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Original Article

Is oral food challenge useful to avoid complete elimination in Japanese patients diagnosed with or suspected of having IgE-dependent hen's egg allergy? A systematic review

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AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events Severity; DBPCFC, double-blind placebo-controlled food challenge; OFC, oral food challenge; SAE, serious adverse event; QOL, quality of life

ABSTRACT

Background: IgE-mediated egg allergy is a common food allergy worldwide. Patients with egg allergy are known to easily achieve tolerance compared to other allergens such as nuts. Oral food challenge (OFC) is often performed on patients diagnosed with or suspected of having IgE-mediated food allergy, but whether hen's egg OFC is useful in IgE-dependent egg allergy patients to avoid complete elimination remains unknown.

Methods: We identified articles in which OFCs were performed in Japanese patients diagnosed with or suspected of having IgE-mediated egg allergy. We evaluated whether the OFCs were useful to avoid the complete elimination of eggs by assessing the following: (1) the number of patients who could avoid complete elimination; (2) the number of patients who experienced serious adverse events (SAEs); or (3) adverse events (AEs); (4) improvement in quality of life (QOL); and (5) immunological changes.

Results: Fifty-nine articles were selected in the study; all the references were case series or case studies in which OFC was compared to pre-challenge conditions. The overall negative ratio against egg OFC was 62.7%, but an additional 71.9% of OFC-positive patients could take eggs when expanded to partial elimination. Of the 4182 cases, 1146 showed AEs in the OFC, and two cases reached an SAE. Two reports showed an improvement in QOL and immunological changes, although the evidence was weak.

Conclusions: OFCs against eggs may be useful to avoid complete elimination, but medical professionals should proceed with the test safely and carefully.

Introduction

Food allergy is an adverse reaction to certain foods that is mediated by an immunologic mechanism,[1–3] and IgE-mediated hen's egg allergy is one of the most frequent food allergies in childhood.[2,4–8] The allergy against hen's egg is known to achieve tolerance by the age of[7,9,10] and resolve more quickly than allergies to other foods, such as nuts and fish.[5] Therefore, the continuous

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evaluation of natural history is needed for egg allergy to minimize the elimination of diet to prevent nutritional deficiencies.

The Japanese Society of Pediatric Allergy and Clinical Immunology has announced that the oral food challenge (OFC) is the most reliable examination for the diagnosis of food allergy in Japanese food allergy guidelines 2005.[3] Thus, OFC is widely used in Japan to confirm the diagnosis, to reconfirm the tolerance, and to determine the threshold for following oral immune therapy. Based on the report by Imai *et al.*, in 2019,[11] 99.8% and 88.4% of large or moderate allergy facilities in Japan performed OFC. Moreover, in the recent publication of the Japanese guidelines for Food Allergy 2020, even low-dose OFC is recommended in high-risk patients to avoid the complete elimination of the suspected food, with the idea that the OFC can now be used in a safe condition and be able to improve QOL.[2]

However, the evidence of whether a hen's egg OFC is useful in IgE-dependent egg allergy patients to avoid complete elimination is not known. Therefore, we performed a systematic review to evaluate whether the OFC is useful to avoid the complete elimination of eggs in Japanese patients diagnosed with or suspected of having an IgE-dependent egg allergy.

Methods

Structured question

We outlined the clinical question as "Is an oral food challenge useful for avoiding complete elimination in Japanese patients who are having/suspected IgE-dependent hen's egg allergy?" The OFC-related outcomes assessed in this study included the following: 1) the number of patients who were able to avoid complete elimination; 2) the number of patients with serious adverse events (SAEs) in OFC; 3) the number of patients with adverse events (AEs) in OFC; 4) the number of patients with improved quality of life (QOL) due to OFC; and 5) immunological changes [IgE, IgG4, skin prick test, basophil activation test, regulatory T cells, etc.] (Table 1).

Using the described process, the information was extracted by patient, intervention, comparison, and outcome.

Data source and search methodology

PubMed and *Ichu-shi* (https://jamas.or.jp/english/) were used as index articles. All the articles were published between January 1, 2000 and August 31, 2019. The literature search was conducted on October 14, 2019 by a literature search specialist at the medical library. The search formulae used in *PubMed* are presented in Table 2. This systematic review included randomized controlled trials, case–control studies, case series studies, cross-sectional case studies, and case reports. The method used in this systematic review was as reported in the original methods, mainly for case reports and case series, and reported in previous guidelines for Hirschsprung's disease analogs.[12]

Table 1
Clinical question list.

PICO	Contents	
Patients	Patients diagnosed with or suspected of having IgE-dependent egg allergy	
Intervention	Egg-OFCs	
Comparison	Patients before Egg-OFCs	
Outcomes	1	Number of patients who enable to avoid complete elimination of Egg
	2	Number of patients with SAEs
	3	Number of patients with AEs
	4	Improvement of QOL
	5	Immunological changes (IgE, IgG4, SPT, basophil activation test, regulatory T cells, etc.)

Egg, Hen's egg; OFC, oral food challenge test; SAEs, severe adverse events; AEs, adverse events; QOL, quality of life; SPT, skin prick test.

Table 2
PubMed search strategy.

