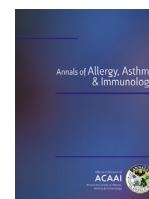




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Oxidative stress in schoolchildren with allergic rhinitis: propensity score matching case-control study

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ABSTRACT

Background: Oxidative stress is defined as an imbalance between the level of reactive oxygen species and antioxidant mechanisms. Compared with asthma, the role of oxidative stress in allergic rhinitis (AR) has received little attention.

Objective: To investigate the association between overall systemic oxidative stress and AR.

Methods: We used a propensity score matching case-control study and selected 90 children who had experienced AR in the previous year. This AR group was then matched with 90 healthy children who comprised the control group. Propensity score matching, a statistical matching technique that accounts for the conditional probability of receiving an exposure given a vector of measured covariates, is used to reduce selection bias and potential confounders in observational study. Serum total antioxidant status (TAS) and total oxidant status (TOS) levels were determined using a commercially available assay kit. Medical records and personal information were also reviewed.

Results: No statistically significant differences were found between patients with regard to age, sex, height, weight, educational level of parent, monthly household income, or distance of home from a main road. The mean TAS and TOS levels in the patient group were significantly higher than those of the control group ($P = .03$ and $.048$, respectively). The oxidative stress index, which is defined as the ratio of TOS to TAS, also increased in the AR group with statistical propensity ($P = .08$). In a multivariate logistic analysis, only TAS and TOS levels were significantly associated with increased risk of allergic rhinitis.

Conclusion: Patients with AR have systemically elevated oxidative stress and systemically elevated TAS levels.

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Introduction

Allergic rhinitis (AR) is the most common allergic disease, with a prevalence of 10% to 40%. It is now the most frequent chronic medical condition in the pediatric age group. During the past few decades there has been a 150% increase in the burden of atopic diseases in Western societies, and the prevalence of AR has also increased rapidly, especially among young persons.^{1–3} It is difficult to address this morbidity change because there are multiple factors involved. However, AR may be linked to changes in exposure to

antioxidants and oxidative stress, which are in turn due to changes in lifestyle and environmental exposure.

Oxidative stress may be defined as an imbalance between the level of reactive oxygen species (ROS) and the antioxidant mechanisms of the organism that detoxify these radicals. Under physiologic concentrations, ROS act as a signaling mediator in the maintenance of physiologic functions. However, higher levels of ROS may cause damage to all components of the cell.^{4,5} In this context, oxidative stress has been thought to be involved in a number of pathophysiologic conditions, including inflammation, obesity, neurodegenerative diseases, and cancer. Because of increased local oxidative burden in inhaled oxidants and systemic ROS generated by the inflammatory and structural cells of the airways, oxidative stress is now recognized as a major predisposing factor in the pathogenesis of asthma and chronic obstructive pulmonary disease.^{6–8}

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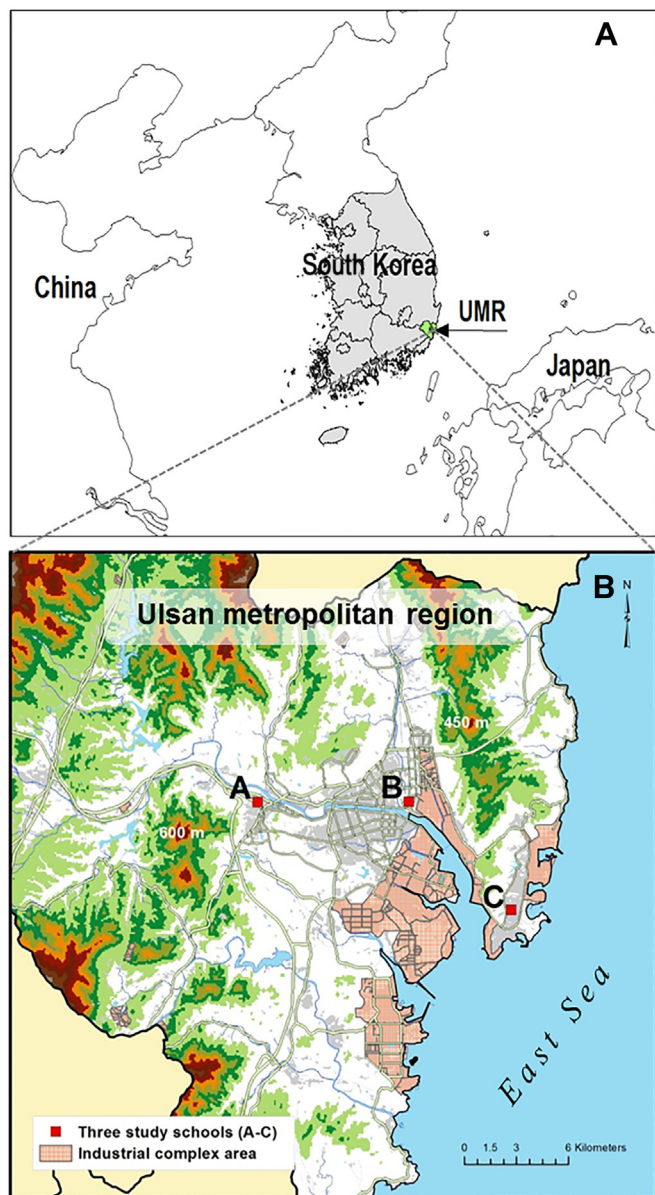


