Dysregulated specific IgE production to bystander foods in children with peanut allergy but not egg allergy

Nurcicek Padem, M.D.,[1] Kristin Erickson,[1,2] Meagan Yong, B.S.,[2] Melanie Makhija, M.D.,[1] Kathryn E. Hulse, Ph.D.,[*2] and Anne Marie Singh, M.D.[*3]

ABSTRACT

Background: *Food specific immunoglobulin E (sIgE) levels are associated with the development of allergic responses and are used in the clinical evaluation of food allergy. Food sIgG4 levels have been associated with tolerance or clinical nonresponsiveness, particularly in interventional studies.*

Objective: *We aimed to characterize food-specific antibody responses and compare responses with different foods in food allergy.*

Methods: *Serum sIgA, sIgG4, and sIgE to whole peanut, egg white, and wheat, along with total IgE were measured in 57 children. Children with food allergy, children with natural tolerance, and controls were studied. The Mann-Whitney test or Kruskall Wallis test with the Dunn correction were used for statistical analysis.*

Results: *As expected, total IgE levels were highest in the subjects with food allergy compared with the subjects who were nonallergic ($p < 0.001$) or the subjects who were naturally tolerant ($p < 0.001$). Peanut sIgE levels were higher in subjects with peanut allergy compared with the subjects who were naturally tolerant ($p < 0.0001$) and the control subjects ($p < 0.03$). Interestingly, peanut sIgG4 levels were also highest in children with peanut allergy compared with subjects who were naturally tolerant and control subjects ($p = 0.28$ and $p < 0.001$, respectively). Subjects with peanut allergy alone had comparable egg white sIgE levels to children with egg white allergy. In addition, the subjects with peanut allergy alone also had higher levels of egg white and wheat sIgE compared with the control subjects ($p < 0.02$ and $p = 0.001$, respectively). In contrast, the subjects with egg white allergy did not demonstrate elevated peanut or wheat sIgE levels.*

Conclusion: *These novel findings suggested that IgE production is dysregulated in patients with peanut allergy, who are much less likely to outgrow their allergy, and suggest that the mechanisms that drive more persistent forms of food allergy may be distinct from more transient forms of food allergy.*

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Food allergy results from a loss of oral tolerance to ingested proteins and a development of food specific immunoglobulin E (sIgE). Allergic responses to different foods vary widely in severity, even in the same person.[1,2] Some food allergies, such as to egg white or wheat, are more readily outgrown than others, e.g., peanut. Treatment options have been limited to strict avoidance of allergen triggers, but results of studies of oral immunotherapy (OIT) suggest that sustained unresponsiveness to specific foods can be achieved in some patients.[3–6] Analysis of data from OIT trials have also revealed changes in immunoglobulin isotypes, with the development of sustained unresponsiveness. For example, an increased egg white sIgG4 level during egg white OIT was associated with clinical unresponsiveness and tracking of allergen sIgG4 levels has been suggested to be useful when assessing the induction of sustained unresponsiveness.[3,7] In addition, The LEAP (Learning Early about Peanut Allergy).[8] study found that children with peanut allergy had a lower peanut sIgG4/IgE ratio[8] and that the sIgG4/IgE ratio was higher in patients who tolerated peanut compared with those who were egg white and peanut allergic.[8–10]

In addition to induction of sustained unresponsiveness by OIT, some patients outgrow their food allergy without intervention (natural tolerance). Development of natural tolerance is more common to some foods, e.g., egg white, cow's milk, and wheat, compared with

From the [1]Division of Allergy and Immunology, Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois, [2]Division of Allergy and Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, and [3]Division of Allergy, Immunology and Rheumatology, Department of Pediatrics, University of Wisconsin-Madison, Madison, Wisconsin

**contributed equally*

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Address correspondence to Anne Marie Singh, M.D., Division of Allergy, Immunology and Rheumatology, Department of Pediatrics, University of Wisconsin-Madison, 00 Highland Ave., Clinical Sciences Center Box 9988, Madison, WI 53792

