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Ovomucoid-specific IgG4 level in cord blood associates negatively with later sensitization

To the Editor

Hen's egg is one of the most common causes of food allergy during infancy in many countries.¹ Ovomucoid (OVM) is a major component of egg white (EW) protein and resistant to heat. Thus, it is thought that OVM consumed in daily meals is the major factor that elicits egg allergy.²

Allergen-specific IgE plays an important role in the development of food allergy. However, a protective role for allergen-specific IgG4 against food allergy was suggested by previous studies of oral immunotherapy.^{3,4} Additionally, in hen's egg allergy, EW-specific IgG4 was increased in the intaking egg protein group but not in the avoidance group in a study of hen's egg oral immunotherapy.⁴ Moreover, a recent study suggested that having more antigen-specific IgG antibodies is negatively associated with sensitization to each antigen in later life.⁵ These reports suggest that EW-specific IgG prevents sensitization to EW.

EW- and OVM-specific IgG subclasses and IgE exist in cord blood (CB). Therefore, it is considered that these specific antibodies in CB influence sensitization in early life. However, we have little knowledge about the association between hen's egg-specific IgG subclass levels in CB and sensitization to hen's egg allergens in early life, which is the most critical period for developing an allergy. Therefore, the present study aimed to analyze the relationship between EW- and OVM-specific IgG subclasses in CB and sensitization to these components at 6 months of age (6M).

This study is a post hoc analysis from our previous birth cohort study.⁶ This study included 72 paired samples from which we could obtain both CB and sera from infants at 6M. We measured EW- and

OVM-specific IgE and IgG subclass levels by using the densely carboxylated protein (DCP) chip.⁶ Sensitization to EW and OVM at 6M was defined as specific IgE level of ≥ 0.35 kU/L by using the ImmunoCAP system (Thermo Fisher Scientific). Statistical analyses were carried out using Prism 6.0 for Windows (GraphPad Software, Inc). *P*-values $< .05$ were considered significant in all analyses.

We did not have sufficient serum volume for two samples to measure OVM-specific IgE level at 6M and one sample to measure EW-specific IgE level at 6M by the ImmunoCAP system. We therefore analyzed 70 infants for OVM-specific immunoglobulins and 71 infants for EW. Seven infants (10%) had OVM sensitization, and 27 infants (38%) exhibited EW sensitization at 6M. Subject characteristics in the OVM sensitization group are shown in Table 1. Infants in the OVM sensitization group had higher total IgE level at 6M compared to the non-sensitization group. However, sex, gestational age, mother's allergy history, feeding type, and eczema until 6M showed no significant difference between the two groups. Total IgE level was significantly higher in infants of the sensitization group compared with that in infants in the non-sensitization group (median [first quartile-third quartile] 16.1 [9.7-55.5] IU/mL vs. 5.9 [2.9-13.4] IU/mL, *P* = .03), primarily because the sensitization group contained more infants with eczema. This trend was more pronounced for EW. In addition, the EW sensitization group had significantly more infants with eczema and higher total IgE level than the non-sensitization group (data not shown).

We next compared OVM-specific IgG subclass levels in CB between OVM sensitization and non-sensitization groups (Figure 1).

TABLE 1 Characteristics of infants analyzed for ovomucoid-specific IgE

	Sensitization	Non-sensitization	P value
No. (N = 70)	7	63	
Male	6 (86%)	32 (51%)	.11
Gestational age, d	277 ± 3	274 ± 0.9	.34
Mother's history			
Atopic dermatitis	1 (14%)	14 (22%)	N/A
Asthma	1 (14%)	9 (14%)	N/A
Allergic rhinitis	1 (14%)	28 (44%)	.13
Food allergy	2 (29%)	7 (11%)	.24
Hen's egg allergy in pregnancy	0 (0%)	0 (0%)	N/A
Feeding type until 6 mo of age			
Breastmilk	4 (57%)	22 (35%)	.43
Mixed milk	3 (43%)	35 (56%)	
Formula milk	0 (0%)	6 (10%)	
EW-specific IgE level at 6 mo of age by ImmunoCAP, UA/mL	5.1 (1.2-5.5)	0.0 (0.0-0.6)	<.01*
OVM-specific IgE level at 6 mo of age by ImmunoCAP, UA/mL	1.2 (0.7-2.0)	0.0 (0.0-0.0)	<.01*
Total IgE at 6 mo, IU/mL	16.1 (9.7-55.5)	5.9 (2.9-13.4)	.03*
Eczema until 6 mo of age	5 (71%)	26 (41%)	.23
Hen's egg consumption until 6 mo of age	0 (0%)	0 (0%)	N/A

Note.: Data are expressed as mean ± SD, median (first quartile-third quartile), or number (percentage). Mother's history and hen's egg consumption until 6 mo of age were based on self-assessments, and infant's eczema was diagnosed by a pediatric allergologist according to the UK working criteria. Significant differences between sex, mother's history, feeding type, and eczema were determined by Fisher's exact test; gestational age by Welch's *t* test; and EW- and OVM-specific IgE and total IgE levels at 6 mo of age by the Mann-Whitney U test.

