Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
www.all-imm.com

CASE REPORT

OPEN ACCESS

Unveiling heterogeneity in individual thresholds: validation using urinary prostaglandin D_2 metabolite in food allergy reactions

Hisako Ogasawara[a], Yusuke Inuzuka[b], Kotaro Umezawa[a], Nanae Nagata[c], Mami Shimada[a], Sayaka Hamaguchi[a], Tatsuki Fukuie[a], Tatsuo Shimosawa[d], Yukihiro Ohya[e], Takahisa Murata[c,f], Kiwako Yamamoto-Hanada[a]*

[a]*Allergy Center, National Center for Child Health and Development, Tokyo, Japan*
[b]*School of Medicine, Hamamatsu University, Shizuoka, Japan*
[c]*Department of Animal Radiology, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo, Japan*
[d]*Department of Clinical Laboratory, International University of Health and Welfare, Chiba, Japan*
[e]*Deparment of Occupational and Environmental Health, Graduate School of Medical Sciences, Nagoya City University, Aichi, Japan*
[f]*Department of Veterinary Pharmacology, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo, Japan*

Received 25 August 2025; Accepted 31 October 2025
Available online 1 March 2026

KEYWORDS
food allergy;
oral food challenge;
prostaglandin;
tolerated dose;
threshold

Abstract
Background: The prevalence of food allergies among children is on the rise, presenting with a spectrum of severity from mild cases to those resulting in anaphylaxis. ▫Ensuring the safe progression of home-based food ingestion is essential in managing food allergy. While the oral food challenge (OFC) test ideally confirms the threshold and tolerated dose, past findings indicated that about 30% of children who passed peanut OFCs experienced peanut-related allergic reactions when introducing peanuts at home.
Objective: It is presumed that the immune reactions occurring within individual patients vary in levels according to the situation. To date, no reports have objectively examined these conditions.
Material and Methods: We present the symptoms and validation of an objective biomarker in eight pediatric cases during home introduction of food allergens. The urinary Prostaglandin D metabolite (PGDM) was measured as a noninvasive biomarker.
Results: Some cases exhibited mild symptoms and elevated urinary PGDM levels during home introduction despite ingesting half the dose that confirmed as safe during OFC.
Conclusion: It underscores the importance of considering individual variability in determining food allergy thresholds.

***Corresponding author**: Kiwako Yamamoto-Hanada, MD, PhD, Chief, Allergy Center, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan. *Email address*: yamamoto-k@ncchd.go.jp

https://doi.org/10.15586/aei.v54i2.1525

Introduction

The number of children with food allergy (FA) is increasing,[1,2] with varying degrees of severity ranging from mild cases to those exhibiting anaphylaxis. Some children experience anaphylaxis even with tiny amounts of causative food, while others develop mild symptoms, such as hives, after ingesting a certain quantity of susceptible food. Oral immunotherapy (OIT) is an established therapeutic approach for FA.[3] Prior to starting OIT, it is common to conduct oral food challenge (OFC) test to determine the safety dose at home. While OFC ideally confirms the threshold and tolerated dose, past findings indicated that some children who passed OFC without symptoms experienced allergic reactions when introducing target food at home.[4] It is presumed that the level of immune reactions occurring in individual patient vary with the situation. To date, no reports have objectively examined these conditions.

Prostaglandin D_2 (PGD_2) is produced especially from the mast cells involved in allergic reactions and can cause allergic symptoms when released in large amounts. We have previously elucidated that urinary PGD metabolite (PGDM) levels elevated during immediate FA symptoms, including subtle symptoms, with a peak occurring approximately 4 h after ingestion of causative food.[5-9] The urinary PGDM, non-invasive and easy to collect, could be useful to assess biological variability if causative food is consumed continuously at home. In this report, we present eight pediatric cases who underwent OIT at home and observed variations in urinary PGDM levels.

Written informed consents from the parents of the patients were obtained for the publication of this report.