Figure 1. Locations of the 3 elementary schools included in this study. A, Map showing locations in the Ulsan Metropolitan Region (UMR), Republic of Korea. B, Geographical features of the UMR and the locations of the 3 elementary schools (A: suburban residential, B: near industrial, and C: coastal residential). Gray-shaded areas indicate urbanized area containing major roads.

Although asthma and AR have similar epidemiologic and immunopathological backgrounds, the role of oxidative stress in AR has received little attention. Several studies have found that molecular targets of oxidative stress in blood,^{9–11} nasal mucosa,¹² and exhaled breath condensate¹³ play a similar role in patients with AR and asthma. However, most of these studies failed to consider the overall oxidant and antioxidant status of the patients and only targeted a few individual oxidant or antioxidant markers.

The goal of the present study was to investigate the association between overall systemic oxidative stress and AR. Because the effects of individual antioxidants are additive and measurement of all individual antioxidants is almost impossible, we measured serum total antioxidant status (TAS) and total oxidant status (TOS), which reflect systemic overall antioxidation and oxidation states, respectively. We used a propensity score matching case control study to reduce selection bias and potential confounders.¹⁴ After selecting patients with a

1-year history of AR and a propensity score—matched healthy control group, we compared and analyzed the TAS level, TOS level, and oxidative stress index (OSI) between the patient level and control groups.

Methods

Study Participants

This study was conducted as a retrospective analysis of a prospective database in a single center. It was approved by the institutional review board of Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea. A large, school-based cohort allergy study was performed from 2009 to 2010 by the Ulsan University Hospital Environmental Health Center in Korea. The study participants were recruited from 3 elementary schools in areas exposed to different local environments (suburban residential, near industrial, and coastal residential areas) (Fig 1). The entire student body responded to a questionnaire and underwent routine medical checkups, including skin prick test and a blood test for total IgE level and eosinophil counts. The Korean version of the International Study of Asthma and Allergies in Childhood questionnaire was used in conjunction with another questionnaire.^{15,16} The parents or legal guardians of all participants provided written informed consent. On completion of the questionnaire, participants' blood serum and urine samples were frozen for further study.

Using propensity score matching under randomization, we selected 90 children who had experienced AR in the last year and 90 healthy children (the control group). The presence of AR was defined if a child's parents reported "yes" to the question, "Has your child been treated with AR by a doctor within the last 12 months?" Patients' medical records and personal information were reviewed. TAS and TOS were also measured from serum samples that were stored frozen. During a routine medical examination as part of this study, the skin prick test was performed to measure the responses to 18 allergens compared with a positive and a negative control. Positive reactions for each allergen were defined as a wheal diameter at least 3 mm greater than that of the negative control.

Propensity Score Matching Analysis

Propensity score matching is used to reduce selection bias and potential confounders in observational studies. Propensity score is the conditional probability of receiving an exposure given a vector of measured covariates.¹⁴ The matching process was conducted with a minimum distance scoring method and a 1-to-1 match between groups; this method consists of randomly ordering the case and control subjects. In the present study, this score was calculated using a multivariable logistic regression model that included covariates of age, school, sex, educational level of parent, monthly household income, birthplace, and distance of home from a main road. After selecting the first case patient and finding the control subject with the closest propensity score, both participants were removed from consideration for matching, and the next case patient was selected. Ultimately, 90 children with a history of AR in the previous year were individually matched to 90 healthy control children using nearest available score matching with SAS software, version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

TAS and TOS Measurements and OSI

Serum samples for the measurement of TAS and TOS were stored at -80°C until analysis. Serum TAS and TOS were measured with a commercially available assay kit (Rel Assay Diagnostics; Mega Tip, Gaziantep, Turkey) developed by Erel.^{17,18} The automated method for TAS measurements is based on the bleaching of characteristic color of a more stable ABTS (2,2'-azinobis[3-ethylbenzothiazoline-6-sulfonic acid]) radical cation by antioxidants. Antioxidants in the sample reduce dark blue-colored ABTS

