Daily baked egg intake may accelerate the development of tolerance to raw egg in egg-allergic children

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Abstract

Recent studies suggest that egg-allergic children who tolerate baked egg (BE) are more likely to outgrow egg allergy than children that do not tolerate it. The question to be answered is whether regular ingestion of BE accelerates tolerance to other forms of egg (cooked and raw). Our aim was to determine if daily ingestion of BE would accelerate tolerance to raw egg in BE-tolerant patients compared to patients who tolerate BE at diagnosis but eliminated it from their diet and to patients who didn't tolerate it. We performed a retrospective analysis of all children diagnosed of IgE-mediated egg allergy at the Pediatric Allergy Unit of the Complejo Hospitalario Universitario A Coruña, from 2008 to 2014. Seventy children were included. At diagnosis, 33 patients tolerated BE and kept its daily ingestion, 16 patients tolerated BE and were recommended to avoid it, and 21 patients didn't tolerate it. Patients tolerating BE who kept daily ingestion achieved tolerance to raw egg significantly earlier ($p < 0.05$) than the other two groups.

Conclusion: Our data suggest that daily intake of BE in BE-tolerant children accelerates tolerance to raw egg.

Keywords Baked egg; Egg allergy; Raw egg; Tolerance; Children; Food allergy

Abbreviations: BE, Baked egg; OFC, Open food challenge; OM, Ovomucoid; OVA, Ovalbumin; SPT, Skinprick test

About 60–70% of egg-allergic children can tolerate baked egg (BE) [4, 5]. It has been proposed that conformational epitopes are destroyed during extensive heating and that baking egg in a wheat matrix may block specific IgE epitope access thus decreasing IgE reactivity [9, 10].

Recent studies have suggested that egg-allergic children who consume BE products on regular bases are more likely to outgrow egg allergy than children that do not tolerate them [2]. The question still to be answered is whether children tolerating extensively heated egg would be more likely to outgrow their allergy naturally sooner than children who present more severe forms of egg allergy or if the regular ingestion of BE, contributes to the achievement of tolerance to cooked and raw egg.

Our aim was to determine if daily ingestion of BE by egg-allergic children would accelerate tolerance to raw egg compared with patients who tolerate BE at diagnosis but eliminated it from their diet from that moment on and with patients who initially didn't tolerate it.

We performed a retrospective analysis of all children diagnosed of IgE-mediated egg allergy at the Pediatric Allergy Unit from 2008 to 2014 and followed up to 2018. To minimize selection bias, we included all egg-allergic children diagnosed during the mentioned period. Seventy children were included, 40 girls and 30 boys.

Diagnosis was defined by compatible clinical history and a positive skin prick test (SPT) and/or detectable (>0.35 kU/L) serum-specific IgE (ImmunoCAP, Thermo Fisher Scientific, Phadia, Sweden) to egg white (EW), ovalbumin (OVA), or/and ovomucoid (OM). Extracts for SPT were provided by ALK, Spain.

During 2008 and 2009, it was a common practice at our Unit to eliminate all forms of egg from the diet of allergic children regardless tolerance to extensively heated forms. From 2010 on, BE-tolerant children are encouraged to keep daily ingestion of BE products.

Tolerance to BE was established by clinical history and if unknown, open food challenge with a muffin containing one egg was carried out at our Unit.

On follow-up, open food challenges (OFC) were performed once a year to determine if the patient had outgrown egg allergy regardless SPT size and specific IgE levels. Children were challenged initially with cooked egg and if tolerated, subsequent OFC with raw egg was performed.

The study was approved by the Hospital's Ethics Committee.

Descriptive analyses were performed for all variables. Quantitative variables were reported using median and interquartile range. For qualitative variables, absolute numbers and percentages were computed. Quantitative variables and means were compared with the Kruskal-Wallis tests and qualitative variables with chi-square test (significance level at 0.05) by SPSS 24 software.

