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Brief Communication

Serum Periostin Is Negatively Correlated With Exposure to Formaldehyde and Volatile Organic Compounds in Children

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ABSTRACT

Epidemiological studies have shown that exposure to tobacco smoke causing irritation and inflammation in the airways tends to reduce serum periostin concentrations in adults. We now investigate prospective cross-sectional study on 135 Korean students aged 7 years in the first grade who were participating in the Seongnam Atopy Project for Children's Happiness 2016 (SAP_{2016}) cohort. To the best of our knowledge, this is the first study to show significant inverse correlations between serum periostin concentration and exposure to xylene and formaldehyde in children. Our findings suggested the need for caution in using the serum periostin level as a marker for allergic diseases, since exposure to volatile organic compounds and formaldehyde may confound the interpretation of these results.

Keywords: Periostin; volatile organic compounds; formaldehyde; children

INTRODUCTION

Periostin, a recently characterized extracellular matrix protein belonging to the fasciclin family, has been shown to be a critical mediator of the amplification and persistence of allergic inflammation in the remodeling process during tissue development or repair.[1] Periostin, which acts downstream of interleukin (IL)-4 and IL-13, has served as a novel diagnostic biomarker and a therapeutic target for allergic disorders.[1-3] Epidemiological studies have shown that exposure to tobacco smoke causing irritation and inflammation in the airways tends to reduce serum periostin concentrations in adults.[2,3]

Similar to exposure to tobacco smoke, exposure to volatile organic compounds (VOCs), including aromatics such as benzene, xylene and styrene, as well as formaldehyde causes airway irritation, increases allergic inflammation, thus exacerbating the risk of allergic diseases.[4] We hypothesized that exposure to VOCs may also reduce circulating serum

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periostin levels. We therefore measured serum concentrations of periostin in 7-year-old children exposed to VOCs such as aromatics and formaldehyde.

MATERIALS AND METHODS

This prospective cross-sectional study involved the general population attending 11 randomly selected elementary schools in Seongnam City, Republic of Korea between January and December 2016. Students in the first grade, aged 7 years, who were participating in the Seongnam Atopy Project for Children's Happiness (SAP_{2016}) cohort performed by the Seongnam City Government for the prevention and education of allergic diseases in Korean children, were recruited.[5] Demographic characteristics and details of allergic diseases were obtained from questionnaires designed according to the International Study of Asthma and Allergies in Childhood (ISAAC).[6-8] Atopic dermatitis (AD), allergic rhinitis (AR) and asthma were defined by characteristic symptoms within 12 months based on the ISSAC questionnaire.[6-8]

Blood and urine samples were obtained from participants. Serum periostin concentrations were measured using a proprietary sandwich enzyme-linked immunosorbent assay (ELISA; Shino-test, Kanagawa, Japan), which utilized antiperiostin antibodies (clones SS18A and SS17B).[9,10] Urine concentrations of the 7 urinary metabolites VOCs, including benzene, toluene, xylene, styrene, as well as formaldehyde, were measured using gas chromatography/tandem mass spectroscopy.[11,12] Urinary metabolites of benzene and xylene consisted of trans,trans-muconic acid (t,t-MA), and o-toluic acid and p-toluic acid, respectively. Urinary metabolites of styrene consisted of mandelic acid (MA) and phenylglyoxylic acid (PGA), and the urinary metabolite of formaldehyde consisted of thiazolidine-4-carboxylic acid (TZCA). Urinary concentrations of these compounds were adjusted based on urinary creatinine concentrations.

The study protocol was approved by the appropriate Institutional Review Board of CHA University (2016-04-031), and written informed consent was obtained from the parents or guardians of children participating in this study. Values are reported as geometric mean (GM) ± geometric standard deviation (GSD). Data were analyzed using Student's *t* test, the one-way analysis of variance on multiple variables and multiple linear regression with SPSS version 23.0 (IBM Co., Armonk, NY, USA). Multiple linear regression models were used to show beta coefficients (B) and standard error (SE) adjusted for sex, age, BMI *z* score and allergic diseases including AD, AR and asthma. A *P* value of <0.05 was considered statistically significant.