No.	Search formula	Results
#01	"Egg Hypersensitivity"[Mesh]	689
#02	"Administration, Oral"[Mesh]	142,151
#03	#1 AND #2	90
#04	egg*[TI] AND (hypersensitivit*[TIAB] OR allerg*[TIAB]) AND (challenge*[TIAB] OR Provocation*[TIAB] OR Introduction*[TIAB])	284
#05	#3 OR #4	330
#06	#5 AND 2000:2019[DP]	287
#07	#6 AND (JAPANESE[LA] OR ENGLISH[LA])	280
#08	#7 AND ("Meta-Analysis"[PT] OR "Meta-Analysis as Topic"[Mesh] OR "meta-analysis"[TIAB])	5
#09	#7 AND ("Cochrane Database Syst Rev"[TA] OR "Systematic Review"[PT] OR "Systematic Reviews as Topic"[Mesh] OR "systematic review"[TIAB])	5
#10	#7 AND ("Practice Guideline"[PT] OR "Practice Guidelines as Topic"[Mesh] OR "Consensus"[Mesh] OR "Consensus Development Conferences as Topic"[Mesh] OR "Consensus Development Conference"[PT] OR guideline*[TI] OR consensus[TI])	10
#11	#8 OR #9 OR #10	17
#12	#7 AND ("Randomized Controlled Trial"[PT] OR "Randomized Controlled Trials as Topic"[Mesh] OR (random*[TIAB] NOT medline[SB]))	42
#13	#7 AND ("Clinical Trial"[PT] OR "Clinical Trials as Topic"[Mesh] OR ((clinical trial*[TIAB] OR case control*[TIAB] OR case comparison*[TIAB]) NOT medline[SB]))	63
#14	#7 AND ("Epidemiologic Methods"[Mesh] OR "Comparative Study"[PT] OR "Multicenter Study"[PT] OR ((cohort*[TIAB] OR comparative stud*[TIAB] OR follow-up stud*[TIAB] OR prospective stud*[TIAB] OR Retrospective study*[TIAB]) NOT medline[SB]))	156
#15	(#12 OR #13 OR #14) NOT #11	161
#16	#7 NOT (#11 OR #15)	102

Eligibility criteria

We thoroughly collected articles in which OFCs were conducted in Japan in patients who were diagnosed or suspected to be allergic to chicken eggs. Reviews, commentary proceedings, and other non-research papers were excluded. Since the OFC for both diagnosing and proving tolerance to food allergy is widely recommended in the Japanese Food Allergy Guideline from 2005, studies published between January 1, 2000 and August 31, 2019, were included. Articles written in English and Japanese were also indexed.

The definitions of SAEs used in this article were those used in clinical research (death, the chance of death, unexpected hospitalizations or prolonged admissions, disabilities/probabilities of being disabled, or being in a serious condition, needing respiratory management that required intubation, cases that required intensive care unit management, hypoxic encephalopathies, and other serious cases), which was also equivalent to the Common Terminology Criteria for Adverse Events Severity (CTCAE ver.5.0), Grades 3,4 and, 5 as per a previous study.[13] We also defined AEs as any unfavorable or unintended medical events that occurred in patients during OFCs, whether or not those events which were equal to CTCAE Grades 1 and 2 were associated with OFCs. We used the same definitions of SAEs and AEs for both the outpatient and

inpatient facilities. The definition of QOL used in this article was indexed according to the CDC's Health-related QOL definition, "an individual's or group's perceived physical and mental health over time." (https://www.cdc.gov/hrqol/methods.htm).

Study selection

For the primary screening of the articles, six physicians/researchers specializing in pediatric allergy independently selected the articles by reading the titles and abstracts. Articles that satisfied the clinical questions were then extracted by two independent physicians/researchers who read the entire article.

Evaluation of the evidence

As most articles were presumed to be case reports or case series, we used qualitative systematic reviews to evaluate the risk of bias by referencing previous guidelines.[12] Briefly, the assessment points were as follows: 1) indirectness, 2) risk of bias, and 3) inconsistency. The evidence was independently judged by six physicians/researchers who specialized in pediatric allergy. The evidence was then combined for each outcome and assessed for the overall evidence of the study.

Results

Study selection

The literature extraction process is illustrated in Figure 1. Briefly, 280 references and 453 articles were selected from the *PubMed* and *Ichu-shi* databases, respectively. Of these 733 articles, 247 *PubMed* and 378 *Ichu-shi* articles were excluded by checking the title and abstract. The remaining 104 references, excluding four duplicates from both *PubMed* and *Ichu-shi*, 45 references were excluded by full-text checking. Finally, 59 references were selected for this study. Detailed information on the selected references is provided in Table 3. There were also large variations in the total OFC intakes, cooking methods, and OFC interval (Table 3).

Research characteristics

Patients who could avoid complete elimination were described in 45 references, SAEs were explained in two references (#4, #23), AEs for 40 references (#1–2, #4, #6–7, #9, #13–15, #18–19, #21–27, #30–42, #49, #52–59), and immunological testing for two references (#1, #54). Since there were no studies that used any internationally validated questionnaires with regard to the QOL,[14] no references were selected for QOL. All the outcomes were written in terms of pre- and post-treatment comparisons, and there were no comparisons made with the placebo group.

Results of individual outcomes

Number of patients who were able to avoid complete elimination

Fifty-eight references (#1–58) were eligible for this study, the overall negative ratio of OFC was 62.7% (3354/5367), and the average rate for each reference was 47.7%. We excluded four references (#11, #12, #41, #46) in which the numbers of OFC patients or OFC-positive patients were unknown. The negative ratio of OFC using raw, heated egg whites or freeze-dried egg white was 45.9% (1932/2270), while the negative ratio of OFC with reduced antigens such as heated egg yolks or ovomucoid-reduced heated eggs was