Case Report

All cases were previously diagnosed with FA and had undergone OFC to determine the dose to be consumed at home, resulting in no symptoms. Following OFC, urine samples were collected prior to and after the introduction of target food for two consecutive days at home.□ The urinary PGDM concentrations were detected using liquid chromatography-tandem mass spectrometer and corrected for □urinary creatinine at the University of Tokyo.[5-7]

The background of all cases is shown in Table 1. All cases had the following immunoglobulin E (IgE)-related food allergies: hen's egg in four cases, milk in three cases, and wheat in one case. Case 8 was also suspected to have had neonatal food-protein-induced enterocolitis syndrome (FPIES), but no FPIES symptoms were observed at >1 year of age. All cases were initiated OIT, and these OFCs were conducted to determine the increasing dose at home.

The detailed symptoms and levels of urinary PGDM during home ingestion are shown in Table 2 and Figure 1. Mild symptoms were observed in three cases, despite the dose being lower than that administered during the OFC. Statistical comparison of day 2 PGDM levels according to the presence or absence of symptoms revealed a significant increase in cases with symptoms (Mann-Whitney U test; Figure 2).

Case 1 was a 5-year-old girl with a history of allergy to cow's milk since infancy. She passed OFC with 150 mL of milk without symptoms. While ingestion of 3-mL milk at home caused no symptoms or change in urinary PGDM levels, subsequent ingestion of 75 mL induced mild oral discomfort and a sixfold increase in urinary PGDM, without requiring treatment. After 2 years, she tolerated 200 mL of milk without objective allergic symptoms but continued to report a bitter taste, leading her to limit the intake to processed milk products within a tolerable range.

Case 4 was a 6-year-old girl with a history of egg allergy since infancy. She tolerated 40 g of boiled egg white during an OFC without symptoms. While ingestion of 0.8 g at home caused no reaction or PGDM elevation, ingestion of 20 g on another day resulted in oral discomfort and a fourfold increase in urinary PGDM. After 1 year, she was able to consume one boiled egg and processed egg-containing foods without objective symptoms, although occasional oral discomfort and mild symptoms occurred, especially during periods of poor physical condition.

Case 5 was an 11-year-old boy with egg allergy since the age of 2 years. He tolerated 8 g of boiled egg white during OFC without symptoms. At home, ingestion of 0.8 g caused no symptoms or significant change in urinary PGDM; however, ingestion of 4 g induced mild abdominal pain, soft stools, and a 3.6-fold increase in urinary PGDM. Subsequently, he exhibited no notable symptoms, and after 3 years, was able to consume processed foods equivalent to one-quarter of a heated whole egg.

Table 1 Patient characteristics and clinical data prior to oral food challenge (OFC) test.

Case	Age (years)	Gender	Age at onset of food allergy	Allergic comorbidities	Food	Serum IgE level*
1	5	Female	0 y 10 m	Asthma, AD, AR	Milk	Milk 4.96, Casein 3.35
2	12	Female	3 y	Asthma, AD, AR	Milk	Milk 5.94, Casein 4.56
3	9	Male	2 y	Asthma, AD, AR	Wheat	Wheat 1.37, ω5-gliadine 0.11
4	6	Female	0 y 9 m	AR	Egg white	EW: 17.70, OVM: 6.16
5	11	Male	2 y	AD	Egg white	EW: 10.30, OVM: 7.06
6	15	Female	5 y	AR	Egg white	EW: 2.64, OVM: 2.43
7	8	Female	0 y 7 m	Asthma, AD, AR	Egg white	EW: 1.31, OVM: 1.11
8	4	Male	0 y 1 m	AD	Milk	Milk 1.11, Casein 1.12

Notes: *Latest result prior to OFC (Ua/mL).
EW: egg white; OVM: ovomucoid.

Table 2 Clinical data and urinary PGDM levels in OFC and home introduction day 1 and day 2.

