

No Association between Serum Vitamin D Status and the Prevalence of Allergic Diseases in Japanese Children

Yasunori Ito^a Yuichi Adachi^a Koichi Yoshida^b Akira Akasawa^b

^aDepartment of Pediatrics, Faculty of Medicine, University of Toyama, Toyama, and ^bDivision of Allergy, Tokyo Metropolitan Children's Hospital, Tokyo, Japan

Dear Sir,

There has been accumulating evidence indicating that an adequate concentration of vitamin D is protective against allergic diseases in children [1, 2]. However, most of these findings have been reported from North America and European countries, and there are only a few studies from other regions of the world, including Asia. The article by Bener et al. [3] demonstrated that vitamin D deficiency was the major predictor of asthma in Qatari children. The authors measured serum vitamin D levels in 483 children with asthma and 483 healthy nonasthmatic children and showed that asthmatic children had significantly lower vitamin D levels compared with nonasthmatic children, supporting the hypothesis that there is a strong association between vitamin D deficiency and asthma risk. Although their study was the first epidemiological study on this association in the Middle East, there have been a few studies evaluating this association in East Asia. Recently we conducted a population-based study in Japanese children and found that there was no relationship between serum vitamin D and the prevalence of allergic diseases.

We performed a cross-sectional study in 4th grade elementary students (9–10 years old) in Toyama, Japan, from June through July 2011. To recruit approximately one third of the same-age children in the city, 14 schools were randomly selected out of 65 schools. All of the eligible children (n = 1,193) in these selected schools were asked to participate in this study. The survey used a Japanese version of the ISAAC questionnaire, which was distributed through teachers of the participating schools and completed by the parents. The questionnaire included questions regarding backgrounds, such as gender, parental history of asthma, parental smoking, and early entrance to kindergarten (<1 year old). Blood samples were collected, body size (height and weight) was measured by nurses at the school, and the serum 25 OH vitamin D₃ concentration was quantified using a radioimmunoassay. Vitamin D deficiency was defined as a serum level <20 ng/ml, and insufficiency was defined as a serum level of 20–29 ng/ml [2]. This study protocol was approved by the institutional review board (IRB) of the University of Toyama, and the parents and children gave their written in-

formed consent to be enrolled into the study.

Of the 1,193 children enrolled, 23 parents declined to participate. After omitting 7 children from whom a sufficient blood volume could not be obtained and 48 children whose questionnaire was not adequately completed, 1,115 children were analyzed. Among these children, the prevalence of current asthma, rhinoconjunctivitis, eczema, and any of these diseases was 10.2, 19.4, 14.7, and 36.4%, respectively (table 1). More than 60% of the children had insufficient or deficient vitamin D levels, and the prevalence of normal vitamin D levels was significantly lower in girls compared to boys, suggesting that boys might play outside more often than girls do. Multivariate analysis showed that there was no association between serum vitamin D status and the prevalence of allergic diseases, even after adjusting for confounding factors, such as gender, obesity (BMI ≥95th percentile), parental history of asthma, parental smoking, pet owning, and early entrance to kindergarten (<1 year old) (table 2).

There is extensive evidence showing that vitamin D has potent immunomodulatory effects.

Table 1. Baseline characteristics of the study participants

	Total (n = 1,115)	Boys (n = 564)	Girls (n = 551)	p value ^a
Current allergic diseases				
Asthma, n (%)	114 (10.2)	55 (9.8)	59 (10.7)	0.334
Rhinoconjunctivitis, n (%)	216 (19.4)	111 (19.7)	105 (19.1)	0.426
Eczema, n (%)	164 (14.7)	81 (14.4)	83 (15.1)	0.403
Any diseases, n (%)	406 (36.4)	210 (37.2)	196 (35.6)	0.303
Obesity				
BMI ≥95th percentile, n (%)	98 (8.8)	48 (8.5)	50 (9.1)	0.752
Serum vitamin D, ng/ml				
Deficiency (<20)	109 (9.8)	47 (8.3)	62 (11.3)	<0.001
Insufficiency (20–29)	563 (50.5)	255 (45.2)	308 (59.0)	
Sufficiency (≥30)	443 (37.7)	262 (46.5)	181 (32.8)	

^a χ^2 analysis for evaluating gender differences.