RESULTS

A total of 328 children were enrolled in the SAP_{2016} cohort group, 135 (41.2%) of whom met the study criteria by completing the blood (missing blood test, n = 37) and urine sampling (missing urine test, n = 178). The 135 participants included 81 (60.0%) boys and 54 (40.0%) girls of mean age 6.7 ± 0.5 years; and mean BMI *z* score 0.012 ± 1.045. Of these 135 subjects, 12 (8.9%) had asthma, 69 (51.1%) had AR, and 42 (31.1%) had AD. The GM urinary concentrations of the VOC metabolites t,t-MA, o-toluic acid, p-toluic acid, MA, PGA, and TZCA were 24.79 ± 2.98 μg/g creatinine, 214.68 ± 3.19 μg/g creatinine, 30.19 ± 2.38 μg/g creatinine, 164.89 ± 2.04 μg/g creatinine, 249.00 ± 3.00 μg/g creatinine, and 95.26 ± 2.28 μg/g creatinine, respectively, while the GM serum concentration of periostin was 109.24 ± 1.26 ng/mL. Serum periostin levels and urinary VOC metabolite concentrations

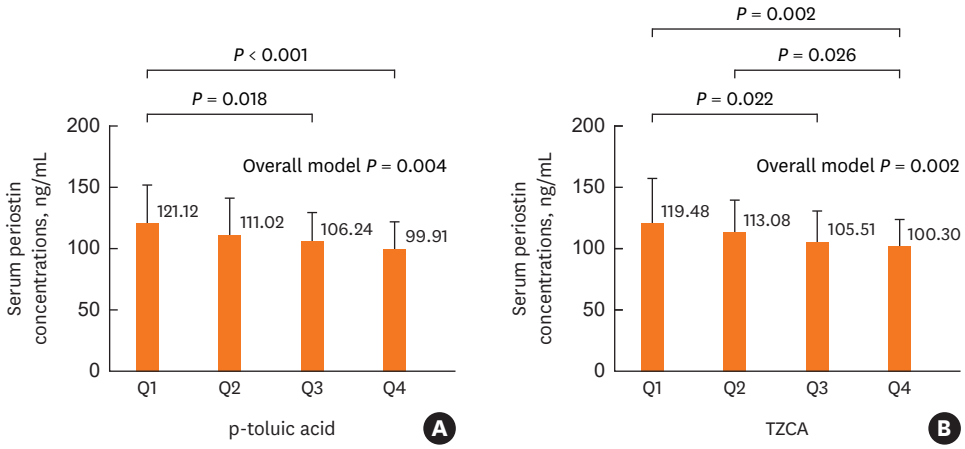

Figure. Associations between serum periostin concentrations and quarter of urinary concentrations of (A) p-toluic acid and (B) TZCA in 7-year-old children (n = 135). Data are presented as GMs with GSD (T bars).
GM, geometric mean; GSD, geometric standard deviation; TZCA, thiazolidine-4-carboxylic acid.

did not differ significantly among subjects with and without asthma, AR and AD. Serum periostin concentrations showed significant inverse associations with urinary p-toluic acid and TZCA (**Figure**). In contrast, serum periostin concentrations did not associated with quarter ofurinary concentrations of t,t-MA, o-toluic acid, MA or PGA. After adjustment for confounding factors (sex, age, BMI *z* score and allergic diseases including AD, AR and asthma), multiple linear regression analysis showed that serum periostin concentration was significantly associated with urinary concentrations of p-toluic acid (B = −7.574; SE = 2.028; $P < 0.001$) and TZCA (B = −6.787; SE = 2.080; $P = 0.001$) (**Table**).

DISCUSSION

To the best of our knowledge, this is the first study to show significant inverse correlations between serum periostin concentration and exposure to xylene and formaldehyde in 7-year-old children. Similar to epidemiological reports showing a correlation between tobacco smoking and decreased serum periostin level in adults,[2,3] exposure to xylene and formaldehyde was negatively correlated with serum periostin level in children. Although serum periostin concentration is regarded as a diagnostic marker to establish therapeutic target levels for allergic diseases,[1,13,14] our findings suggested the need for caution in using serum periostin level as a marker for allergic diseases, since exposure to VOCs and formaldehyde may confound the interpretation of these results.