E-mail address: amsingh@wisc.edu

others, e.g., peanut.[11–16] It remains unknown why reactions to certain foods remain persistent, and few studies have investigated the mechanisms that might contribute to the development of natural tolerance in humans.[17–26] Fishbein et al.[27] showed lower egg white sIgG4/sIgE ratios in the subjects with egg white allergy compared with the subjects who were naturally tolerant. However, use of the sIgG4/sIgE ratio or sIgG4 levels as a prognostic factor remains controversial.[3,28]

In contrast to IgE and IgG4, the role of serum sIgA remains understudied. IgA is known to play protective roles in the gut and is important for maintenance of gut homeostasis.[29–33] Studies in murine models of food allergy have shown that tolerance to β-lactoglobulin was characterized by low serum sIgA titers but increased gut secretory sIgA levels.[34] However, data from OIT trials with regard to serum sIgA have been inconsistent.[7,35,36] In this study, we sought to understand specific immunoglobulin levels in a real-world setting by elucidating the relationship of different immunoglobulin isotypes, specifically food sIgG4, sIgA, and sIgE, in children with or without food allergy and children who developed natural tolerance.

METHODS

This cross-sectional study was approved by the institutional review board at Ann and Robert H. Lurie Children's Hospital (Lurie Children's), Chicago, Illinois. Patients were recruited from the outpatient clinics at Lurie Children's. Patients between 6 months and 18 years of age were included. The subjects with food allergy had allergist-diagnosed food allergy to egg white, wheat, and/or peanut, given that these were the most common allergens in our cohort. The diagnosis was made after the development of typical symptoms of hypersensitivity, such as urticaria, angioedema, cough, wheezing, emesis, and/or anaphylaxis, that met the National Institute of Allergy and Infectious Diseases clinical criteria[37]within 2 hours after ingestion of egg white, wheat, and/or peanut, together with sensitization (skin-prick test result of $\geq$95% positive predictive value[38] or food sIgE value of $\geq$95% positive predictive value),[39] or by failed supervised oral food challenge. The subjects who were naturally tolerant had previously been diagnosed with food allergy and then had subsequently outgrown their allergy within 6 months of the blood draw. "Outgrowing" the food allergy was defined as passing oral food challenge to a food to which they were previously allergic. The control subjects were nonallergic and had no history of food allergy.

A total of 5–10 mL of peripheral whole blood was collected in a heparinized tube, and serum was separated for the measurement of immunoglobulins. Written informed consent was obtained, and assent was obtained from children between ages 12 to 18 years. Exclusion criteria were diagnosis or suspicion of non-IgE–mediated food reactions or reactions not consistent with immediate hypersensitivity; eosinophilic esophagitis; enrollment in OIT trials; autoimmune disease, including inflammatory bowel disease; multiple complex medical problems; and the use of oral steroids or other immunomodulatory medications. Food sensitization was evaluated by measurement of food sIgA, sIgE, and sIgG4 to peanut, wheat, and egg white as well as total IgE levels by using Phadia ImmunoCAP (Thermo Fisher Scientific, Waltham, MA) at Lurie Children's hospital laboratories and/or at Thermo Fisher Scientific Phadia US Inc (Waltham, MA). The Mann-Whitney test or the Kruskall Wallis test with the Dunn correction was used for statistical analysis of paired or multiple comparisons, respectively. One-way analysis of variance or the Fisher exact test was conducted for analysis of demographics data. The level of significance was accepted as $p < 0.05$. Analyses were performed by using SPSS software (SPSS Inc, Chicago, IL).