Case	Food	Oral food challenge at hospital				Home introduction day 1				Home introduction day 2			
		Cumulative dose	OFC result	Urinary PGDM (ng/mg Cre)		Loading dose	Urinary PGDM (ng/mg Cre)		Symptoms	Loading dose	Urinary PGDM (ng/mg Cre)		Symptoms
				Before	After*		Before	After**			Before	After**	
1	Milk	150 mL	Pass	1.17	1.24	3 mL	3.01	2.41	None	75 g	1.46	**8.78**	Oral discomfort
2	Milk	15 mL	Pass	0.65	1.17	0.3 mL	0.82	1.19	None	7.5 mL	1.52	1.53	None
3	Wheat	60 g	Pass	0.81	0.59	1.2 g	1.86	2.60	None	30 g	0.37	0.85	None
4	Egg white	40 g	Pass	1.95	2.08	0.8 g	3.37	6.22	None	20 g	3.99	**15.97**	Oral discomfort
5	Egg white	8 g	Pass	1.20	2.96	0.8 g	1.78	2.72	None	4 g	1.83	**6.56**	Abdominal painloose stool
6	Egg white	0.05 g	Pass	0.97	0.90	0.005 g	0.85	2.17	None	0.025 g	1.68	0.94	None
7	Egg white	4 g	Pass	1.68	2.45	0.4 g	3.38	2.23	None	2 g	1.84	3.73	None
8	Milk	6 mL	Pass	1.89	1.53	0.6 mL	1.61	1.04	None	3 mL	1.59	2.20	None

Notes: *Collected about 2 h after ingestion of food.
**Collected about 4 h after ingestion of food.
PGDM: prostaglandin D metabolite; AD: atopic dermatitis; AR: allergic rhinitis.

Cases 2, 3, 6, 7, and 8 showed no symptoms with home ingestion, and no significant changes in urinary PGDM levels were observed. All cases continued OIT with the goal of achieving remission, undergoing regular OFC and adjusting the dose based on their results.

Discussion

We reported eight cases in which urinary PGDM was detected during home introduction of allergenic foods. In most cases, mild symptoms occurred during home introduction at doses lower than the negative threshold confirmed by OFC, accompanied by fluctuations in urinary PGDM levels. The reference range for urinary PGDM has not been established yet. In our previous study, the urinary PGDM levels measured 4 h after ingestion during OFC was 1.48 ± 1.11 ng/mg Cre in patient without symptoms and 3.66 ± 3.01 ng/mg Cre in those who presented with only oral allergy syndrome (OAS). The urinary PGDM level tended to increase with higher symptom grades, reaching 17.11 ± 12.40 ng/mg Cre in grade 4 reactions. [5] In another study, we measured urinary PGDM levels 4 h after a normal meal in non-atopic children across different age groups. The urinary PGDM levels were higher in the preschool group, 4.03 (3.36–5.06) ng/mg Cre, compared to the school-age and adult groups 2.37 (1.56–3.10) ng/mg Cre and 1.97 (1.29–2.35) ng/mg Cre, respectively. [8] Considering these findings, the present results suggest that the three symptomatic cases showed a clear increase in urinary PGDM levels, even after accounting for age.

If symptoms do not occur during OFC, patients are often instructed to consume the same quantity at home. However, it was observed from past reports that approximately 30% of cases experienced symptoms if consuming the same dose at home.[4] Past reports addressed that the tolerating dose varies day-to-day due to the situation and timing of exposure.[10-12] Our report does not focus on the observation of threshold changes per se but rather on the objective demonstration of these variations using urinary biomarkers. Mild subjective symptoms in three cases were physical manifestations accompanied by immunological reactions, rather than psychological issues. We believe that careful consideration should be afforded in case of determining the dose of food to be introduced at home. It is imperative to recognize that the threshold and tolerated dose cannot be unequivocally determined solely through OFC results.

Our report has several limitations. Given the small sample size (n = 8), analyses by food type and dose could not be conducted, and the statistical analysis was insufficient. However, this report aimed to observe and describe in detail and accurately the characteristics of the threshold's fluctuations in a specific population over time in individual cases. Future studies with a larger sample size are warranted to allow comparisons that are more comprehensive. Additionally, the open methodology was applied for OFC; however, we limited the analysis to children exhibiting no allergic reactions, ensuring that this approach did not influence the assessment of this report. Moreover, although PGDM doses are currently available commercially on daily basis, we advanced the practical implementation of clinical testing by utilizing PGDM markers in urine.