Abbreviations: EW, egg white; OVM, ovomucoid.

**P* < .05.

The OVM sensitization group had lower OVM-specific IgG4 level than the non-sensitization group (median [first quartile -third quartile] 52.58 [50-68] BUg4/mL vs. 454.8 [84-1187] BUg4/mL, *P* < .01). OVM-specific IgG1 and IgG2 levels were also significantly lower in the sensitization group than the non-sensitization group (IgG1: 198 [170-236] BUg1/mL vs. 686 [274-1559] BUg1/mL, *P* < .01. IgG2: 54 [50-61] BUg4/mL vs. 176 [64-402] BUg4/mL, *P* = .013). However, no significant difference was observed in OVM-specific IgG3 between the two groups, perhaps because OVM-specific IgG3 levels were too low. Although the

EW sensitization group tended to have lower EW-specific IgG4 level (507.9 [69-1168] BUg4/mL vs. 998.6 [359-1782] BUg4/mL, *P* = .06), all EW-specific IgG subclasses were not significantly different between these two groups. To measure EW- or OVM-specific IgG subclass and IgE levels, we carried out correlation analysis with EW- or OVM-specific IgE level measured by the DCP chip at 6M (Table 2). There was a negative correlation between OVM-specific IgG4 level in CB and OVM-specific IgE level at 6M (*r* = -0.31, *P* < .01), whereas no correlation was observed for the other OVM-specific IgG subclasses and IgE levels in CB. Furthermore, EW-specific IgE level at 6M had no significant correlation with levels of all five EW-specific immunoglobulins in CB (Table 2). We previously indicated that eczema is associated with EW- and OVM-specific IgE levels at 6M.⁶ In EW-specific immunoglobulins, the lack of an association between EW-specific IgG subclass levels in CB and sensitization to EW at 6M may have been due to the effect of eczema. Eczema also had a key effect on OVM sensitization. Therefore, we analyzed whether OVM-specific IgG4 in CB contributed to eczema until 6M by comparing children with and without eczema. No difference in OVM-specific IgG4 levels in CB was observed between infants with and without eczema (374.6 [56-1108] BUg4/mL vs. 423.4 [75-1171] BUg4/mL, *P* = .87, Welch's *t* test). This result indicated that OVM-specific IgG4 in CB had an effect through a different route by directly increasing eczema.

A previous study showed that some antigen-specific IgGs were supplied from the mother through the placenta and transfer of antigen-specific IgGs from the mother prevented sensitization in offspring in murine model of food allergy.⁷ Another group showed that allergen-specific IgG antibody promotes food tolerance through FcγRIIB⁸ and human IgG4 antibody can bind to FcγRIIB.⁹ Thus, our findings might suggest that OVM-specific IgG4 transferred from mothers through the umbilical cord binds to FcγRIIB in their infants and reduces OVM sensitization later in life.

Some oral immunotherapy reports showed that EW-specific IgG4 level increased following EW ingestion,^{3,4} Recently, the elimination of a particular antigen during pregnancy was not shown to provide a beneficial effect for preventing the development of food allergy in the child.¹⁰ The present study supported the concept that eliminating EW during pregnancy has no effect of decreasing infant's OVM sensitization.

There are some limitations associated with the present study. First, the sample size was small. Second, there were no data on oral food challenge and for children older than 6M. It was unclear whether infants in the sensitization group had allergic reactions and if OVM sensitization persists with aging. However, hen's egg is introduced during infancy and higher OVM-specific IgE level facilitates subsequent allergic reaction to hen's egg. Third, this study did not present results for other allergen-specific IgE such as those seen for OVM. No relationship was found in sensitization with the specific IgG4 level of milk-related allergen consumed earlier than hen's egg (data not shown). Nevertheless, the findings of this study might contribute to the development of strategies to prevent OVM sensitization with ingesting hen's egg.