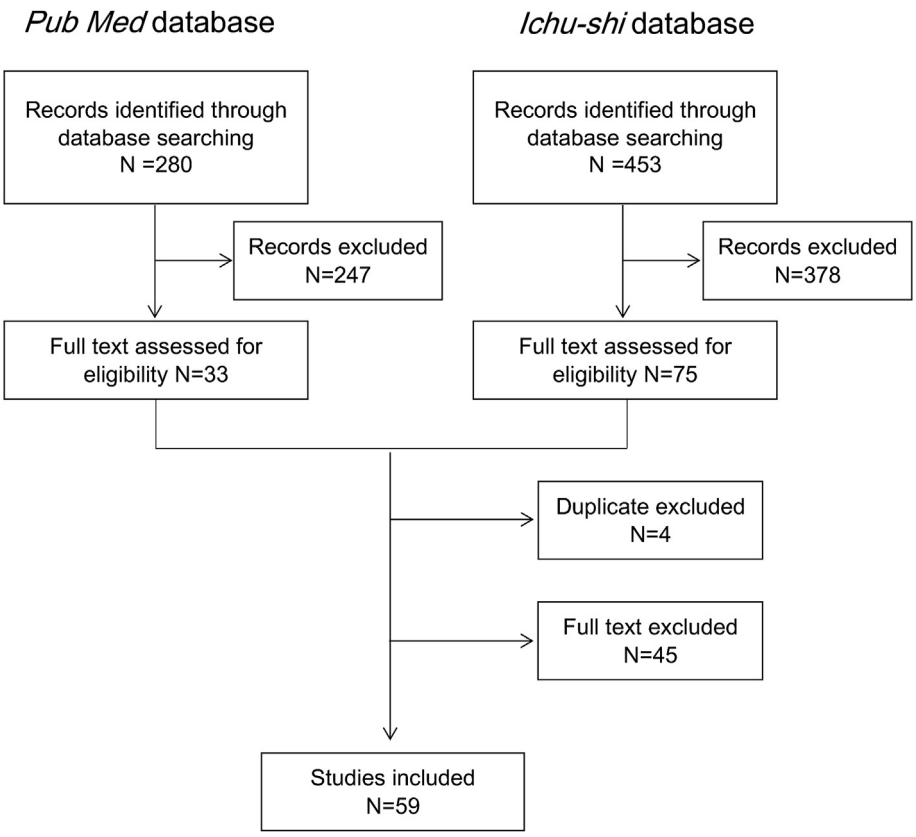

Fig. 1. Flow diagram for indexing the articles on oral food challenge against hen's egg allergy.

Table 3
The list and the detailed information of indexed articles in this study.

No.	Author name, Title, Journal, year, volume, pages	Loading food[†]	Total loading dose	Intervals of OFC
# 1	Inuzuka Y, Natsume O, Matsunaga M *et al.* "Evaluation of slow oral immunotherapy for food allergies in our hospital" Jpn. J. Pediatr. 2019; 72(7): 863–870	HEW	10 g	30 min
# 2	Okura Y, Oshima Y, Yanazume N *et al.* "Validation of egg white oral food challenges under three years of age" Med. J. KKR Sapporo Med. Cent. 2017; 14(1): 26–32	HEW	18 g	20 min
# 3	Kunitomo A, Aota A, Yamada S *et al.* "Examination of hen's egg yolk, egg white, and ovomucoid specific IgE level as the negative predictive marker of the oral food challenge for heated hen's egg yolk" Jpn. J. Pediatr. Allergy Clin. Immunol. 2017; 31(5): 705–713	HEY	1 egg yolk	15 min
# 4	Hirase S, Okafuji I, Tanaka Y *et al.* "Analysis of safety oral food challenge using egg yolk" Jpn. J. Pediatr. Allergy Clin. Immunol. 2017; 31(5): 699–704	HEY	1 egg yolk	15 min/30 min
# 5	Tatsumoto C, Nagao M, Fujisawa T, "Diagnostic utility of changes in egg—specific IgE in infants with atopic dermatitis" Jpn. J. Pediatr. Allergy Clin. Immunol.2017; 31: 692–698	Other; (dried HE)	1/2 egg	30 min
# 6	Inuo C, Mori Y, Kondo M *et al.* "Safety of baby food containing ovomucoid—reduced egg white for atopic dermatitis infants and children without previous egg white exposure" Jpn. J. Pediatr. Allergy Clin. Immunol. 2017; 31: 135–140	Other; (baby food including HE)	1 meal (3g of HE)	30 min
# 7	Ito K, Sato S, Urisu A *et al.* "An Evaluation of spontaneous histamine release and the low respoders in a basophil histamine release test" Arerugi 2016; 65: 48–56	HEW, Other (cake)	1 egg	20 min
# 8	Yanagida N, Minoura T, Kitaoka S. "The Effect on Reduction of Eliminated Foods by Start of Stepwise Oral Food Challenge Test" IRYO 2015; 69: 471–478	HEY, HE	1 egg (HEY, HE)	1 time
# 9	Sato S, Ito K, Urisu A *et al.* "Utility of the Allerport® HRT in the diagnosis of hen's egg allergy: a pediatric multicenter challenge study" Arerugi 2015; 64:136–148	HEW, other (cake)	1 egg (≥2y) or 1/2 egg (<2y)	unknown
#10	Imai T, Yanagida N, Ogata M *et al.* "The skin prick test is not useful in the diagnosis of the immediate type food allergy tolerance acquisition" Allergol. Int. 2014; 63(2): 205–210	HE	1/2 egg	60 min
# 11	Yanagida N, Shukuya A, Sato S *et al.* "Evaluation of 'A Popular Guide on Indication for Intramuscular Injection of Adrenalin by EPIPEN®' decided and released by The Anaphylaxis Exploratory Working Group of Japanese Society of Pediatric allergy and Clinical Immunology" Jpn. J. Pediatr. Allergy Clin. Immunol. 2014; 28: 329–337	HE	1/2 egg	30 min
# 12	Kobayashi T, Kando N, Haneda Y *et al.* "Diet instructions to increase the tolerated dose in patients with positive egg challenge test results (2nd report)" Jpn. J. Pediatr. Allergy Clin. Immunol. 2013; 27: 692–700	HEW	38 g	20 min
# 13	Manabe T, "The effects of ingesting small amounts of egg white in egg-allergic younger children" Jpn. J. Pediatr. 2014; 67: 439–443	HE	2.4 g	20 min
# 14	Isozaki A, Tanaka A, Kikuchi N *et al.* "Retrospective study on the use of a challenge test with heated egg-containing products for hen's egg allergy patients aged less than 2 years" Clin. Immunol. & Allergol. 2012; 58: 246–250	Other (egg cookie)	12.75 cookies (HE 5.73g)	unknown
# 15	Manabe T, Machida H, Tomita N *et al.* "Oral immunotherapy for food allergy in children" Jpn. J. Pediatr. 2013; 66(2): 297–303	HE, other	2.8 g of egg	unknown
# 16	Yanazume N, Kato R, Tsumagari S *et al.* "Experience of oral food challenge test and specific oral tolerance induction in our hospital" Med. J. KKR Sapporo Med. Cent. 2011; 8(1): 33–38	HE, other (dried HE powder)	1 egg	15 or 20 min
# 17	Tsuge I, Kondo Y, An Z *et al.* "Issues to be solved for standardization of oral immune therapy" Jpn. J. Pediatr. Allergy Clin. Immunol. 2010; 24(1): 47–51	other (OVM reduced heated egg)	1/2 egg	unknown
# 18	Komata T, Shukuya A, Imai T *et al.* "Single blind food challenge using dried food powder—1st Report. Raw whole egg and egg yolk" Arerugi 2009; 58(5): 524–536	other (dried UEW, dried UEY, HE)	4.0 g (dried UEW, dried UEY) 1/2 egg	15 min
# 19	Kusunoki T, Mikuni T *et al.* "Studies of Loading Test with Egg Containing Foods against Infants under the Age of 3 with Positive Egg-specific IgE" J. Jpn Pediatr. Associ. 2007; 111(8): 1035-1041	HEY, HEW, other (mayonnaise, Egg cookies)	1 egg (HEY, HEW), 12g(mayonnaise), 12 egg cookies	30 min
# 20	Tashiro M, Kuniyoshi Y, Hasegawa H, Yasuda S, Masuda Y, Ebisawa M. "Experiences of oral food challenge tests by using dried food powders (single-blind method)" Med. J. Kensei Hosp. 2006; 29:10–15	other (dried egg, dried UEY)	1egg	15 min
# 21	Kajiyama M, Sasaki K, Oyazato Y *et al.* "Examination of oral food challenge tests in the department of pediatrics at rokko island hospital" J. Konan Hosp. 2005; 22: 21–26	HE, HEW, HEY, other (Egg cookies)	1 egg (HE, HEW), 1egg yolk (HEY, Egg cookies)	15 min
# 22	Yamada K, Morita Y, Urisu A *et al.* "A simple and easy method to make hypoallergenic egg white, heated and ovomucoid-depleted egg white" Jpn. J. Pediatr. Allergy Clin. Immunol. 2001; 15(1): 106–111	HEW, other (HEW without Ovomucoid)	1 egg	30 min