RESULTS

Patient Demographics

Fifty-seven patients were enrolled, including 31 subjects with food allergies, 6 subjects who were naturally tolerant, and 20 control subjects who were nonallergic (Table 1). The subjects with food allergy included 12 with peanut allergy only, 8 with peanut and egg white allergy, and 11 with egg white allergy only. One subject had egg white, peanut, and wheat allergy. The majority of the subjects who were food allergic were white, which reflected our general food allergy cohort. The subjects who were naturally tolerant had outgrown their peanut, egg white, or cow's milk allergies. The control subjects were less likely to have atopic diseases and were older compared with the subjects with food allergy ($p < 0.03$ and $p < 0.01$, respectively.). However, there were no statistically significant differences in demographic data among the peanut, egg white, and peanut plus egg white allergy groups (Table 2).

Total IgE Levels

As expected, total IgE levels were elevated in the subjects with food allergies (602.5 kU/L) compared with the subjects with no food allergies (40.0 kU/L, $p < 0.0001$) and those who developed natural tolerance (34.3 kU/L) ($p < 0.001$) (Supplemental Fig. s1). Interestingly, the levels of total IgE were higher among the subjects with peanut allergy (peanut only) (533.0 kU/L, $p < 0.03$ vs only egg allergy) and the subjects with peanut plus egg white allergy (667.5 kU/L, $p < 0.04$ vs only egg allergy) compared with the subjects with egg white-only allergy (44.3 kU/L). In

Table 1 **Features of the subjects**

	Subjects with Food Allergy (*n* = 31)	Control Subjects (*n* = 20)	Subjects with Natural Tolerance (*n* = 6)
Age, mean (range), y	4.7 (0.8–12.3)	9.9 (0.5–18.3)	5.5 (0.7–10.6)
Age, median (IQR), y	4.2 (6.27)	10.6 (6.27)	5.1 (2.71)
Girls, *n* (%)	14 (45)	5 (25)	3 (50)
Ethnicity, *n* (%)			
White	24 (77)	7/20 (35)	4/6 (66)
African American	2 (6)	3/20 (15)	NA
Hispanic	4 (13)	10/20 (50)	2/6 (33)
Asian	1 (3)	NA	NA
Atopic profile, *n* (%)			
Asthma	8 (26)	3 (15)	1 (17)
Atopic dermatitis	20 (65)	4 (20)	3 (50)
Allergic rhinitis	12 (39)	3 (15)	3 (50)
Food allergy, *n* (%)			
Egg white	11 (35)	NA	1 (17)
Peanut	12 (39)	NA	4 (66)
Egg white and peanut	8 (26)	NA	NA
Cow's Milk	NA	NA	1 (17)

IQR = Interquartile range; NA = not applicable.

contrast, we did not detect a significant difference in the total IgE levels between the subjects with peanut-only allergy and those with peanut plus egg white allergy ($p = 0.9$) (Supplemental Fig. s1). Next, we evaluated food sIgE, sIgG4, and sIgA levels (Supplemental Table s1).

Food sIgA Levels

Peanut sIgA levels were undetectable in the majority of our cohort (89%) (Supplemental Fig. s2). Of the five subjects who had detectable sIgA levels to peanut, one was a control subject, one was a subject with peanut plus egg white allergy, and three were subjects with peanut-only allergy. Similar to our findings with regard to peanut sIgA, the majority of our cohort (96%) was found to have undetectable egg white sIgA levels. Both subjects with detectable egg white sIgA levels had peanut allergy with no egg white allergy. In contrast, wheat sIgA levels were detectable in 60% of the subjects. The median wheat sIgA level was 1.28 mg/L in the subjects who were nonallergic. This level was comparable with the median sIgA levels of the subjects with peanut-only allergy (0.90 mg/L) and the subjects with peanut plus egg white allergy (1.25 mg/L) ($p > 0.6$ and $p > 0.8$, respectively). One subject with egg white, peanut, and wheat allergy had an undetectable wheat sIgA level (Supplemental Table s1).