FIGURE 1 Median values of ovomucoid (OVM)-specific IgG subclass levels in cord blood (CB) between infants with and without OVM sensitization. Sensitization to OVM at 6 months of age was defined as having a specific IgE level of ≥ 0.35 kUA/L by using the ImmunoCAP system. OVM-specific IgG1 level (A). OVM-specific IgG2 level (B). OVM-specific IgG3 level (C). OVM-specific IgG4 level (D). All statistical analyses were conducted using Mann-Whitney U test, $*P < .05$

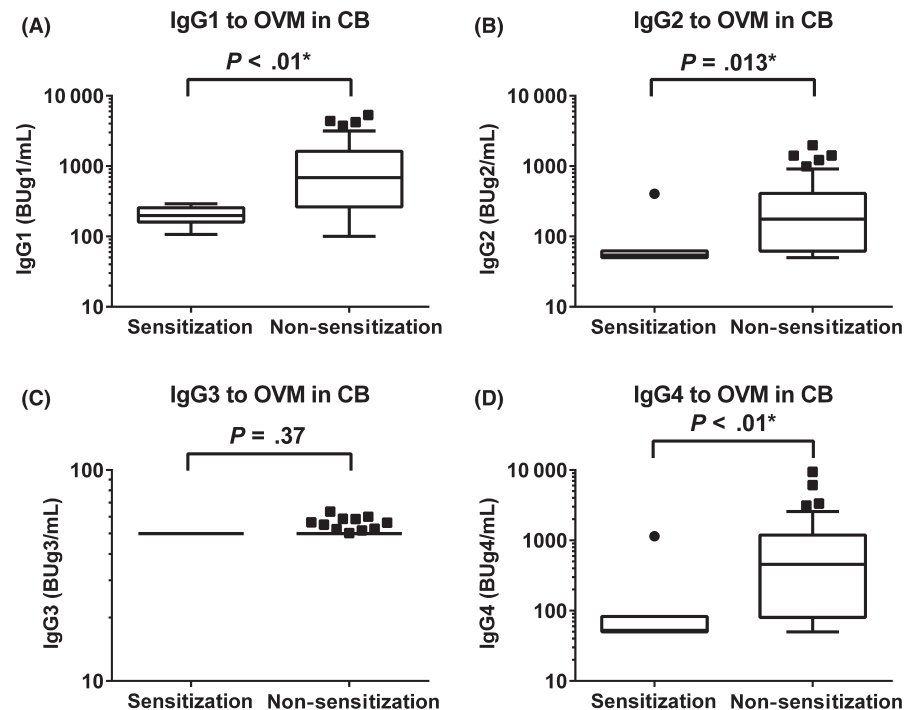


TABLE 2 Correlation between egg white- and ovomucoid-specific IgE and IgG subclasses in cord blood and egg white- and ovomucoid-specific IgE levels at 6 mo of age

Antigen-specific IgE at 6 mo of age	Specific IgE and IgG subclass levels in cord blood	Rs	P value
Egg white-specific IgE (BUe/mL)	IgE (BUe/mL)	0.20	.09
	IgG1 (BUg1/mL)	0.05	.68
	IgG2 (BUg2/mL)	0.00	.95
	IgG3 (BUg3/mL)	0.10	.42
	IgG4 (BUg4/mL)	-0.09	.47
Ovomucoid-specific IgE (BUe/mL)	IgE (BUe/mL)	-0.17	.16
	IgG1 (BUg1/mL)	-0.22	.06
	IgG2 (BUg2/mL)	-0.17	.16
	IgG3 (BUg3/mL)	-0.15	.20
	IgG4 (BUg4/mL)	-0.31	<.01*

Note.: Specific IgE and IgG subclass levels in cord blood and egg white- and ovomucoid-specific IgE level at 6 mo of age were measured by using the DCP chip.

All statistical analyses were conducted using Spearman's rank correlation.

* $P < .05$.

In conclusion, we showed that infants sensitized at 6M had lower OVM-specific IgG4 in CB. Further, large-scale, long-term studies evaluating food-specific IgG subclass levels in CB are needed to elucidate the precise mechanisms involved in OVM sensitization.

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CONFLICT OF INTEREST

The authors declare no competing interests.

This study was approved by the Ethics Committee of Tokushima Prefecture Naruto Hospital (Permit #1314), and written informed consent was obtained from each mother.

AUTHOR CONTRIBUTIONS

Makoto Irahara and Hiroshi Kido formulated the research hypothesis; Makoto Irahara, Wakako Shinahara, Mayumi Sugimoto, Yukiko Ogawa, Keiji Sitsukawa, and Kenji Kubota conducted the experimental work, analyzed the data, and interpreted the results; Makoto Irahara conducted the statistical analysis; Makoto Irahara and Hiroshi Kido drafted the manuscript; Hirohisa Saito, Yukihiro Ohya, and Shoji Kagami critically revised the manuscript.

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