At diagnosis, 33 patients tolerated BE and kept its daily ingestion, 16 patients tolerated BE but were recommended to avoid it, and 21 patients didn't tolerate it. Median age at the time of first reaction was 12 (10.8–14) months. Most frequently reported symptoms after egg ingestion were: perioral urticaria (41 patients), vomiting (20 patients), facial edema (19 patients), and generalized urticaria (18 patients). There were no cases of severe anaphylaxis and no patient required adrenaline. Twenty-one patients developed moderate (grade II) anaphylactic reactions according to Brown's severity score of anaphylaxis [2]:

- Among egg-allergic patients who did not tolerate BE, 2 children developed urticaria and mild dyspnea, 5 urticaria and vomiting, and 1 patient vomiting, urticaria, and mild dyspnea.
- Among egg-allergic patients who tolerated BE and kept eating it, 2 patients presented urticaria and mild dyspnea and 8 urticaria and vomiting.
- Regarding egg-allergic patients who tolerated BE and remove it from their diet, 1 presented vomiting and urticaria, 1 angioedema, mild dyspnea, and rhinoconjunctivitis, and 1 vomiting and dyspnea.

The rest of the patients presented only with skin symptoms (urticaria and/or angioedema) after egg ingestion. These reactions would correspond to Grade I (mild) [6].

The three groups were comparable regarding age at onset and severity of the allergic reactions. Demographic and clinical data are summarized in Table 1.

There were no significant differences regarding size of SPT wheal but patients who initially tolerate BE showed specific IgE levels to OVA and OM significantly lower than BE nontolerant patients ($p < 0.05$). None of the patients included were sensitized to egg yolk.

Patients tolerating BE at diagnosis who kept daily BE ingestion achieved tolerance to raw egg after 27 (15–36) months, significantly earlier ($p < 0.05$) than the other two groups. Tolerance to raw egg was achieved by BE tolerant with exclusion diet patients after 58 (39–103) months and by BE nontolerant patients after 54 (29–90) months.

Patients who tolerated BE on diagnosis and followed an exclusion diet showed a similar evolution than patients who initially did not tolerate BE.

Outcomes regarding tolerance to raw egg as well as baseline SPT and specific IgE are summarized in Table 2.

Leonard et al [6] had previously reported that egg-allergic patients tolerating BE were 14.6 times more likely to develop tolerance to cooked egg than BE reactive patients and that they developed tolerance earlier (median 50.0 versus 78.7 months). We found that BE-tolerant allergic children need to keep a regular ingestion of BE to accelerate tolerance, otherwise they behave as those patients who do not tolerate BE at the moment of diagnosis, outgrowing egg allergy significantly later. Netting et al [8] in a recent randomized controlled trial concluded that regular ingestion of baked egg did not affect the achievement of tolerance to raw egg. There are methodological issues that could explain this different outcome. Their intervention period was much shorter (6 months) than ours, and also, they recommended BE ingestion 2–3 times a week, while our recommendation was to keep a daily intake.

Up to date, there are no definitive data on the SPT wheal and specific IgE level cut-offs for baked egg reactivity [3]. It has been suggested that OM-specific IgE may be useful to predict BE reactivity, since OM is less affected by heating than OVA. We found that BE-tolerant patients showed significantly lower levels of specific IgE to OVA and OM than BE reactive children. Moreover, SPT wheals were similar in size for OVA, EW, and OM in the three groups studied, as reported previously by Lieberman et al [7]. Larger cohorts and a standardized protocol for baked egg are needed to establish cut-offs for predicting BE reactivity.

Recently, oral immunotherapy with baked egg has been proposed [1]. Reactions during the procedure were mild, and all patients who completed the protocol were able to ingest whole egg reassuring once more the role of BE on the achievement of tolerance to other forms of egg.

Our data suggest that daily intake of BE in BE-tolerant children accelerates tolerance to raw egg. The main limitation of the present study is its retrospective design. It would be necessary to perform prospective studies analyzing the impact of regular ingestion of BE on tolerance to other forms of egg, including a control group of BE-tolerating children to whom BE should be eliminated from their diet.

