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Original Article

Is oral food challenge test useful for avoiding complete elimination of cow's milk in Japanese patients with or suspected of having IgE-dependent cow's milk allergy?

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3, Outcome-3; O-4, Outcome-4; O-

5, Outcome-5; OFC, Oral Food Challenge

Test; QOL, Quality of Life; RCT, Randomized

Controlled Trial; SAE, Serious Adverse

Event; SPT, Skin Prick Test

ABSTRACT

Background: Cow's milk, along with hen's egg, are common causes of food allergies in children worldwide. Accidental ingestion of milk is common and often induces severe allergic reactions. Oral food challenge test (OFC) is usually performed in patients with or suspected of having a food allergy. However, the evidence of whether cow's milk OFC is useful in IgE-dependent cow's milk allergy patients to avoid total elimination is not known.

Methods: After setting the clinical question and outcomes, we performed a systematic review for relevant articles published from January 1, 2000 to August 31, 2019 using PubMed® and Ichushi-Web databases. Each article was then evaluated for the level of evidence. All positive results of the OFC were defined as adverse events.

Results: Forty articles were selected in this study. Our review revealed that cow's milk OFC was able to avoid the complete elimination of cow's milk in 66% of the patients with cow's milk allergy. We also found that adverse events occurred frequently (50.5%).

Conclusions: This analysis supports the recommendation of conducting cow's milk OFC to avoid complete elimination of cow's milk, however the test should be conducted with careful consideration of the patient's safety. As the methods of OFC and subjects varied among the articles selected in this study, further studies are needed to obtain higher quality evidence.

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Introduction

Cow's milk (CM), along with hen's egg, are common causes of food allergies in children worldwide.^{1,2} The prevalence of self-reported CM allergy varies between 1% and 17.5% in preschoolers, 1% and 13.5% in school-age children, and 1% and 4% in adults.³ A meta-analysis⁴ reported CM sensitization rates of 0.5%–2%, 0.5%,

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and less than 0.5% in preschoolers, school-age children, and adults, respectively. The rate of milk allergies diagnosed by oral food challenge tests (OFC) has been reported as 1.2%–7.2%.^{5–7} In addition, CM is the second most frequent cause (after hen's eggs) of accidental ingestion that induces allergic reactions in Japanese children.⁸ The prevalence rates of CM allergy symptoms have been reported as: 15%–22%, respiratory; 32%–60%, gastrointestinal; 5%–90%, skin; and 0.5%, anaphylaxis.^{6,9–11} CM allergy is one of the leading causative foods associated with adrenaline use and is reported to account for 10%–28% of anaphylaxis cases, which requires treatment with more than one dose of adrenaline.^{12–16}

Information collected from patient interviews, allergen-specific IgE tests, skin prick test (SPT), and/or OFC are required to diagnose food allergies. A previous study reported that allergen-specific IgE tests and SPT for CM showed good sensitivity but low specificity; therefore, sensitization is not always the cause of allergies.¹⁷ If the diagnosis of CM allergy was only based on specific IgE or SPT results, a group of sensitized but non-allergic subjects would pointlessly undergo a CM elimination diet. Hence, it is generally believed that OFC is most useful for the diagnosis of food allergies.

The World Allergy Organization Diagnosis and Rationale for Action against CM Allergy Guidelines¹⁸ shows that the OFC is currently considered the “gold standard” for diagnosing food allergies, which can minimize false positives. However, little evidence exists regarding whether CM OFC is useful in IgE-dependent CM allergy patients to avoid complete elimination. According to the European Academy of Allergy and Clinical Immunology Food Allergy and Anaphylaxis Guidelines,¹⁹ the evidence level of an OFC is currently Level IV (no reference standard) and is considered a matter of expert opinion.

In Japan, OFC has been widely conducted²⁰ and has been covered by insurance since 2006. According to a 2016 report²¹ of 419 facilities that employ doctors who belong to the Japanese Society of Pediatric Allergy and Clinical Immunology, the OFC implementation rate was 88.4%–99.8% (hospitals that treat more than 50 food allergic patients) indicating that OFC is already used in the routine diagnostic procedures for food allergies in our country.

The 2020 Japanese guidelines for food allergy²² indicate that an OFC is the most reliable method for identifying the causative food for a food allergy. OFC is usually required to confirm the diagnosis of a food allergy, monitor food allergies, or prove oral tolerance to a specific food.¹⁹ In addition to diagnosis and confirmation of tolerance acquisition, the 2020 Japanese guidelines for food allergy²² recommend a low-dose OFC, even in high-risk children, to potentially avoid complete elimination of the causative food. Based on the results of the OFC, the patient is instructed on which foods are safe to consume. The patient is then permitted to consume as much of each specific food up to the maximum dose achieved in the OFC. It is conceivable that this would improve a patient's quality of life (QOL) by avoiding an elimination diet.

In this study, we conducted a systematic review to determine whether CM OFC is useful in avoiding complete elimination of CM from the diets of patients in Japan with or suspected of having IgE-dependent CM allergy.

Methods

Structured question

We framed the clinical question as “Are oral food challenge tests useful for avoiding complete elimination of CM in Japanese patients with or suspected of having IgE-dependent CM allergy?” (Table 1). The OFC-related outcomes were set as follows: Outcome-1 (O-1): number of patients who were able to avoid complete elimination of CM; Outcome-2 (O-2): number of patients who

experienced serious adverse events (SAEs); Outcome-3 (O-3): number of patients who experienced adverse events (AE); Outcome-4 (O-4): improvement of QOL; and Outcome-5 (O-5): immunological changes (i.e., IgE, IgG4, SPT, basophil activation, regulatory T cells, etc.) (Table 1).