Peanut sIgE and sIgG4 Levels

We next evaluated the levels of peanut sIgE and sIgG4. As expected, the median peanut sIgE level was elevated in serum from the subjects with peanut allergy (peanut only and peanut plus egg white, 93.3 kU/L and 18.7 kU/L, respectively; $p > 0.9$) compared with the subjects who were nonallergic (0.09 kU/L) and those who were naturally tolerant (0.16 kU/L) ($p < 0.0001$ and $p < 0.03$, respectively). Moreover, we did not detect a significant difference in peanut sIgE levels between the subjects who were nonallergic and the subjects who were naturally tolerant ($p = 0.8$) (Fig. 1A). In addition, and as expected, the median peanut sIgE level in serum from the subjects with egg white-only allergy was 0.14 kU/L, which was comparable with the levels in the subjects who were nonallergic and the subjects who were naturally tolerant ($p = 0.41$ and $p > 0.9$, respectively.) (Fig. 1A). Ara H 2 sIgE levels were measured in the subjects with peanut allergy, those who were nonallergic, and those who were naturally tolerant. Similar to the pattern in (whole) peanut sIgE levels, the median sIgE levels to Ara H 2 were found to be higher in the subjects with peanut allergy (peanut only and peanut plus egg white, 39.25 kU/L and 9.29 kU/L, respectively; $p > 0.2$) compared with the subjects who were nonallergic (0.09 kU/L) and the subjects who were naturally tolerant (0.15 kU/L) ($p < 0.0001$ and $p < 0.001$, respectively). We did not detect a difference in Ara H 2 sIgE levels between the subjects who were nonallergic and the subjects who were naturally tolerant ($p > 0.9$) (data not shown).

We found that the median peanut sIgG4 level was elevated in the subjects with peanut allergy versus the subjects who were nonallergic (0.44 mg/L versus 0.06

Table 2. **Demographics and atopic profile of the subjects with food allergy**

	Subjects with Egg White-Only Allergy (n = 11)	Subjects with Peanut-Only Allergy (n = 12)	Subjects with Egg White + Peanut Allergy (n = 8)
Age, mean (range), y	2.98 (1.01–9.63)	6.27 (1.65–10.09)	4.86 (0.80–12.33)
Age, median (IQR), y	2.08 (1.83)	5.71 (4.41)	4.26 (4.26)
Girls, *n* (%)	5 (45)	5 (42)	4 (50)
Ethnicity, *n* (%)			
White	9 (82)	10 (83)	5 (63)
American African	NA	1 (8)	1 (13)
Hispanic	2 (18)	1 (8)	1 (13)
Asian	NA	NA	1 (13)
Atopic profile, *n* (%)			
Asthma	NA	4 (33)	4 (50)
Atopic dermatitis	5 (45)	9 (75)	6 (75)
Allergic rhinitis	2 (18)	5 (42)	5 (63)

IQR = Interquartile range; NA = not applicable.