Contributions

Olinda Pérez-Quintero attended and followed up patients at our Allergy Unit. She also reviewed patients' charts and she created the database. Oihana Martínez-Azcona also attended and followed up patients at our Allergy Unit. She reviewed patients' charts as well and helped fulfil the database with patients' data. Vanesa Balboa performed the statistical analysis. Leticia Vila attended and followed up patients at our Allergy Unit and supervised the present study.

Ethics declarations

Conflict of interest

The authors declare that they have no conflicts of interest related to the manuscript contents.

Ethical approval

This article describes a retrospective study performed with human participants.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Table 1 Demographic, clinical, and laboratory characteristics of egg-allergic children

	BE-tolerant with BE ingestion	BE-tolerant with BE exclusion diet	BE nontolerant
Patients (*n* = 70)	*n* = 33	*n* = 16	*n* = 21
Age of first reaction (months)			
Mean ± SD	13.4 ± 3.7	12.7 ± 3.85	12.3 ± 3.8
Median (range)	12 (5–24)	12 (4–24)	12 (7–24)
Sex, n (%)			
Male: 40 (57.1)	18 (54.5)	10 (62.5)	10 (62.5)
Female: 30 (42.9)	15 (45.5)	6 (37.5)	6 (37.5)
Personal history of atopy, *n* (%)	20 (60.6)	13 (81.3)	17 (81)
Rhinitis	9 (27.3)	12 (75)	8 (38.1)
Asthma	6 (18.2)	11 (68.8)	11 (52.4)
Atopic dermatitis	8 (24.2)	8 (50)	6 (28.6)
Food allergy	9 (27.3)	5 (25)	9 (42.9)
Family history of atopy, *n* (%)	26 (78.8)	14 (87.5)	14 (66.7)
Clinical manifestations, *n* (%)			
Perioral urticaria	18 (54.5)	10 (62.5)	13 (61.9)
Urticaria (UA)	6 (18.2)	6 (37.5)	6 (28.6)
Facial edema	9 (27.3)	3 (18.8)	7 (33.3)
Vomiting	11 (33.3)	3 (18.8)	6 (28.6)
Dyspnoea	2 (6.1)	2 (12.5)	3 (14.3)

BE baked egg, *OVA* ovalbumin, *OM* ovomucoid

Table 2 Clinical outcome and baseline SPT and specific IgE in BE-tolerant patients who kept BE ingestion, BE-tolerant patients with egg exclusion diet and BE nontolerant patients

	BE tolerant-BE ingestion	BE tolerant-BE exclusion diet	BE nontolerant
Months to tolerance			
Cooked egg	27.4 ± 17.1	47.7 ± 34.3	51.4 ± 39.2
Raw egg*	31.4 ± 20.7	67.4 ± 31.4	61.6 ± 44.9
Specific IgE (kU/L)			
EW	2.4 ± 4.5	2.4 ± 3.3	5.5 ± 11.3
OVA**	1.01 ± 1.2	1.7 ± 3.6	4.7 ± 10.7
OM**	0.67 ± 1.7	1.4 ± 3.2	2.5 ± 5.4
SPT (mm)			
EW	5.4 ± 2.6	4.9 ± 2.8	5 ± 3
OVA	3.2 ± 2	4 ± 3.4	3.6 ± 2.6
OM	2.65 ± 3.3	3.4 ± 4	3.7 ± 3.5

*BE-tolerant patients who kept BE ingestion tolerated raw egg significantly ($p < 0.05$) sooner than BE-tolerant patients with BE exclusion diet and BE-non tolerant patients;

**BE-tolerant patients showed significant lower levels of specific IgE to OM and OVA than BE-non tolerant patients.

BE baked egg, EW egg white, OVA ovalbumin, OM ovomucoid, SPT skin prick test