Table 1
General population characteristics

Characteristic	Cases (n=90)	Controls (n=90)	P value ^a
Age, mean (SD), y	9.02 (1.27)	8.86 (1.31)	.39
Height, mean (SD), cm	135.98 (10.17)	135.81 (9.35)	.91
Weight, mean (SD), kg	34.39 (9.92)	34.23 (8.90)	.91
Ln EOS, mean (SD), / μ L	1.31 (0.89)	0.96 (0.79)	.007
Ln total IgE, mean (SD), IU/L	5.27 (1.35)	4.56 (1.57)	.001
School, No. (%)			.02
A	28 (31.1)	36 (40.0)	
B	55 (61.1)	54 (60.0)	
C	7 (7.8)	0	
Grade, No. (%)			.84
First-third	59 (65.6)	63 (70.0)	
Fourth-sixth	31 (34.4)	27 (30.0)	
Sex, No. (%)			.30
Male	39 (43.3)	46 (51.1)	
Female	51 (56.7)	44 (48.9)	
Father's educational level, No. (%)			.48
High school or less	35 (38.9)	34 (37.8)	
University	26 (28.9)	29 (32.2)	
Greater than university	29 (32.2)	25 (27.8)	
Other	0	2 (2.2)	
Mother's educational level, No. (%)			.88
High school or less	38 (42.2)	39 (43.3)	
University	27 (30.0)	28 (31.1)	
Greater than university	23 (25.6)	21 (23.3)	
Other	2 (2.2)	2 (2.2)	
Monthly household income, US\$, No. (%)			.89
<2000	5 (5.6)	4 (4.4)	
2000–3000	40 (44.4)	45 (50.0)	
3000–4000	29 (32.2)	28 (31.1)	
>4000	16 (17.8)	13 (14.4)	
Birthplace, No. (%)			.53
Ulsan	75 (83.3)	78 (86.7)	
Outside Ulsan	15 (16.7)	12 (13.3)	
House distance from main road, m, No. (%)			.39
Besides	18 (20.0)	9 (10.0)	
Within 50	16 (17.8)	19 (21.1)	
Within 100	31 (34.4)	30 (33.3)	
Within 200	22 (24.4)	28 (31.1)	
Within 300	3 (3.3)	4 (4.4)	

Abbreviations: Ln, natural log; Eos, blood eosinophil.

^aCalculated by the *t* test or χ^2 test.

radical to a colorless reduced ABTS form. The change in absorbance at 660 nm is related to the TAS of the sample. The assay is calibrated with a stable antioxidant standard solution, which is traditionally called Trolox equivalent and is a vitamin E analog. The results were expressed as millimoles of Trolox equivalent per liter. Color intensity, which can be measured spectrophotometrically for TOS measurements, is related to the total amount of oxidant molecules in the sample. That is, oxidants present in the sample oxidize the ferrous ion-chelator complex to ferric ion. This oxidation reaction is enhanced by abundant glycerol molecules in the reaction medium. The ferric ion forms a colored complex with xylenol orange in an acidic medium. The assay is calibrated with hydrogen peroxide, and the results are expressed in terms of micromoles of hydrogen peroxide equivalent per liter. The OSI was defined as the ratio of TOS to TAS and was calculated as follows: OSI (arbitrary unit) = (TOS, μ mol H₂O₂ Eq/L)/(TAS, mmol Trolox Eq/L). This is often used to quantify the net oxidative stress in the body.

Statistical Analysis

Demographic data and matched variables were compared between case and control groups using the *t* test and χ^2 test for categorical and continuous variables, respectively. Total serum IgE level, eosinophil count, TAS, and TOS were logarithmically transformed for statistical analyses. Differences in mean concentrations

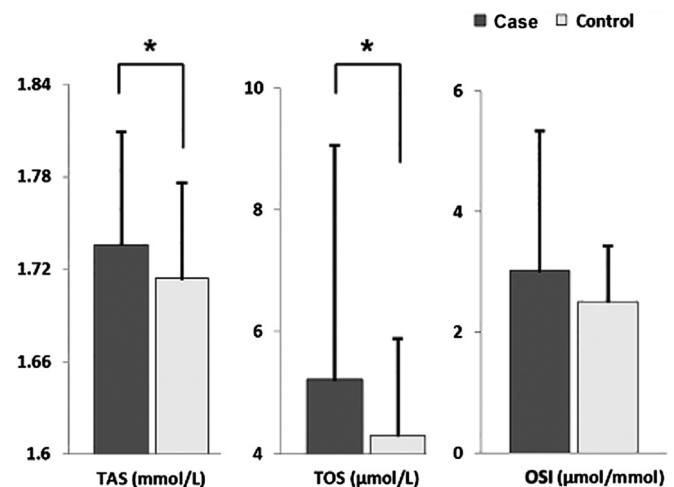


Figure 2. Comparisons of mean concentrations of total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI) between the patient and control groups. **P* < .05.