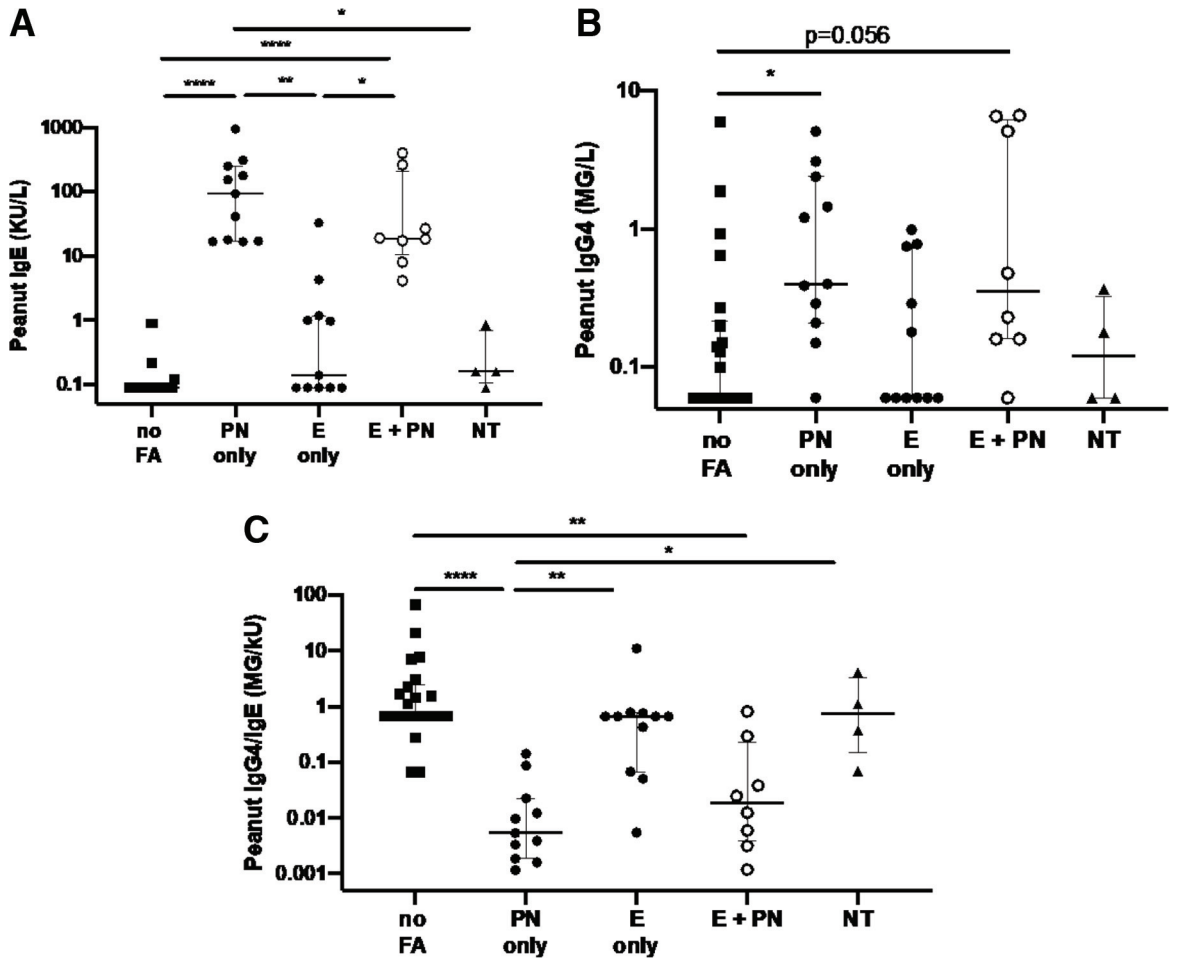

Figure 1. *(A) Peanut serum IgE levels, (B) IgG4 levels, and (C) IgG4/IgE ratio by using the ImmunoCAP system. (A and B) Peanut sIgE and sIgG4 levels were highest in the subjects with peanut allergy. The ratio of peanut sIgG4/sIgE was highest in the subjects who were non-allergic. (C) Median values with interquartile ranges are marked. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, ****p ≤ 0.0001, by using the Kruskal-Wallis test. IgE = Immunoglobulin E; sIgE = specific IgE.*