Table 3 (*continued*)

No.	Author name, Title, Journal, year, volume, pages	Loading food[†]	Total loading dose	Intervals of OFC
# 23	Matsuyama A, Yabuta K, Tokuda R, "Usefulness of histamine release test using HRT Shionogi in predicting the results of freeze-dried egg white and heated Egg white oral food challenge" Jpn. J. Pediatr. 2004; 57(6): 097–1101	other (freeze dried UEW)	1egg	unknown
# 24	Sakihara T, Kawamitsu Y, "Twenty-minute boiled egg white oral food challenge for Infants" Jpn. J. Pediatr. Allergy Clin. Immunol. 2019; 33(1): 106–116	HEW	3.7g, 8.5g, 18g	40 min
# 25	Matsuda T. "Status of oral food challenge tests in my hospital - graduate increasing of feeding by active dietary guidance for reduction of eliminated foods, from elimination to feeding, what kind of dietary guidance is safe at the clinic?" Mie Ken Syonika Ikai Kaiho 2016; 100:16–25	HEY, HEW, HE	1 egg (over 3years), 1/2 egg (under 3 years)	20–30 min
# 26	Matsui T, Sugiura S, Nakagawa T *et al.* "Oral food challenge test of heated egg yolk in patients with an egg white allergy that tolerate 1g of boiled egg white" Jpn. J. Pediatr. Allergy Clin. Immunol.2017; 31(1): 63–71	HEY	1egg	1 time
# 27	Koike Y, Yanagida N, Imai T *et al.* "Whole egg mayonnaise oral food challenge in children who became tolerant to one heated egg" Jpn. J. Pediatr. Allergy Clin. Immunol. 2016; 30(4): 562–566	other (mayonnaise)	10g	30 min
# 28	Hayashi D, Suzuki H, Morishita N *et al.* "Questionnaire survey on the usefulness of Japanese sponge cake oral food challenge for children with hen's egg allergy" Jpn. J. Pediatr. Allergy Clin. Immunol 2015; 29(1): 99–107	other (cake)	1cut	15–30 min
# 29	Yamada K, Hirata N, Komatsubara R *et al.* "Evaluation of allergenicity of baby food containing ovomucoid-reduced heated whole egg" J. Pediatr. Pract. 2013; 76(6): 1009–1014	other (baby food)	1 meal	30 min
# 30	Kazuma N, Wakamatsu K. "Usefulness and problems in outpatient oral food challenge" J. Saitama Med. Soc. 2009; 44(1): 299–301	unknown	unknown	10–15 min
# 31	Kazuma N, Wakamatsu K, Shimanuki K. "Ingenuity for safe oral food challenge" J. Saitama Med. Soc. 2007; 42(1): 203–208	HE, HEW, HEY, other (mayonnaise)	1 egg(HEW), unknown	15 min
# 32	Kato Y, Ozawa K, Mori R *et al.* "Evaluation of allergen activity of ovomucoid-removed heated whole egg by skin prick test and oral food challenge" Allergology 2005; 19(1): 90–96	other (dried HE without ovomucoid)	10 g	20 min
# 33	Kojima H, Shimojo N, Numata T *et al.* "Clinical evaluation of unicap ovomucoid-specific IgE antibody measurement in immediate-type heated hen's egg allergy" Jpn. J. Pediatr. 2001; 54(1): 31–35	HEW	1 egg	15 min
# 34	Takaoka Y, Maeta A, Takahashi K *et al.* "Effectiveness and Safety of Double-Blind, Placebo-Controlled, Low-Dose Oral Immunotherapy with Low Allergen Egg-Containing Cookies for Severe Hen's Egg Allergy: A Single-Center Analysis" Int. Arch. Allergy Immunol. 2019; 180(4): 244–249	HEW	4.0g	20 min
# 35	Kido J, Nishi N, Matsumoto. "The Oral Provocation Test for Raw Egg in Patients with Hen Egg Allergy." Int. Arch. Allergy Immunol 2018; 177(1): 40–44	UEY, UEW HEY, HEW	8.5 ml(UEY),18.5 ml (UEW), 8.5g (HEY), 37.5g (HEW)	20 min
# 36	Maeta A, Matsushima M, Muraki N *et al.* "Low-Dose Oral Immunotherapy Using Low-Egg-Allergen Cookies for Severe Egg-Allergic Children Reduces Allergy Severity and Affects Allergen-Specific Antibodies in Serum" Int. Arch. Allergy Immunol 2018; 175(1–2): 70–76	HEW	4.0g	20 min
# 37	Itoh-Nagato N, Inoue Y, Nagao M *et al.* "Desensitization to a whole egg by rush oral immunotherapy improves the quality of life of guardians: A multicenter, randomized, parallel-group, delayed-start design study" Allergol. Int. 2018; 67(2): 209–216	Other (dried UEW)	500 mg	unknown
# 38	Yanagida N, Sato S, Asaumi T *et al.* "Safety and feasibility of heated egg yolk challenge for children with egg allergies" Pediatr. Allergy Immunol. 2017; 28(4): 348-354	Other (cake with 1egg yolk)	1 cut (1/32 egg)	60 min
# 39	Akashi M, Yasudo H, Narita M *et al.* "Randomized controlled trial of oral immunotherapy for egg allergy in Japanese patients" Pediatr. Int. 2017; 59(5): 534–539	other (dried UEW)	4.0g (dried UEW)	15 min
# 40	Okada Y, Yanagida N, Sato S *et al.* "Heated egg yolk challenge predicts the natural course of hen's egg allergy: a retrospective study" World Allergy Organ. J. 2016; 9(1): 31	Other (cake with egg yolk or whole egg)	1 cut (1egg yolk (HEY), 1/2egg (HE))	15–30 min
# 41	Sato S, Ogura K, Takahashi K *et al.* "Usefulness of antigen-specific IgE probability curves derived from the 3gAllergy assay in diagnosing egg, cow's milk, and wheat allergies" Allergol. Int. 2017; 66(2): 296–301	Other (cake with egg yolk or whole egg)	1 cut (1egg yolk (HEY), 1/2egg (HE))	30 min
# 42	Furuya K, Nagao M, Sato Y, Ito S, Fujisawa. "Predictive values of egg-specific IgE by two commonly used assay systems for the diagnosis of egg allergy in young children: a prospective multicenter study" Allergy 2016; 71(10): 1435–1443	other (dried UEW, dried HEW)	1egg or 1/2 egg	15-30 minutes
# 43	Sato S, Tachimoto H, Shukuya A *et al.* "Basophil activation marker CD203c is useful in the diagnosis of hen's egg and cow's milk allergies in children" Int. Arch. Allergy Immunol. 2010; 152 Suppl 1: 54–61	HE, other (dried UE)	1 egg (HE), unknown (dried UE)	15 min
# 44	Itoh N, Itagaki Y, Kurihara. "Rush specific oral tolerance induction in school-age children with severe egg allergy: one year follow up" Allergol.Int. 2010; 59(1): 43-51	other (dried EW)	unknown	20 min