of TAS and TOS according to matched variables were analyzed by the paired *t* test. The associations between 1-year history of AR treatment and biological indicators (total serum IgE level, eosinophil count, TAS, TOS, and allergic sensitization) were examined using multivariate logistic regression models adjusted for school, grade, sex, parent's educational level, family income, birthplace, and distance of home from a main road. After adjusting for other variables, an adjusted odds ratio (aOR) was calculated with a 95% CI. The statistical significance level was set to *P* < .05. All statistical analyses were performed using Excel 2010 (Microsoft Inc, Redmond, Washington) and SPSS software, version 21 (IBM Corp, Armonk, New York).

Results

Characteristics of the Study Participants

A total of 180 children were included in this analysis. The mean (SD) age was 8.96 (1.32) years (range, 6–13 years). The mean (SD) height was 135.90 (9.74) cm (range, 112.8–163.5 cm), and the mean (SD) weight was 34.31 (9.40) kg (range, 19.1–84.0 kg). As expected, significant differences were found in serum total IgE level and eosinophil count. No significant differences were found with regard to age, sex, height, weight, educational level of parent, monthly household income, or house distance from main road (Table 1).

Comparison of TAS, TOS, and OSI

The overall mean (SD) TAS level was 1.73 (0.07) mmol/L (range, 1.52–1.96), and the overall mean (SD) TOS level was 4.76 (2.97) μ mol/L (range, 2.00–31.90). In the case group, the mean (SD) TAS and TOS levels were 1.74 (0.07) mmol/L (range, 1.59–1.96) and 5.21 (3.84) μ mol/L (range, 2.40–31.90), respectively. In the control group, the mean (SD) TAS and TOS levels were 1.71 (0.06) mmol/L (range, 1.52–1.85) and 4.30 (1.59) μ mol/L (range, 2.00–12.60), respectively. Both mean TAS and TOS levels in the case group were significantly higher than those of the control group (*P* = .03 and .048, respectively). The OSI, which is defined as the ratio of TOS to TAS, increased in the AR group with statistical propensity (*P* = .08) (Fig 2).

Associations Between 1-Year History of AR and Clinical Variables

A binominal logistic regression was conducted with each clinical variable to examine the associations between 1-year history of AR

Table 2

Summary of logistic regression of 1-year history of allergic rhinitis and related variables

Variable	Adjusted OR ^a (95% CI)	P value
TAS, mmol/L	1.007 (1.001–1.012)	.02
TOS, μ mol/L	1.176 (1.007–1.373)	.04
Eosinophils, / μ L	1.012 (0.904–1.134)	.83
Total IgE, IU/L	1.001 (0.999–1.002)	.34
SPT positivity	2.152 (0.916–5.057)	.08

Abbreviations: CI, confidence interval; OR, odds ratio; SPT, skin prick test; TAS, total antioxidant status; TOS, total oxidant status.

^aAdjusted by school, grade, sex, parent's educational level, family income, birthplace, and house distance from main road.

and risk factors. Univariate analysis revealed that 1-year history of AR was correlated with serum total IgE level, eosinophil count, skin test positivity, and TAS and TOS levels. Risk factors for AR were determined with a multivariate logistic regression analysis using variables that were statistically significant in the univariate analysis. After adjusting for age, sex, educational level of parent, monthly household income, birthplace, and house distance from main road, only TAS and TOS levels were found to be significantly associated with increased risk of allergic rhinitis (TAS: aOR, 1.007; 95% CI, 1.001–1.012; TOS: aOR, 1.176; 95% CI, 1.007–1.373) (Table 2).