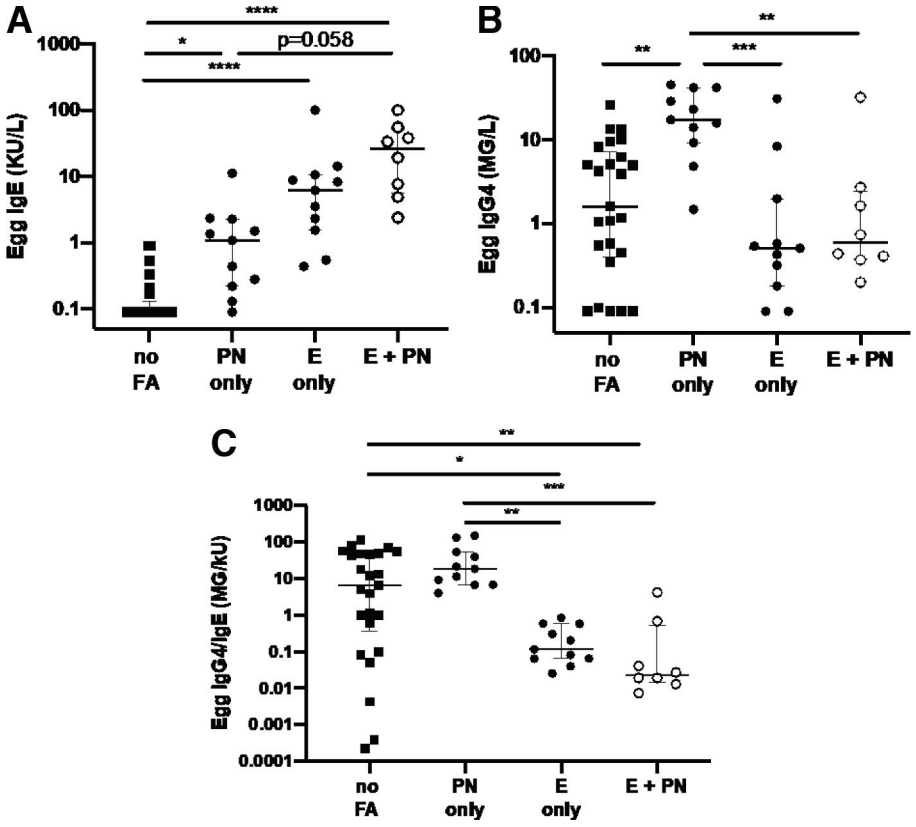

*Figure 2. (A) Egg white serum IgE, (B) IgG4 levels, and (C) IgG4/IgE ratio by using the ImmunoCAP system. (A) The subjects who were egg white allergic had the highest levels of egg white sIgE, but the subjects with peanut allergy who tolerated eggs also had elevated egg white sIgE levels compared with the subjects who were nonallergic. (B and C) Egg white sIgG4 levels and the egg white sIgG4/IgE ratio were highest in the subjects who tolerated eggs. The median values with interquartile ranges are marked. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$, by using the Kruskal-Wallis test. IgE = Immunoglobulin E; sIgE = specific IgE.*

mg/L; $p < 0.001$). This increase was found in the subjects with peanut allergy only (1.33 mg/L) and peanut plus egg white allergy (2.42 mg/L) compared with the subjects who were nonallergic (0.06 mg/L) ($p < 0.02$ and $p = 0.056$, respectively) (Fig. 1B). Interestingly, peanut sIgG4 was not significantly elevated in the subjects who were naturally tolerant versus the subjects with peanut allergy (0.12 mg/L versus 0.44 mg/L; $p = 0.28$). In addition, we did not detect a significant difference in peanut sIgG4 levels between the subjects who were nonallergic versus those who were naturally tolerant (0.06 mg/L versus 0.12 mg/L; $p = 0.8$). The median peanut sIgG4 levels in the subjects with egg white-only allergy (0.06 mg/L) was found to be comparable with the subjects who were nonallergic ($p > 0.9$).

