear. Second, we could not evaluate this relationship in children due to a lack of laboratory data. Third, the presence of AD and asthma was defined by self-reported questionnaires. However, this study is novel in investigating the relationship between AD and chronic HBV infection in an adult population using a large, national, population-based database.

In conclusion, AD may be inversely associated with chronic HBV infection in adults.

Additional studies are needed to investigate the mechanism underlying the possible interaction between HBV infection and AD.

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Figure 1. Flow chart regarding the number of the subjects enrolled in this study.

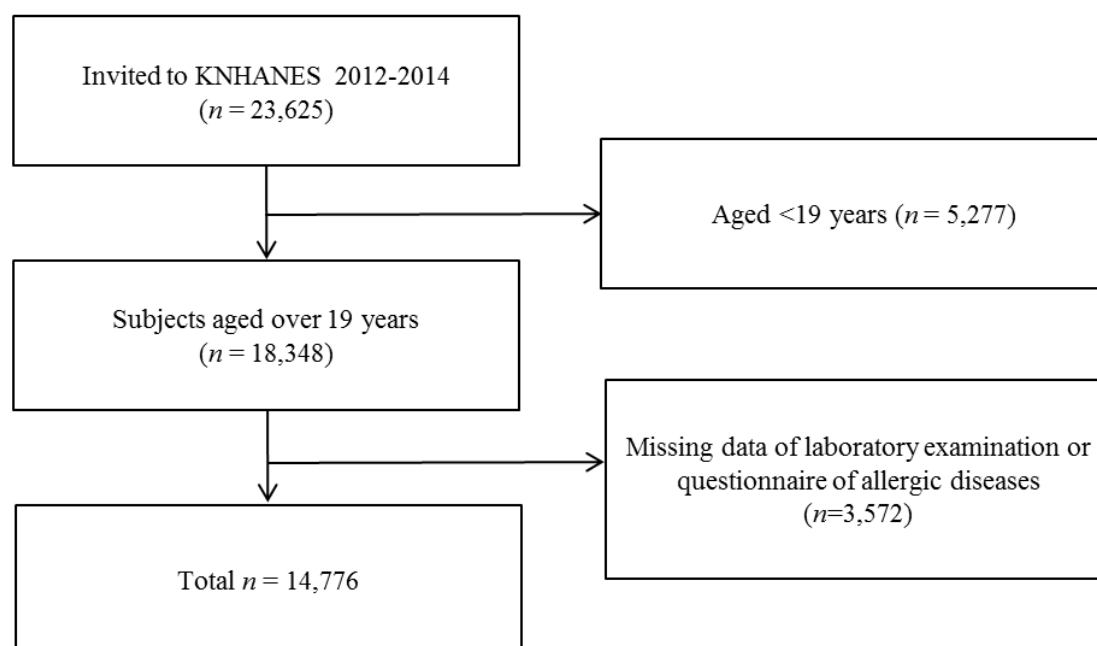


Table 1. Demographics of participants

	AD			Asthma		
	No	Yes	P value	No	Yes	P value
n	14397	379		14038	738	
Mean Age (years)	45.6(0.2)	32.1(0.7)	<.0001	45.1(0.2)	46.9(0.9)	<.0001
19-39	38.2(0.7)	79.1(2)		39.4(0.7)	39(2.4)	
40-64	42(0.6)	13.9(1.8)		41.6(0.6)	32.5(2.2)	
65-	19.8(0.5)	7(1.1)		19(0.5)	28.5(1.9)	
Gender (Male, %)	50(0.4)	49.3(3)	0.810	49.9(0.4)	53.1(2.2)	0.153
Current smoker (%)	22.2(0.5)	17.6(2.5)	0.095	21.7(0.5)	29(2.2)	0.0004
Alcohol consumption (%)	58.7(0.5)	61.8(2.9)	0.295	58.9(0.5)	56.3(2.2)	0.237
Exercise (%)	38.9(0.6)	45.4(3.1)	0.035	39.3(0.6)	34.6(2.3)	0.053
Metabolic syndrome (%)	27.2(0.5)	12.6(1.8)	<.0001	26.5(0.5)	31.4(2.2)	0.028
BMI (kg/cm²)	23.7(0)	23.5(0.2)	0.255	23.7(0)	24.1(0.2)	0.060
Waist circumference (cm)	80.8(0.1)	79.1(0.6)	0.008	80.7(0.1)	82.3(0.6)	0.004
ALT (IU/L)*	18.41(18.18,18.64)	17.33(16.06,18.7)	0.121	18.35(18.12,18.58)	18.82(17.84,19.86)	0.363
AST (IU/L)*	20.5(20.33,20.66)	18.94(18.22,19.69)	0.0001	20.44(20.28,20.6)	20.54(19.87,21.23)	0.788
Atopic dermatitis (%)				2.9(0.2)	4.9(0.9)	0.007
Asthma (%)	4.9(0.2)	8.2(1.5)	0.007			
HBs Ag positivity (%)	3.7(0.2)	0.7(0.4)	0.001	3.7(0.2)	2.8(0.8)	0.284

*Geometric mean (95% CI)

Table 2. Regression analysis for dependent variable of AD or asthma

		AD	Asthma
Model 1	HBsAg positivity	0.184 (0.058,0.584)	0.746 (0.435,1.278)
Model 2	HBsAg positivity	0.223 (0.069,0.72)	0.75 (0.435,1.292)

Model 1: Not adjusted

Model 2: age, sex adjusted