(*continued on next page*)

Table 3 (*continued*)

No.	Author name, Title, Journal, year, volume, pages	Loading food[†]	Total loading dose	Intervals of OFC
# 45	Ando H, Moverare R, Kondo Y *et al.* "Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy" J. Allergy Clin. Immunol. 2008; 122(3): 583–588	HEW, UE	1 egg	unknown
# 46	Yamada K, Urisu A, Kakami M *et al.* "IgE-binding activity to enzyme-digested ovomucoid distinguishes between patients with contact urticaria to egg with and without overt symptoms on ingestion" Allergy 2000; 55(6): 565–569	other (dried UEW)	1 egg	30 min
# 47	Horino S, Kitazawa H, Satou T *et al.* "Hyperresponsiveness to Boiled Egg Yolk in Early Life Leads to Prolonged Egg Allergy" Allergy Asthma Immunol. Res. 2019; 11(3): 433–437	HEY	1 egg	30 min
# 48	Okamoto S, Taniuchi S, Sudo K *et al.* "Predictive value of IgE/IgG4 antibody ratio in children with egg allergy" Allergy Asthma Clin. Immunol. 2012; 8(1): 9	HE	50.4g	30 min
# 49	Yanagida N, Minoura T, Kitaoka S *et al.* "A three-level stepwise oral food challenge for egg, milk, and wheat allergy" J. Allergy Clin. Immunol.: In Practice 2018; 6(2): 658–660.e10	HEY	1/4 egg yolk	60 min
# 50	Yanagida N, Sato S, Asaumi T *et al.* "Safety and Efficacy of Low-Dose Oral Immunotherapy for Hen's Egg Allergy in Children" Int. Arch. Allergy Immunol. 2016; 171(3–4): 265–268	HE	1/32 egg	60 min
# 51	Yamazaki M, Isozaki A, Tanaka A *et al.* "An adult case of egg allergy treated with rush oral immunotherapy." Arerugi 2017; 66(9): 1181–1184	Other; (dried UEW)	0.03g	unknown
# 52	Okada Y, Akasawa A. "A successful case of egg allergy tolerance achieved at a local clinic" Allergol. Int. 2017; 66(3): 504–506	HEW	10g	30 min
# 53	Masumi H, Takemura Y, Arima T *et al.* "A 6-year-old girl who developed egg allergy triggered by atopic dermatitis that developed in early childhood" Pediatrics 2019; 60(3): 313–5	HEW	8g	30 min
# 54	Hayashi R, Akamine Y, Ogawa E *et al.* "A food allergic child who was treated successfully for egg and wheat allergy by oral food challenge and dietary intervention" J. Nihon Univ. Med. Assoc. 2018; 77(3): 175–180	HEY	10.5g	unknown
# 55	Ogawa N, Mikami K, Noma T. "A infant Case of hypoactivity due to oral food intake" Allergy Prac. 2013; 33(12): 1144–1147	HE	6.0g	unknown
# 56	Kazuma N. "Heart rate variability of a boy with anaphylaxis caused by egg challenge" Jpn. J. Pediatr. 2009; 62(11): 2411–2417	HE	40g	15 min
# 57	Ito N, Inuo T, Takamasu T *et al.* "Successful treatment of rush specific oral tolerance induction for hen's egg allergy" Kanagawa Children's Med. Cent. J. 2008; 37(3): 121–124	other (dried EW)	45 mg	90 min
# 58	Horikawa Y, Kobayashi M, Misaki T *et al.* "A case of a 5-year-old girl with food allergy who was successfully partially tolerated by oral food challenge test" Ann. Saiseikai Nakatsu Hosp. 2005; 15(2): 192–196	HEY, Other (hamburger with1/6 HE, mayonnaise)	1/4 egg yolk (HEY), 1/6 egg (hamburger) 5g (mayonnaise)	1 time
# 59	Yanagida N, Minoura T, Kitaoka S, "Allergic reactions to milk appear sooner than reactions to hen's eggs: a retrospective study" World Allergy Organ. J. 2016; 9:12	HE	1 egg	1 time

[†] HE, heated egg; HEY, heated egg yolk; HEW, heated egg white; UE, unheated egg; UEY, unheated egg yolk; UEW, unheated egg white.