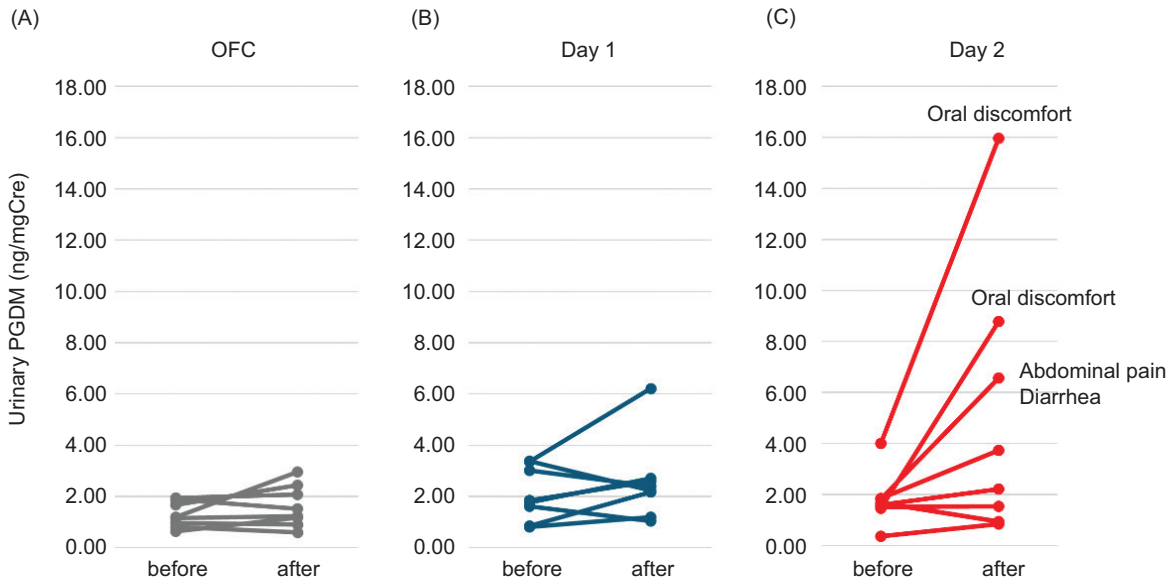

Figure 1 Level of urinary PGDM prior to and after taking food. (A) On OFC, (B) on day 1 of home introduction, (C) on day 2 of home introduction. PGDM: prostaglandin D metabolite; OFC: oral food challenge test.

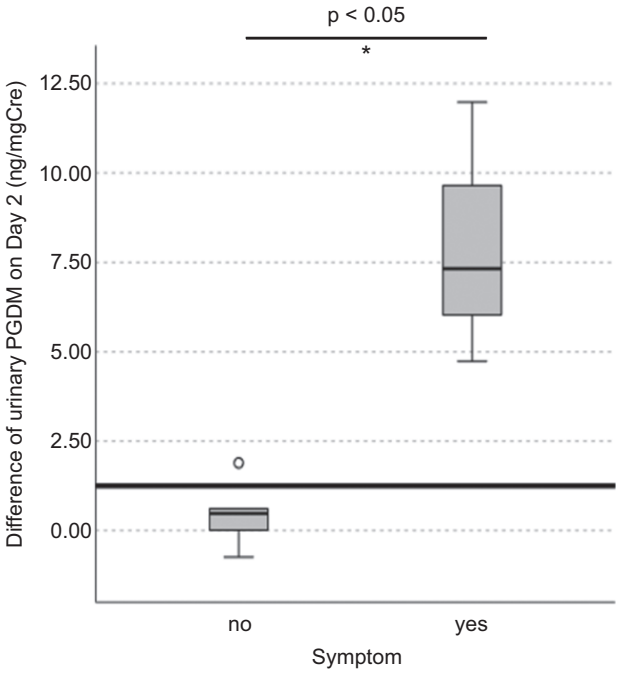

Figure 2 Difference in urinary PGDM levels prior to and after taking of food on day 2. Comparison of urinary PGDM levels between symptomatic and asymptomatic cases. PGDM: prostaglandin D metabolite (*Mann–Whitney U test).

Conclusion

To our knowledge, this is the first report to describe symptoms and fluctuations in an objective biomarker during home ingestion of allergen in FA. Easily measurable urinary PGDM levels could serve as an objective indicator to guide dose adjustment when subtle symptoms arise during home-based OIT. We hope that this will help readers understand the variability of thresholds and lead to more appropriate determination of intake quantities at home in future.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

Author Contributions

All authors contributed equally to this report.