Serum periostin concentration has been regarded as a biomarker for Th2-high phenotype in patients with asthma and a predictor of eosinophilic airway inflammation.[15,16] Because exposure to tobacco smoke has been associated with non-eosinophilic airway inflammation and/or a Th2-low phenotype among asthmatic patients, smokers with non-eosinophilic airway inflammation and/or a Th2-low phenotype asthma had lower serum periostin levels.[3] Our results are consistent with those from studies showing that serum periostin levels negatively correlated with xylene and formaldehyde that included in tobacco.[2,3]

The mechanisms underlying the inverse correlations between exposure to VOCs and serum periostin level remain unclear. Short-term exposure to cigarette smoke has been found to

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Table. Multiple linear regression models showing the correlations of urinary metabolites of VOCs and formaldehyde with serum concentrations of periostin in 7-year-old children (n = 135)

VOCs and formaldehyde	Quarter of urinary metabolites (μg/g creatinine)		Serum periostin (ng/mL)				
			GM (GSD)	Model	B	SE	*P* value
Benzene	t,t-MA	Q1	105.49 (1.27)	Crude	−1.294	3.000	0.668
		Q2	104.88 (1.21)	Adjusted	−0.863	3.401	0.801
		Q3	111.74 (1.29)				
		Q4	99.47 (1.21)				
Xylene	o-toluic acid	Q1	105.61 (1.30)	Crude	−0.166	2.086	0.937
		Q2	114.92 (1.25)	Adjusted	−0.638	2.106	0.762
		Q3	108.39 (1.24)				
		Q4	108.47 (1.25)				
	p-toluic acid	Q1	**121.12 (1.28)**	Crude	**−7.431**	**1.971**	**< 0.001**
		Q2	**111.02 (1.27)**	Adjusted	**−7.710**	**2.042**	**< 0.001**
		Q3	**106.24 (1.22)**				
		Q4	**99.91 (1.22)**				
Styrene	MA	Q1	114.82 (1.32)	Crude	−0.992	2.085	0.635
		Q2	103.16 (1.24)	Adjusted	−1.180	2.164	0.587
		Q3	107.40 (1.21)				
		Q4	112.23 (1.24)				
	PGA	Q1	104.35 (1.31)	Crude	0.966	2.085	0.644
		Q2	110.94 (1.27)	Adjusted	1.367	2.134	0.523
		Q3	112.69 (1.23)				
		Q4	109.29 (1.22)				
Formaldehyde	TZCA	Q1	**119.48 (1.31)**	Crude	**−7.185**	**1.978**	**< 0.001**
		Q2	**113.08 (1.23)**	Adjusted	**−7.018**	**2.085**	**< 0.001**
		Q3	**105.51 (1.23)**				
		Q4	**100.30 (1.22)**				

Risk factors were adjusted for sex, age, BMI *z* score and presence of allergic diseases including AD, AR and asthma. Numbers in bold indicate significant associations between serum periostin concentration and urinary concentrations of metabolites of VOCs and formaldehyde ($P < 0.05$).
B, beta coefficients; GM, geometric mean; GSD, geometric standard deviation; MA, mandelic acid; PGA, phenylglyoxylic acid; SE, standard error; t,t-MA, trans,trans-muconic acid; TZCA, thiazolidine-4-carboxylic acid; VOCs, volatile organic compounds.

induce a Th2 inflammatory response, increasing the concentration of IL-13 and differentially affecting the IL-13-induced expression profile, including the marked down-regulation of periostin (*POSTN*) gene expression, as in Th2-high phenotype asthma.[17] In addition, an epidemiological study showed that chronic exposure to high levels of VOCs was significantly associated with reduced serum IL-13 concentrations.[18]

This study had several limitations. We were unable to demonstrate inverse correlations between exposure to benzene, toluene and styrene and serum periostin concentrations. In addition, we did not analyze immunological factors such as IL-13 concentration or genetic factors, including expression of the *POSTN* gene. Large-scale studies are needed to assess these factors in children.

In conclusion, our findings suggest that in 7-year-old children, serum periostin concentrations correlated negatively with exposure to xylene and formaldehyde. Measurements of serum periostin levels should be interpreted with caution in patients with allergic disorders. Moreover, our results provide novel insights into interactions of aromatic VOCs and formaldehyde with serum periostin, interactions reflecting Th2-associated inflammation.

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