85.1% (1932/2270). The average symptom-free ratio of antigen-reduced eggs was as high as 73.0%. The symptom-free ratio of the OFC, which aimed for initiation of oral immunotherapy, was lower than that of OFCs for defining the threshold (22.4%, 50/223), and the average symptom-free ratio of each report was 13.9%.

There were five references (#1, #15, #37, #39, #44) with a symptom-free ratio of 0%. All of these articles judged whether nutritional guidance or oral immunotherapy was applicable to the patients. Partial ingestion of eggs was possible even when the OFC was positive in 19 reports (#2, #6, #11–13, #15–18). A total of 71.9% (556/771) of OFC-positive patients could eat a small amount of eggs after OFC. The mean ratio of patients who ended up consuming a certain amount of eggs was 73.5% in each report. By performing OFC, it would be possible to prove tolerance either completely or partially. As a result, we can avoid complete elimination.

Number of patients with SAEs in OFC

A total of 4182 cases of OFCs in 40 references (#1–2, #4, #6–7, #13–15, #18–19, #21–37, #49, #52–59) were indexed in this outcome. SAEs occurred in two patients in two references (#4, #23), and the rate of SAEs was 0.05% (2 cases/4182 cases). The details of the reported SAEs were as follows: 1) Unexpected hospitalization due to the development of urticaria with heated egg white OFC in an outpatient clinic (#23, 1 case) and 2) Extended hospital stay due to egg yolk OFC, although the reason for this was unknown (#4). Although the items did not meet the criteria for SAE, adrenaline was administered intramuscularly because of the induced symptoms in 33 (1.5%) of 2191 egg OFCs in 14 articles (#4, #6, #13–14,#18, #24–25, #27, #38, #42, #49, #53, #56, #58). The average ratio of adrenaline use for OFC in each article was 0.3%, the ratio of adrenaline use in all provoked symptoms in the articles was 4.8% (33 cases/686 cases = number of adrenaline used/total number of provoked symptoms), and the average rate of adrenaline use for provoked symptoms in each study was 3.7%. Some cases in the indexed articles needed a fluid infusion, suggesting there might be a possibility that extended hospitalization existed other than the previous two SAE cases, although this was not mentioned in the literature. There were five reports (#4, #14, #38, # 49, #58) on the adverse effects of OFCs when egg yolk or hypoallergenic egg were administered, and five reports (#13, #18, #24, #27, #42) on the adverse symptoms of OFCs when plain eggs, such as egg whites, were administered. The average ratio of adrenaline used for the

adverse effects of OFCs with hypoallergenic eggs and plain eggs was 4.5% and 4.1%, respectively.

All the 40 references included in this study were either case series or case reports; most of the indexed articles used open methods except for three references (#7, #37, #57). In those three references, one article used the combination of an open method and a double-blind placebo-controlled food challenge (DBPCFC); although the total ingestion amount and the duration of challenge was not clear (#7), one reference was a DBPCFC with a total amount of 1000 mg of freeze-dried raw egg powder in 15–20 min intervals; however, the number of participants were not described (#37), and the last case report used DBPCFC with freeze-dried egg whites in 15–20 min interval, and a threshold of 45 mg (#57). Since the purpose for the OFCs in those three references was recruitment for other studies, such as oral immunotherapy, and the small number of reliable blinded trials conducted in Japan, we should consider both performance and detection biases. We should also consider the inconsistencies in the differences in severity and the challenging dose of antigens for the patients.

Number of patients with AEs in OFC

Forty articles (#1–2, #4, #6–7, #13–15, #18–19, #21–37, #49, #52–59) were included in this outcome. Of the 4182 OFCs, AEs were reported in 1146 (27.4%) OFCs. The dosage of eggs varied in each OFC ranging from high antigenic food, such as unheated eggs (8 references) (#18, #23, #25, #35, #37, #39, #42, #57) to low antigenic food, such as heated egg yolks (22 references) (#4, #6, #14–15, #18–19, #21–22, #25–28, #31–32, #40, #41, #47, #49, #54, #58). In some OFCs, both high antigenic and low antigenic foods were challenged in the same patients. There were 20 references which reported that allergic symptoms occurred in OFC (#2, #4, #6–7, #9, #13, #15, #18, #21, #23, #26–27, #24–40, #49). The frequency of occurrence varied greatly among the references, ranging from 6% to 100% for skin symptoms, 4%–100% for gastrointestinal symptoms, and 0%–60% for respiratory symptoms, without counting case reports. Cardiovascular symptoms and neurological symptoms were reported in 0.6% of all reports. None of the references included in this study provided details of the allergic symptoms, severity, and duration of symptoms. Although there were a certain number of AEs reported in the indexed articles (27.4%, 1146/4182), all of the symptoms were manageable with medication. Thus, OFCs should be conducted with adequate preparation for the management of AE.

Number of patients with improved QOL due to OFC

Two case series (#12 and #28) discussed the health-related QOL without using internationally validated questionnaires. Since no other studies assessed QOL, we did not select any articles for this question.