Discussion

ROS are byproducts of aerobic metabolism. Three of the most common and biologically important ROS are superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH\cdot$). All have inherent chemical reactivity to different biological targets. Both exogenous (eg, pollutants, tobacco, drugs, radiation) and endogenous (eg, mitochondrial electron transport chain, endoplasmic reticulum, NADPH oxidase complex) sources contribute to intracellular ROS level. Cellular ROS accumulation is controlled by a variety of endogenous antioxidant defense systems, divided into 2 categories: enzymatic and nonenzymatic. The most representative enzymatic antioxidants are superoxide dismutase, catalase, and glutathione peroxidase. Nonenzymatic antioxidants are albumin, ceruloplasmin, ferritin, and an array of small molecules, including vitamin C (ascorbic acid), vitamin E (α -tocopherol), and carotenoids (β -carotene). During the past 2 decades, it has been established that ROS are not only molecules that invoke damage (ie, oxidative stress) but also regulating molecules in normal physiologic and biological signaling pathways (ie, redox biology).^{19,20}

There is an increasing body of evidence that ROS play a critical role in the pathogenesis of many diseases. In terms of inflammation regulation, ROS are essential second messengers in immune cells and act as proinflammatory cytokines during an appropriate immune response. Several studies have found that a decreasing ROS level inhibits proper immune responses, leading to immunosuppression, whereas an elevated level increases the release of proinflammatory cytokines and proliferation of specific subsets of adaptive immune cells, contributing to autoimmunity.^{4–6} During the T_H1 -type cellular immune response, release of interferon γ (the most important stimulator of ROS formation) can elicit ROS production, which, in a vicious cycle, accelerates the T_H1 -type immune response in an autocrine way via nuclear factor- κ B (redox-sensitive signal transduction elements) and tumor necrosis factor α (proinflammatory cytokine). This continued immune activation will increase the inflammatory process, which may initiate a chronic inflammatory disease.^{21,22}

In summary, our results indicate that both serum TAS and TOS levels are significantly higher in the AR group compared with a control group. OSI, which is a more objective evaluation of oxidative stress conditions compared with separately evaluating the TAS

and TOS, indicated the exact degrees of imbalance of oxidative stress toward the oxidant status. In this study, serum TAS and TOS reflect the global effect of all molecules involved in oxidative stress. Therefore, higher serum TOS and OSI in the AR group suggest systemic oxidative stress in children with AR. These results combined with those of previous studies reporting high oxidative stress in the airway^{11,13} indicate that oxidative stress is increased in patients with AR not only in the airway but also in circulation. A recent study of asthmatic patients reported a spillover of ROS produced in response to various allergic stimuli from the lung to the systemic circulation and similar correlations between blood and lung oxidant and antioxidant parameters.²³ Thus, the systemic circulation probably reflects an oxidant-antioxidant imbalance in the nasal cavity of patients with AR.

Intriguingly, systemic TAS levels in this study were significantly elevated, which differs from most previous studies that observed a low level of antioxidants at the site of inflammation, likely because the elevated oxidant level wiped out the antioxidant. Only one previous study reported results similar to ours, in which the investigators found that children with AR had higher serum TAS and TOS levels than children without AR.¹⁰ This finding might be regarded as an adaptive response to the associated systemic oxidative stress because an increased level of glutathione has been observed in lung samples of patients with asthma.⁸ An elevated systemic TAS level suggests that supplementation of extra-exogenous antioxidants might not have an additional benefit. This finding may explain the results of the following previous studies. First, numerous clinical trials that used antioxidants as a new treatment modality have not been successful until now because no clinical studies have found that antioxidant treatment alone is beneficial.⁷ Second, excess intake of antioxidants may increase susceptibility to allergic disease by slowing the T_H1 -type immune response and thereby favoring the T_H2 -type cell response.²⁴ Third, large clinical trials of antioxidant vitamin supplementation to prevent cancer and cardiovascular diseases found that there is insufficient evidence to assess the benefits and harms of multivitamins for the prevention of cardiovascular disease or cancer in the general adult population.²⁵

Further study is required to obtain an in-depth understanding of the mechanism of systemically elevated oxidative stress and TAS level in patients with AR and how to apply these results to the treatment of AR. One strength of the current study is that it included an epidemiologic investigation in which almost all possible environmental factors were taken into consideration, and a propensity score matching case-control study was used to elucidate the results. To the best of our knowledge, propensity score matching is the best way to overcome selection bias and confounding factors in observation studies because baseline covariates between the 2 study groups are balanced during study design.¹⁴

This study has some limitations, namely, that the sample size was relatively small and the design was retrospective. One major limitation is that treatment of AR might affect the result of this study. Previous studies found that antihistamine caused an increase in total antioxidant status, but the finding was not statistically significant,²⁶ and steroids reduced oxidative stress in animal model of asthma by a rapid nongenomic mechanism.²⁷ More studies are necessary to determine the role of certain medication in systemic oxidative stress. Despite these shortcomings, this study provides meaningful information about systemic oxidative stress status in children with AR.

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