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Article type : Brief Report

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Total number of text pages: 3

Total number of words of the manuscript: 1049

Number of references: 5

Number of figures: 0

Number of tables: 1

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/APA.15706](https://doi.org/10.1111/APA.15706)

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Could cooked eggs provide a quantifiable immunologic stimulus that could accelerate allergy resolution?

A hens' egg allergy (HEA) is one of the most common childhood allergies and avoidance until spontaneous resolution is advised. However, one study reported that about 80% of infants who were allergic to raw eggs tolerated cooked eggs (1).

When an HEA does not spontaneously resolve, introducing cooked eggs can accelerate the resolution of allergies to slightly cooked egg, improving quality of life and tolerance (2).

We developed a two-step egg oral immunotherapy (OIT) protocol (Table S1). Children regularly consumed a safe amount of cooked eggs, identified during the OFC that confirmed their HEA, then attempted a raw egg OFC, then raw egg OIT.

This retrospective analysis investigated the plasma immune responses before starting OIT (T0), after one year of regular cooked eggs (T1) and after one year of the raw egg OIT (T2). The Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy, approved the study and parental consent was obtained.

We studied 86 children referred for immunoglobulin E (IgE) mediated HEA, from January 2013 to December 2017, with sufficient follow-up data to December 2019 (Figure S1). An IgE mediated HEA was a convincing clinical history of recent anaphylaxis, a positive open OFC and positive skin prick test or detectable (>0.35 kU/L) serum-specific IgE (sIgE). We excluded subjects with no IgE-mediated clinical manifestations and children with known immunodeficiencies.

The cooked egg OFC used Pavesini cookies (Barilla SpA, Parma, Italy), which include 0.5g of whole egg and 50 mg of protein. Unrestricted cooked eggs were authorised if there were no symptoms after eating 12 biscuits. The hospital-based raw egg OFC used raw egg emulsion, with a

general rush challenge schedule comprising 3, 10, 30, 100, 300, 1000 and 3000mg of food protein at intervals of at least 20 minutes, according to the PRACTALL guidelines (3).

We compared sIgE and serum-specific IgG4 (sIgG4) levels to hens' eggs and their major components, ovomucoid and ovalbumin, at T0, T1 and T2 (Figure S2). Table 1 lists the pairwise analysis results.

Quantitative variables, including immunoglobulin differences in the three periods, were compared with the Mann-Whitney test and qualitative variables with the chi-square test. SPSS, version 21 (IBM Corp, New York, USA) was used for the analyses, with significance set at 0.05.

We found that 50/86 (58%) of patients ingested 6g of cooked egg without symptoms and introduced cooked eggs without substantial restrictions, 21/86 (24%) refused to eat 12 cookies and 15/86 (17%) had mild to moderate symptoms.

Patients with a negative OFC for cooked egg were allowed to an unrestricted cooked egg diet.

Patients consuming limited amounts of cooked egg started the OIT from the maximum dose taken before refusal, while 15 patients with a positive cooked egg OFC started the OIT with a quarter of the maximum dose ingested before symptoms occurred (Table S1).

All 86 children eventually underwent the raw egg OFC after regularly eating cooked eggs for a year: 49/86 (57%) were tolerant and introduced raw egg to their diet. Of the 15 patients with a previous positive cooked egg OFC, seven successfully introduced raw egg after the raw egg OFC while the eight children with symptoms started the OIT with cooked eggs .

When we looked at the participants who underwent OIT with cooked eggs, we saw that the SIgE of egg white, and its components, decreased significantly ($p<0.01$) between T0-T1 (Figure S2A) and non-significantly between T1 and T2.

From T0-T1, IgG4 rose significantly ($p<0.01$) for white egg and ovomucoid and sIgG4 rose significantly ($p<0.01$) for ovalbumin (Figure S2B).

One study reported that only 17 % of participants presented with relevant symptoms after an OFC with cooked eggs, but they could all introduce it after an OIT with Pavesini cookies (5),

We observed increased sIgG4 levels in heat stable ovomucoid and heat labile ovalbumin in children regularly exposed to cooked eggs. This could partly be because the allergic reaction

occurred when at least two portions of the allergen were recognised by mast cells, although only one epitope was needed to cause a type-1 T helper response (2).

The study's limitations included the small cohort, with no control group.

We did not perform a raw egg OFC, because the primary outcome was sIgG4 levels when children who previously avoided any eggs were regularly exposed to cooked eggs. Our results, based on data on the immunologic processes sustained by cooked eggs, suggest a positive change in the immunological parameters of IgE-mediated sensitisation to all eggs. This was not always enough to induce tolerance to raw eggs (4). However, cooked eggs could provide an easy, first step in HEA management, improve quality of life, reduce diet limitations and positively influence the natural history of HEA. This cohort had higher initial sIgE (Table 1) than another study (5) and participants had less chance of spontaneous allergy resolution.

The cooked egg OIT reduced sIgE and increased IgG4 for ovomucoid and ovalbumin, suggesting that cooked eggs could provide a quantifiable immunologic stimulus that could accelerate allergy resolution. Further studies are needed to clarify how it would affect the natural history of HEA.

Conflicts of interest

None

Funding

None

Abbreviations

HEA, hens' egg allergy; OFC, oral food challenge; OIT, oral immunotherapy; SIgE, serum-specific immunoglobulin E; SIgG4, serum-specific immunoglobulin G4.

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Table 1. sIgE and IgG₄ immunoglobulins values at T₀, T₁, T₂, together with the average age

sIgE and IgG ₄ immunoglobulins – mean values (IR)	Before introduction of BE (T ₀) <i>n</i> =86	During OIT or unrestricted diet for BE (T ₁) <i>n</i> =86	After introduction of RE (T ₂) <i>n</i> =86
Egg-specific IgE	19.10 (7.58-55.10)	7.15 (2.36-25.20) *	3.46 (1.68-6.84) <i>p</i> 0.6
OVO IgE	2.57 (1.24-12.25)	0.67 (0.22-3.80) *	0.38 (0.05-1.54) <i>p</i> 0.239
OVA IgE	3.90 (1.76-11.00)	1.56 (0.27-3.96) *	0.63 (0.23-2.86) <i>p</i> 0.345
Egg-specific IgG ₄	0.25 (0.08-0.76)	1.97 (0.18-5.11) *	14.65 (4.15-23.30) *
OVO IgG ₄	0.07 (0.01-0.15)	0.29 (0.05-1.87) *	5.04 (0.11-13.02) <i>p</i> 0.41
OVA IgG ₄	0.19 (0.07-0.83)	1.59 (0.54-3.31) *	17.00 (8.25-29.75) *
Average age in years (IR)	4.2 (2.90-7.30)	6.4 (4.30-9.20)	8.0 (4.50-11.30)

sIgE, specific immunoglobulins; IR, interquartile range. OVO, ovomucoid; OVA, ovalbumin, CE, cooked egg; RE, raw egg; *: *p*<0.01.

Supplementary material

Table S1. Study protocol.

Figure S1. Population data on the follow-up study period.

Figure S2. sIgE (A) and sIgG4 (B) levels to egg and 2 components (OVO-OVA) in participants before starting OIT (T_0), after one year of BE regular consumption (T_1), and after one year of OIT with RE (T_2). OVO: ovomucoid; OVA: ovalbumin.