Immunological changes

Two studies (#1, #54), which followed the alterations in serum IgE, were included in this question. One study was a case series that evaluated the alternation of egg white- and ovomucoid-specific IgE within 3 months of OFC and after 1 year of OFC. The participants in this study were 10 patients who were positive for OFC with less than 10 g of heated egg white. There was no significant difference in sIgE levels within 3 months or after 1 year. Another study was a case report of egg yolk-positive patients that compared the pre-OFC status of sIgE and post sIgE for egg yolk. In this case, the sIgE level was reduced after nutritional guidance followed by OFC. Patients in both studies received oral immunotherapy (nutritional guidance) after OFC; both studies were not blinded and did not have negative controls. Therefore, immunological alterations may be provoked by nutritional guidance rather than by OFC. For these results, indirectness, inconsistency, performance, detection, publication, and selection biases exist in this outcome. Evidence of immunological changes in OFC is poor. No studies were available which followed the alteration of the IgG4 and IgE levels in the OFCs.

Integration of results

The overall negative ratio of OFC was 62.7% (3354/5367), while the average symptom-free ratio of each report was 47.7%. Although only performing the OFC could not result in avoiding complete elimination of the egg, the percentage of OFC-positive patients who could improve in partial intake was 71.9% (556/771 positive patients), and the average percentage of patients who could partially intake in each report was 73.5%. The incidence of AE in the OFC was 27.4% (1146/4182) in all references. SAE occurred in two cases, and the rate of SAE was 0.05% (2 cases/4182 cases). Of the 2191 OFCs (1.5%), 33 required adrenaline intramuscular injection. Although two references exist that assess QOL for the egg OFC, these references had serious detection, and publication biases. Two references described immunological changes in the patients, but the results were inconsistent and hence, inconclusive.

The strength of the evidence related to this study

The evidence levels for each outcome are shown in Table 4. All the articles included in this study consisted of case series and case reports. Since most of the articles were open-labeled OFCs, there was a moderate risk of performance bias in every outcome. In contrast, the existence of an attrition risk of bias was lower in the features of OFC.

Discussion

In this study, we systematically reviewed the articles to evaluate whether OFC effectively prevents the complete elimination of hen's egg in patients diagnosed with IgE-mediated hen's egg allergy. An OFC is useful to avoid the complete elimination of eggs.

In previous reports, the ratio of hen's egg allergy differed based on the assessment and evaluation method using which the patient was diagnosed.[4,15] This result indicated that multiple assessments, as well as self-reported assessments, are essential for accurate results. Our results indicated that over 60% of the patients who were suspected of or diagnosed with egg allergy could avoid elimination of eggs; moreover, over 70% of the patients could avoid complete elimination of eggs, when including the patients who can partially tolerate eggs or those in whom it is not completely tolerated. For these reasons, by using OFC, a large number of patients could avoid the complete elimination of eggs. Compared to previous studies, the ratio of elimination was slightly higher in our study.[4] The accuracy of the diagnosis of food allergy may be the difference between previous studies, and that most of the cases included in this study in Japan were diagnosed by a board-certified allergologist and were not self-reported. We reviewed the negative ratio of the OFC for evaluation of the number of patients who were able to avoid complete elimination, which indicated slight differences in evidence and data, i.e., we could not determine whether the patients would eat at home even after the negative OFC test because of the anxiety of anaphylaxis or the emerging allergic symptoms at home. While there were few reports in the systematic review confirming whether patients who tested negative for food allergy could consume food or not, the risk of indirectness may exist. However, The Japanese Pediatric Guideline for Food Allergy 2016 has recommended rechecking at the outpatient clinic whether dose administration at the OFC has been appropriately undertaken at home to confirm that the food

Table 4
Assessment of evidence in each outcome.

Outcomes	The assessment point of evidence	Evidence levels of each outcome
1. Number of patients who were able to avoid complete elimination	1. Indirectness: weak 2. Risk of bias: performance 3. Inconsistency: weak	C
2. Number of patients with serious adverse events in OFC	1. Indirectness: weak 2. Risk of bias: performance, selection 3. Inconsistency: weak	C
3. Number of patients with adverse events in OFC	1. Indirectness: weak 2. Risk of bias: performance, selection 3. Inconsistency: weak	C
4. Number of patients who improved quality of life (QOL) due to OFC	1. Indirectness: strong 2. Risk of bias: detection, publication 3. Inconsistency: strong	D
5. Immunological changes	1. Indirectness: strong 2. Risk of bias: performance, detection, selection, publication 3. Inconsistency: strong	D

can be safely consumed even after the negative OFC test, and suggest repeated OFC test in undetermined cases, such as allergic symptoms at home even after a negative OFC result.[2] Furthermore, the guidelines suggested that by monitoring uncertain cases in OFC at home, more than 79% of patients were considered to have tolerance at the final diagnosis at the outpatient clinic.[16] The Japanese Pediatric Guideline for Food Allergy 2016 also made the following proposals: a limited elimination of the causative food, considering the severity of symptoms and ingestion of allergens even in patients with positive OFC; and educating patients about foods that are safe to consume and the efforts to improve QOL after OFC results.[2] The cumulative ratio of OFC negative patients may increase the number of patients who could avoid complete elimination.

Our results indicate that 27.4% of the patients showed AEs, and only 2 of 4182 patients (0.05%) showed SAEs, which were unexpected admissions and prolonged hospitalizations. The criteria for unexpected hospitalizations, extended admissions, and the use of medical equipment, including administration of adrenaline, may vary depending on the size and the situation of the facility, while the timing of the use of medication in anaphylaxis is standardized according to the Japanese Pediatric Food Allergy Guideline 2016 to some extent. In our review, there were a few reports that described cardiovascular symptoms. This may have been due to the incidences of cardiovascular symptoms being underestimated because of the lack of continuous monitoring of the cardiovascular conditions, such as continuous blood pressure monitoring or electrocardiogram during OFCs. There were no examinations related to death, intubation, or sequelae. Itazawa *et al.* reported in their multicenter study that 8.5% of broad food allergy patients experienced a certain AEs in OFC.[17] In contrast, our results showed that the ratio of AEs was relatively low compared to them. The OFC of cow's milk, which was performed at the same time, was also shown to be as high as 51% (Maeda *et al.*, *Allergol. Int. in press*). These results would indicate that egg OFC can be performed safely compared to other antigens. Egg white contains more than 20 different proteins and proteoglycans, whereas egg yolk contains fewer antigens than egg white.[6,18] Contrary to this evidence, our results showed that the incidence of AEs was not correlated with the difference in antigens such as egg yolk or egg white. Because most OFCs in this study were planned with open-label and stepwise increase methods in Japan, the majority of low-risk patients who performed OFC against highly antigenic food, had a tendency to skip OFC to egg yolk according to the decision of allergologists. In addition, the articles referenced in this report had large variability in the upper limits of antigen administration and the intervals of the OFCs. Therefore, these results need to be interpreted with caution.

