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Histamine skin reactivity increases with body mass index in Korean children

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ABSTRACT

Objective: Histamine skin prick testing is most commonly used to diagnose immunoglobulin E (IgE)-mediated allergic diseases, and histamine reactivity is used as a standardized positive control in the interpretation of a skin prick test. However, reactivity to histamine differs among individuals for reasons that are poorly understood. The present study aimed to evaluate the potential association between body mass index (BMI) and histamine skin reactivity in children.

Methods: A total of 451 children (246 boys, 205 girls) aged 7–8 years were enrolled in this study. The skin prick test was performed with 26 aeroallergens commonly found in Korea. Other information was collected, including sex, age, BMI, parental allergy history, and parental smoking status. Multivariate analysis was used to confirm the association between histamine skin reactivity and BMI.

Results: The histamine wheal size was revealed to be associated with BMI (Spearman's Rho 0.161, $p < 0.001$). This association was confirmed by multivariate analysis, after adjusting for sex, age, parental allergy history, parental smoking status, and allergic sensitization (coefficient B 0.071, 95% confidence interval 0.030–0.112).

Conclusions: Skin responses to histamine were primarily correlated with increased BMI. Further studies are needed to understand the clinical implication of BMI when interpreting the results of skin prick test.

1. Introduction

The prevalence of allergic diseases has been increasing [1], and although most are not life threatening, they contribute to significant impairment of daily activities such as sleep, work, and study [2]. Moreover, there are considerable socioeconomic burdens imposed on patients with allergic diseases [3,4]. Several tests are used to diagnose these conditions, such as the skin prick test, radioallergosorbent test, multiple allergen simultaneous test, and provocation test. Each assessment has advantages and limitations, but the skin prick test is the most commonly used to discriminate allergic conditions [5,6]. Studies for the standardization of the skin prick test are ongoing [7].

Histamine skin reactivity was used as a standardized positive control in the allergy skin test. In addition, it is possible to compare the size of the wheal induced by allergen extracts to that elicited by a histamine solution to determine the grade of allergic reaction or criteria for a positive reaction [8,9]. Therefore, understanding the factors influencing histamine skin reactivity is important. Previous reports have identified certain factors affecting histamine skin reactivity, including patient age, sex, smoking, seasonal changes, ethnicity, physician techniques, and certain medications [6,10–13]. However, there are insufficient data on individual differences in histamine skin reactivity to draw conclusions.

Previous studies have shown that obesity is significantly associated with allergic diseases such as asthma, atopy, and allergic rhinitis in children [14–16]. In addition, some studies have found an association between body mass index (BMI) and

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bronchial hyper-responsiveness [14,17]. However, the relationship between histamine skin reactivity and BMI has not been investigated. In this study, we evaluated whether there is a relationship between histamine skin reactivity and BMI in Korean school-aged children.

2. Materials and methods

2.1. Study population

The study included children living on Jeju Island, South Korea. We randomly selected six elementary schools located in Seogwipo City, Jeju Island. The details of the study were explained to the students and parents, and written informed consent was obtained from legal guardians. The study questionnaire was distributed, filled out by students and parents, and collected between October 15 and 30, 2010. Skin prick tests and physical examinations were carried out by trained nurses from November 8 to 11, 2010. From a total of 687 first and second grade children from six elementary schools, 602 were included in the study. We excluded 85 children who did not perform the skin prick test or those from whom we could not obtain the legal guardian's written informed consent. This study was approved by the institutional review board at the Jeju National Hospital University.

2.2. Skin prick test

A total of 26 common aeroallergens were used for skin prick test. The skin prick test included the following additional allergens: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, citrus red mite, dog, *Cladosporium*, *Alternaria*, Timothy grass, mugwort, barley, rapeseed, Japanese hop, Japanese cedar, rye grass, hen's egg (white), tuna, cow's milk, soya flour, mussel, yolk, shrimp, chicken meat, pork, peach, peanut, and wheat flour. Allergens except citrus red mite and Japanese cedar were purchased from Allergo-pharma (Reinbek, Germany). For Japanese cedar, the commercial allergen was purchased (Greer Laboratories Inc., Lenoir, NC, USA). Citrus red mite allergen was prepared as described in a previous report [18]. Histamine hydrochloride was used as a positive control at a concentration of 1 mg/mL (Allergo-pharma, Reinbek, Germany), whereas normal saline solution with 50% glycerin was used as negative control. Skin pricking was performed on the forearms by trained researchers using a 23G lancet. Fifteen minutes after the skin prick test, the size of each wheal was calculated as the mean of (A) the longest diameter and (B) the diameter perpendicular to the first axis at the midpoint (i.e. (A + B)/2). The skin test was considered positive if an allergen elicited a wheal $\geq$3 mm. Allergic sensitization was categorized based on frequency of sensitization: none, mono-sensitization, and poly-sensitization.