However, the ratio of peanut specific IgG4/IgE was significantly elevated in both the subjects who were naturally tolerant (0.75 mg/kU) and those who were nonallergic (0.66 mg/kU) compared with the subjects who were peanut allergic (0.01 mg/kU) ($p < 0.02$ and $p < 0.0001$, respectively) (Fig. 1C). This ratio was not found to be different between the subjects who were peanut-only allergic and the subjects who were peanut plus egg white allergic (0.005 mg/kU and 0.018 mg/kU, respectively) ($p > 0.9$). In addition, the subjects who were egg white-only allergic had a comparable peanut IgG4/IgE ratio to the subjects who were nonallergic ($p > 0.9$) (Fig. 1C). Altogether, analysis of these data indicated that all the subjects with peanut allergy made both IgE and IgG4 to peanut, whereas the subjects who tolerated peanuts, including those with egg white allergies, only made IgG4 (and not IgE) to peanut. Our findings also indicated that the ratio of peanut IgG4/IgE was associated with tolerance to peanut.

Egg White sIgE and sIgG4 Levels

We next sought to determine whether the subjects with egg white allergy had similar antibody profiles to egg white (as the subjects with peanut allergy had to peanut). As expected, the median egg white IgE level was elevated in the subjects with egg white allergy (egg white only and peanut plus egg white, 6.22 kU/L and 26.65 kU/L, respectively; $p > 0.9$) compared with the subjects who were nonallergic (0.09 kU/L) ($p < 0.0001$). Interestingly, the subjects with peanut-only allergy and who tolerated eggs also had elevated median egg white IgE levels versus the subjects who were nonallergic (1.90 kU/L versus 0.09 kU/L; $p < 0.02$) (Fig. 2A).

In contrast to our findings in peanut allergy, in which the subjects with peanut allergy had higher levels of peanut sIgG4 compared with the subjects who

were nonallergic, those with egg white allergy did not have elevated egg white sIgG4 levels versus the subjects who were nonallergic (0.51 mg/L versus 1.61 mg/L; $p > 0.9$) (Fig. 2B). Moreover, the subjects with peanut-only allergy had higher egg white sIgG4 levels (17.4 mg/L) compared with the subjects who were nonallergic (1.61 mg/L), egg white-only allergic, (0.51 mg/L), and egg white plus peanut allergic (0.59 mg/L), $p < 0.004$, $p < 0.001$, and $p < 0.01$, respectively) (Fig. 2B).

Similar to our findings with peanut allergy, the subjects who were nonallergic had a higher egg white IgG4/IgE ratio (6.44 mg/kU, $p = 0.04$) compared with the subjects who were egg white-only allergic (0.12 mg/kU, $p = 0.04$) and the subjects who were egg white plus peanut allergic (0.02 mg/kU, $p = 0.008$) (Fig. 2C). Interestingly, an elevated egg white IgG4/IgE ratio was also detected in the subjects with peanut-only allergy (18.41 mg/kU) compared with the subjects with egg white-only allergy and those with peanut plus egg white allergy ($p < 0.002$ and $p < 0.001$, respectively) (Fig. 2C). Taken together, analysis of these data suggested that the subjects with peanut allergy had dysregulated production of egg white sIgE and sIgG4, which was not observed for peanut-specific antibodies in the subjects with egg white-only allergy. In addition, analysis of these data suggested that egg white IgG4 levels alone may be sufficient to support tolerance to egg white, whereas peanut IgG4 levels alone are not sufficient in peanut tolerance.

Wheat sIgE and sIgG4 Levels

To further investigate whether the subjects with peanut allergy have dysregulated production of IgE to other tolerated foods, we analyzed serum wheat IgE levels in our cohort. Similar to the findings for egg white, we found that the subjects with peanut allergy (peanut only and peanut plus egg white, 0.37 kU/L and 1.14 kU/L, respectively; $p > 0.9$) had elevated levels of wheat sIgE compared with the subjects who were nonallergic (0.09 kU/L) and the subjects with egg white-only allergy (0.09 kU/L) ($p < 0.0001$ and $p < 0.01$, respectively) (Supplemental Fig. s3A). The subjects with peanut-only allergy had the highest levels of wheat sIgG4, and this was significantly different from the subjects with egg white-only allergy (7.03 mg/L versus 0.44 mg/L; $p < 0.0$) (Supplemental Fig. s3B). Interestingly, and in contrast to our findings with peanut and egg white IgG4/IgE ratios, the wheat IgG4/IgE ratio was comparable among all the groups (Supplemental Fig. s3C). Analysis of these results indicated that the subjects with peanut allergy had dysregulated IgE production to wheat, whereas the subjects with egg white allergy did not show this pattern.