Conflict of Interest

There were no financial or other issues resulting in any conflict of interest.

Funding

This study was funded by the National Center for Child Health and Development and KAKENHI Grant-in-Aid for Scientific Research (S) 20H05678, 25K00746

References

1. Warren CM, Jiang J, Gupta RS. Epidemiology and burden of food allergy. Curr Allergy Asthma Rep. 2020;20(2):6. https://doi.org/10.1007/s11882-020-0898-7

2. Yamamoto-Hanada K, Pak K, Saito-Abe M, Yang L, Sato M, Irahara M, , et al. Allergy and immunology in young children of Japan: The JECS cohort. World Allergy Organ J. 2020;13(11):100479. https://doi.org/10.1016/j.waojou.2020.100479
3. Miyaji Y, Yamamoto-Hanada K, Yang L, Fukuie T, Narita M, Ohya Y. Effectiveness and safety of low-dose oral immunotherapy protocols in paediatric milk Upon checking the journal, we confirmed that no page numbers are listed in the available bibliographic information. Accordingly, we have left the page number unspecified in the revised manuscript. egg allergy. Clin Exp Allergy. 2023;53(12):1307–9. https://doi.org/10.1111/cea.14400
4. van Erp FC, Boot J, Knulst AC, Pasmans SG, van der Ent CK, Meijer Y. Reintroduction failure after negative peanut challenges in children. Pediatr Allergy Immunol. 2014;25(6):580–5. https://doi.org/10.1111/pai.12266
5. Inagaki S, Maeda S, Narita M, Shimosawa T, Murata T, Ohya Y, et al. Urinary PGDM, a prostaglandin D(2) metabolite, is a novel biomarker for objectively detecting allergic reactions of food allergy. J Allergy Clin Immunol. 2018;142(5):1634–6.e1610. https://doi.org/10.1016/j.jaci.2018.06.032
6. Inagaki S, Nakamura T, Yamamoto-Hanada K, Shimosawa T, Murata T, Ohya Y, et al. Urinary prostaglandin D(2) metabolite appears to be a useful biomarker for evaluating the status of egg oral immunotherapy in children. J Allergy Clin Immunol Pract. 2021;9(11):4164–6.e4162. https://doi.org/10.1016/j.jaip.2021.06.040
7. Inuzuka Y, Yamamoto-Hanada K, Nakamura T, Shimosawa T, Murata T, Ohya Y. Detection of allergic reactions during oral food challenge using noninvasive urinary prostaglandin D2 metabolites. Clin Exp Allergy. 2022;52(1):176–9. https://doi.org/10.1111/cea.14006
8. Shimada M, Yamamoto-Hanada K, Nakamura T, Shimosawa T, Murata T, Ohya Y, et al. Association of age, allergic rhinitis, and regular food intake with urinary tetranor-PGD metabolite levels. J Lab Prec Med. 2022;7:36–40. https://doi.org/10.21037/jlpm-22-46
9. Ito N, Nakamura T, Sakamoto N, Hayashi A, Murata T. Extraction and measurement of urinary tetranor-PGDM in disposable diapers. J Pharmacol Sci. 2021;147(2):208–10. https://doi.org/10.1016/j.jphs.2021.06.011
10. Patel N, Adelman DC, Anagnostou K, Mills ENC, Javed B, Purington N, et al. Using data from food challenges to inform management of consumers with food allergy: A systematic review with individual participant data meta-analysis. J Allergy Clin Immunol. 2021;147(6):2249–62.e2247. https://doi.org/10.1016/j.jaci.2021.01.025
11. Turner PJ, Patel N, Campbell DE, Sampson HA, Maeda M, Katsunuma T, et al. Reproducibility of food challenge to cow's milk: Systematic review with individual participant data meta-analysis. J Allergy Clin Immunol. 2022;150(5):1135–43.e1138. https://doi.org/10.1016/j.jaci.2022.04.035
12. World Health Organization (WHO). Risk assessment of food allergens. Part 2: Review and establish threshold levels in foods for the priority allergens: meeting report. Food Safety and Quality Series 15. Geneva, Switzerland: WHO, 2023.