2.3. Other variables

Height and weight were measured, and BMI was calculated as weight (kg)/the square of height (m^2). Sex, school grade, and parental smoking status and allergy history were obtained from the self-reported survey. Parental smoking status was classified as smokers and non-smokers, based on the presence of a smoking parent. Parents were asked if they had a medical diagnosis of allergic disease such as asthma, allergic rhinitis, or atopic dermatitis. Parental allergy history was categorized by the number of parents with allergic diseases: none (neither parent has allergic disease), single (one parent has allergic disease), and both (both parents have allergic disease). We also surveyed whether the children took allergy or cold medication within the 7 days prior to skin prick testing, because cold medication may contain antihistamines, which could affect the histamine skin reactivity.

2.4. Statistical analysis

Demographic data were presented as mean ± standard error (SE) for diameter of the histamine wheal, and as BMI according to study variables. The differences in histamine wheal sizes were compared using the Student's *t*-test and ANOVA test. Correlation between the diameter of the wheal and BMI was analyzed in 602 children (Model A) with Spearman's correlation test. Then, we analyzed the linear relationship between BMI and wheal size in 451 children (Model B), after excluding participants (151 children) who had taken cold medication. Finally, a linear regression analysis was used to show an independent effect in both Models A and B, after adjusting for confounding variables. SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses. A p-value <0.05 (two-tailed) was considered significant.

3. Results

Demographic data of the study population are presented in Table 1. Among these variables, the mean histamine wheal size was significantly larger in second grade students than in first grade students ($p = 0.003$). Moreover, histamine skin reactivity was significantly reduced due to cold medicines ($p = 0.008$). The mean histamine wheal size was larger for boys than for girls; however, this difference was not statistically significant. The mean histamine wheal sizes did not differ among children, when grouped by parental smoking status, parental allergy history, and allergic sensitization.

The linear relationship between BMI and histamine wheal size was analyzed in 602 children using Spearman's correlation test, which revealed a positive correlation between BMI and histamine

Table 1
Demographic data of study population.

Variables	*n*	Wheal size of histamine skin test (mm)[a]	*p*-value[b,c]	BMI (kg/m^2)[a]	*p*-value[b,c]
Sex					
Boy	320	3.86 ± 0.07	0.176	17.77 ± 0.15	0.375
Girl	282	3.99 ± 0.07		17.58 ± 0.16	
Grade					
1st	301	3.78 ± 0.06	**0.003**	17.20 ± 0.15	**<0.001**
2nd	301	4.06 ± 0.07		18.17 ± 0.16	
Parental smoking					
Non-smoker	255	3.93 ± 0.07	0.816	17.56 ± 0.17	0.334
Smoker	347	3.91 ± 0.06		17.77 ± 0.14	
Parental allergy history					
None	370	3.98 ± 0.06	0.272	17.70 ± 0.14	0.418
Single	185	3.83 ± 0.10		17.78 ± 0.18	
Both	47	3.81 ± 0.16		17.20 ± 0.43	
Cold medication					
No	151	3.70 ± 0.96	**0.008**	17.27 ± 0.21	**0.030**
Yes	451	3.99 ± 0.06		17.82 ± 0.13	
Allergic sensitization					
None	338	3.94 ± 0.68	0.898	17.46 ± 0.14	0.073
Mono-sensitization	83	3.91 ± 0.11		17.89 ± 0.28	
Poly-sensitization	181	3.89 ± 0.09		18.00 ± 0.22	

Abbreviation: BMI: body mass index.
[a] Values are presented as mean ± standard error.
[b] Student's *t*-test is used for binary variables, and ANOVA is was used for multiple variables.
[c] The χ^2 test was used for binary variables, and linear by linear by association test were used for multiple variables. Italic and bold value noted $p < 0.05$.