Consequently, egg yolk OFC may draw more serious patients in comparison with egg white OFC. Possible selection bias may exist in terms of the patients' severity against egg yolk and egg white OFC. On the other hands, a careful adjustment of the initial intake dose in severe egg allergy might have been made in the study. Thus, a careful assessment of the severity of egg allergies is important in preventing AEs. Although SAEs were rarely observed, intramuscular adrenaline was used in 1.5% of the egg OFCs. These data indicate that patients may require a high level of medical care in cases of AEs. Healthcare providers who are in charge of OFCs should be prepared and ready for anaphylaxis.[19–22]

A limitation of our study was that all the articles that met the inclusion criteria were case series or case reports without controls. In addition, with low levels of evidence, it was challenging to determine whether OFC negative patients continued consuming eggs even after the OFC test. Moreover, there were inconsistencies due to differences in the amount of allergens, antigen preparation and cooking methods, severities of the patients, and differences in the purposes of OFCs, such as elimination of food avoidance or introduction of oral immunotherapy.

In conclusion, among the patients in Japan diagnosed with or suspected of having IgE-mediated egg allergies, OFCs should be performed to avoid the complete elimination of eggs. However, the examiners should proceed with the OFC with great caution to prevent AEs. Further studies are needed to analyze the QOL improvement related to OFC in Japan.

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Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

HM performed the quality assessment and analyzed the data, and was the primary author of the systematic review. MI, MS, YT, KT, and TW entered and analyzed the data and revised the manuscript. KYH, IO, YY, and MF planned the study design, and ME supervised the study and critically reviewed the manuscript. All authors have read and approved the final manuscript.

References

1. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014;**69**:1008–25.
2. Ebisawa M, Ito K, Fujisawa T, Committee for Japanese Pediatric Guideline for Food Allergy, The Japanese Society of Pediatric Allergy and Clinical Immunology; Japanese Society of Allergology. Japanese guidelines for food allergy 2020. *Allergol Int* 2020;**69**:370–86.
3. Urisu A, Ebisawa M, Mukoyama T, Morikawa A, Kondo N, Japanese Society of Allergology. Japanese guideline for food allergy. *Allergol Int* 2011;**60**:221–36.
4. Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy* 2014;**69**:992–1007.
5. Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol* 2014;**134**:1016–25.e43.
6. Urisu A, Kondo Y, Tsuge I. Hen's egg allergy. *Chem Immunol Allergy* 2015;**101**:124–30.
7. Lee S. IgE-mediated food allergies in children: prevalence, triggers, and management. *Korean J Pediatr* 2017;**60**:99–105.
8. Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM, et al. Prevalence and severity of food allergies among US adults. *JAMA Netw Open* 2019;**2**:e185630.
9. Boyano-Martínez T, García-Ara C, Díaz-Pena JM, Martín-Esteban M. Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy. *J Allergy Clin Immunol* 2002;**110**:304–9.
10. Hattevig G, Kjellman B, Johansson SG, Björkstén B. Clinical symptoms and IgE responses to common food proteins in atopic and healthy children. *Clin Allergy* 1984;**14**:551–9.
11. Imai T, Sugizaki C, Ebisawa M. [A report on 2011 nationwide survey of immediate type food allergies in Japan (supported by a grant from "Consumer Affairs Agency, Government of Japan")]. *Arerugi* 2016;**65**:942–6 (in Japanese).
12. Muto M, Matsufuji H, Taguchi T, Tomomasa T, Nio M, Tamai H, et al. Japanese clinical practice guidelines for allied disorders of Hirschsprung's disease, 2017. *Pediatr Int* 2018;**60**:400–10.
13. Santos AF, Du Toit G, O'Rourke C, Becares N, Couto-Francisco N, Radulovic S, et al. Biomarkers of severity and threshold of allergic reactions during oral peanut challenges. *J Allergy Clin Immunol* 2020;**146**:344–55.
14. Mizuno Y, Ohya Y, Nagao M, DunnGalvin A, Fujisawa T. Validation and reliability of the Japanese version of the food allergy quality of life questionnaire-parent form. *Allergol Int* 2017;**66**:290–5.
15. Rona RJ, Keil T, Summers C, Gislason D, Zuidmeer L, Sodergren E, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007;**120**:638–46.
16. Miura T, Yanagida N, Sato S, Ogura K, Ebisawa M. Follow-up of patients with uncertain symptoms during an oral food challenge is useful for diagnosis. *Pediatr Allergy Immunol* 2018;**29**:66–71.
17. Itazawa T, Adachi Y, Takahashi Y, Miura K, Uehara Y, Kameda M, et al. The severity of reaction after food challenges depends on the indication: a prospective multicenter study. *Pediatr Allergy Immunol* 2020;**31**:167–74.
18. Caubet JC, Wang J. Current understanding of egg allergy. *Pediatr Clin North Am* 2011;**58**:427–43. xi.
19. Allen CW, Bidarkar MS, vanNunen SA, Campbell DE. Factors impacting parental burden in food-allergic children. *J Paediatr Child Health* 2015;**51**:696–8.
20. Franxman TJ, Howe L, Teich E, Greenhawt MJ. Oral food challenge and food allergy quality of life in caregivers of children with food allergy. *J Allergy Clin Immunol Pract* 2015;**3**:50–6.
21. Greenhawt M. Food allergy quality of life and living with food allergy. *Curr Opin Allergy Clin Immunol* 2016;**16**:284–90.
22. Warren CM, Jiang J, Gupta RS. Epidemiology and burden of food allergy. *Curr Allergy Asthma Rep* 2020;**20**:6.