Table 2. Association between vitamin D status and the prevalence of allergy diseases

25 OH vitamin D ₃ ng/ml	Current asthma			Current rhinoconjunctivitis			Current eczema			Any allergy diseases		
	n (%)	adjust- ed OR*	95% CI	n (%)	adjust- ed OR*	95% CI	n (%)	adjust- ed OR*	95% CI	n (%)	adjust- ed OR*	95% CI
<20 (n = 109)	10 (9.2)	1.06	0.51–2.21	21 (19.3)	0.85	0.48–1.50	16 (14.8)	0.84	0.46–1.55	35 (32.1)	0.73	0.46–1.18
≥20 to <30 (n = 563)	63 (11.2)	1.22	0.80–1.88	101 (17.9)	0.80	0.58–1.12	78 (13.9)	0.83	0.58–1.20	202 (35.9)	0.93	0.71–1.22
≥30 (n = 443)	41 (9.3)	1		94 (21.2)	1		70 (15.8)	1		169 (38.1)	1	

OR = Odds ratio; CI = confidence interval. ORs were determined for each 25 OH vitamin D₃ category with respect to the reference group (≥30 ng/ml).

* Adjusted for gender, obesity (dichotomous, BMI ≥95th percentile), parental history of asthma, parental smoking, pet owning, and early kindergarten (dichotomous, before age 1 year).

latory properties, and its deficiency is associated with many chronic illnesses, including cancer and autoimmune, infectious, cardiovascular, and allergic diseases [4]. Many epidemiological studies, including the study of Bener et al. [3], support this association. However, we could not find an association between vitamin D insufficiency and allergic diseases, even after adjusting for several confounding factors. Although this study was performed during the summer season in Toyama, located at 36° N, vitamin D insufficiency was found in more than 60% of the children, with similar rates reported in the USA and Europe [5]. Consistent with our results, Deverux et al. [6] showed that there was no difference in serum vitamin D levels between adult asthma patients and age- and gender-matched control subjects in the

UK. Hollams et al. [7] showed that there was no significant cross-sectional association between serum vitamin D levels and current asthma in 6- or 14-year-old children in the UK. Our results cannot exclude a role of vitamin D earlier in life. A prospective study showed that higher maternal vitamin D intake during pregnancy decreased the risks for asthma and allergic rhinitis in offspring at the age of 5 years, although maternal serum levels of vitamin D were not measured [8]. Another cohort study revealed that low vitamin D levels at 6 years of age were associated with asthma at 14 years of age in boys [7]. Apart from serum vitamin D levels, vitamin D receptor gene polymorphisms might be associated with allergic diseases [9]. Further studies will be needed to provide a clear answer to the hypothesis that vitamin D

could have a role in preventing the development and reducing the morbidity of allergic diseases.

Acknowledgments

We thank Dr. Kumiko Kanatani from the Department of Health Informatics, Kyoto University School of Public Health, for consultation regarding statistical analysis. This study was supported by a grant from the Japanese Ministry of Health, Labor, and Welfare to the Japanese Asthma Survey Group.

References

- 1 Paul G, Brehm JM, Alcorn JF, Holguin F, Auja SJ, Celedon JC: Vitamin D and asthma. *Am J Respir Crit Care Med* 2012;185:124–132.
- 2 Bozzetto S, Carraro S, Giordano G, Boner A, Baraldi E: Asthma, allergy and respiratory infections: the vitamin D hypothesis. *Allergy* 2012;67:10–17.
- 3 Bener A, Ehlayel MS, Tulic MK, Hamid Q: Vitamin D deficiency as a strong predictor of asthma in children. *Int Arch Allergy Immunol* 2012;157:168–175.
- 4 Holick MF: Vitamin D deficiency. *N Engl J Med* 2007;357:266–281.
- 5 Lips P: Worldwide status of vitamin D nutrition. *J Steroid Biochem Mol Biol* 2010;121:297–300.
- 6 Devereux G, Wilson A, Avenell A, McNeill G, Fraser WD: A case-control study of vitamin D status and asthma in adults. *Allergy* 2010;65:666–667.
- 7 Hollams EM, Hart PH, Holt BJ, Serralha M, Parsons F, de Klerk NH, Zhang G, Sly PD, Holt PG: Vitamin D and atopy and asthma phenotypes in children: a longitudinal cohort study. *Eur Respir J* 2011;38:1320–1327.
- 8 Erkkola M, Kaila M, Nwaru BI, Kronberg-Kippila C, Ahonen S, Nevalainen J, Veijola R, Pekkanen J, Ilonen J, Simell O, Knip M, Virtanen SM: Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clin Exp Allergy* 2009;39:875–882.
- 9 Raby BA, Lazarus R, Silverman EK, Lake S, Lange C, Wjst M, Weiss ST: Association of vitamin D receptor gene polymorphisms with childhood and adult asthma. *Am J Respir Crit Care Med* 2004;170:1057–1065.