DISCUSSION

We sought to better understand the role of food-specific immunoglobulins in the development of food allergy and natural tolerance. Our work showed increased egg white and wheat sIgE levels in the subjects with peanut allergy, even if they tolerated these foods. Interestingly, we did not detect this finding in the subjects with egg white allergy. These results differentiated peanut allergy from egg white allergy and suggested dysregulated total IgE and sIgE production in the subjects with peanut allergy. In support of previous research, we found that food sIgA levels in serum were undetectable in the majority of our cohort.[35] However, this does not rule out an important role for food sIgA in the regulation of food allergy because the role of IgA may be better understood with local sampling in stool or intestinal mucosa.

Our results also revealed higher peanut IgG4 levels in the peanut allergic group compared with the subjects who were nonallergic and the subjects who developed a natural tolerance to peanut. This finding contrasted with OIT trials in which an increase in food sIgG4 over time was predictive of sustained unresponsiveness.[3,7] With increased peanut sIgG4 results in the subjects with peanut allergy (compared with those with natural tolerance), our findings pointed to the potential differences between natural tolerance and sustained unresponsiveness induced by OIT to peanut. With regard to other allergens, Bunning et al.[40] showed comparable IgG4 levels to egg white and cow's milk between the OIT and natural tolerance groups. Furthermore, in contrast to peanut, this study, and our previous work,[27] found elevated egg specific IgG4 levels in natural tolerance to egg, which suggested that IgG4 patterns in the subjects with egg white and peanut allergies may differ when compared with the subjects who were nonallergic. This finding would also suggest that the immunologic response to egg white and peanut antigens differ. Finally, our results showed a lower food sIgG4/sIgE ratio in the subjects with peanut and egg white allergies, which supported previous studies.[8–10,27] We also found that the subjects with peanut allergy but not egg white allergy had elevated levels of bystander food sIgE. Specifically, we found that the subjects with peanut allergy had elevated egg white and wheat sIgE levels, even though they had been eating those foods.

In contrast, the subjects with egg white allergy did not have elevated levels of bystander food sIgE (peanut and wheat). We propose that these novel findings indicated that antibody production to food, particularly for IgE, is dysregulated in patients with peanut allergy. This dysregulated production of food sIgE, which also included production of peanut sIgE, may be one factor that contributes to the inability of these patients to

outgrow their allergy compared with patients with egg white or wheat allergy. In addition, this finding has implications for testing to other foods in the setting of peanut allergy because these patients can have elevated IgE levels even when the food is tolerated. Further studies are needed to elucidate the mechanisms that regulate IgE production to foods in subjects with peanut allergy. Interestingly, these subjects with peanut allergy also had elevated levels of egg white and wheat sIgG4.

Our findings are intriguing in that there are different antibody responses in subjects with peanut and egg white allergy. However, we also acknowledge that this study had some limitations, including a relatively small patient population with few subjects who were naturally tolerant and a cross-sectional design. Further studies are needed to elucidate these mechanisms with a larger sample size and perhaps in a longitudinal manner. Nevertheless, the current study is important in that it is the first study to our knowledge to demonstrate these food-specific differences in antibody responses and food-specific bystander IgE elevation.

CONCLUSION

Overall, analysis of our novel findings suggests that IgE production is dysregulated in patients with peanut allergy, who are much less likely to outgrow their allergy, and that the mechanisms that drive persistent forms of food allergy may be related to this dysregulated IgE production. To better characterize humoral immunity in food allergy, future work on investigating B-cell phenotypes, B- and T-cell interactions, and alterations in class switching are needed.

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