Data sources and search methodology

We searched for articles published from January 1, 2000 to August 31, 2019 using PubMed® and Ichushi-Web databases. We requested a literature search expert from the medical library for the literature search, which was conducted on October 14, 2019. The search strategy used for PubMed® is shown in Table 2, and the corresponding PubMed® search fields were used for the Ichushi-Web database search that is managed by the NPO Japan Medical Abstract Society. This systematic review included all study designs (randomized controlled trials [RCTs]; case reports; and case–control, cross sectional, and case series studies).

The systematic review method used in this study was based on the evaluation method described in the guidelines²³ on Hirschsprung's disease, which does not include strong evidence and only consists of case reports.

Eligibility criteria

We comprehensively collected academic papers of studies on OFC conducted at medical institutions in Japan for patients diagnosed with or suspected of having CM allergy. In this study, CM allergy was defined as IgE-dependent CM allergy; therefore, studies reporting on non-IgE-dependent CM allergy were excluded. The Japanese Food Allergy Management Guideline 2005 recommends conducting OFC for the diagnosis of food allergies.²⁴ In addition, we considered the recommendations from each country,^{18,19,25} set the search start date to January 1, 2000, and included articles written in Japanese or English.

Study selection

Five researchers who were pediatric allergists performed the study selection. The selection of articles was conducted in a three-stage process by two or more independent researchers. First, each researcher scanned the identified articles by title and classified each article as “include,” “exclude,” or “unclear.” Second, the abstracts of every article categorized as “include” or “unclear” were reviewed. Third, the full text of the articles rated as “include” or “unclear” was assessed according to the eligibility criteria described above.

Table 1
Clinical question and outcomes.

PICO	Are oral challenge tests useful for avoiding complete elimination of CM in Japanese patients with or suspected of having IgE-dependent CM allergy?
Patients	Patients with or suspected of having IgE-dependent CM allergy
Intervention	CM-OFCs
Comparison	Patients before CM-OFCs
Outcomes	1 Number of patients who were able to avoid complete elimination of CM 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.)

AEs, adverse events; CM, cow's milk; OFCs, oral food challenge tests; QOL, quality of life; SAEs, serious adverse events; SPT, skin prick test.

Table 2

PubMed search strategy.

Search No.	Search terms [search field description]
#01	"Milk Hypersensitivity" [MH]
#02	"Administration, Oral" [MH]
#03	#1 AND #2
#04	milk [TI] AND (hypersensitivity*[TIAB] OR allergy*[TIAB]) AND (challenge[TIAB] OR Provocation*[TIAB] OR Introduction*[TIAB])
#05	#3 OR #4
#06	#5 AND 2000:2019 [DP]
#07	#6 AND (JAPANESE [LA] OR ENGLISH [LA])
#08	#7 AND ("Meta-Analysis" [PT] OR "Meta-Analysis as Topic" [MH] OR "meta-analysis" [TIAB])
#09	#7 AND ("Cochrane Database Syst Rev" [TI] OR "Systematic Review" [PT] OR "Systematic Reviews as Topic" [MH] OR "systematic review" [TIAB])
#10	#7 AND ("Practice Guideline" [PT] OR "Practice Guidelines as Topic" [MH] OR "Consensus" [MH] OR "Consensus Development Conferences as Topic" [MH] OR "Consensus Development Conference" [PT] OR guideline*[TI] OR consensus [TI])
#11	#8 OR #9 OR #10
#12	#7 AND ("Randomized Controlled Trial" [PT] OR "Randomized Controlled Trials as Topic" [MH] OR random*[TIAB] NOT Medline [SB])
#13	#7 AND ("Clinical Trial" [PT] OR "Clinical Trials as Topic" [MH] OR (clinical trial*[TIAB] OR case control*[TIAB] OR case comparison*[TIAB]) NOT Medline [SB])
#14	#7 AND ("Epidemiologic Methods" [MH] 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])
#15	NOT #11 (#12 OR #13 OR #14) NOT #11
#16	NOT #7 (#11 OR #15)

DP, Date of Publication; LA, language; MeSH, Medical Subject Headings; MH, MeSH Terms; PT, Publication Type; SB, Subset; TI, Title; TIAB, Title/Abstract.
*Wild card character.

Data collection process and data items

The following data items were extracted from the articles by each researcher: study design, sample size, definition of disease, and results of interventions, including the incidence of AEs. The data were recorded in spreadsheets using Microsoft Excel 2013® (Microsoft Corporation; Redmond, Washington, USA). Each set of extracted data items was structured like an abstract.

All positive results of the OFC were defined as AEs. AEs may or may not have a causal relationship with the OFC. Although most of the symptoms associated with OFC are within the programmed results and may not be "adverse" reactions, we defined all positive results of the OFC as AEs because unexpected or severe symptoms other than those anticipated could occur. SAEs were defined as events leading to death; risk of death; hospitalization or extension of hospital stay; and disability or risk of disability. In addition, cases requiring respiratory and intensive care unit management with intubation and serious cases, such as hypoxic encephalopathy, were included.

Evaluation of 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.²³ Briefly, the assessment points were as follows: 1) indirectness, 2) risk of bias, and 3) inconsistency. We classified evidence for each outcome into the following four basic categories: A) high grade (indicating high confidence that the evidence reflects the true effect and that further research is highly unlikely to change our confidence in the estimate of the

effect); B) moderate grade (indicating moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of the effect and may change the estimate); C) low grade (indicating low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and D) insufficient grade (indicating that evidence is unavailable or too inadequate to draw a conclusion).

This review was not pre-registered with the International Prospective Register of Systematic Reviews (PROSPERO) because this review includes not only English articles, but also Japanese articles to represent the unique situation of OFC in Japan. However, the Food Allergy Committee of the Japanese Society of Pediatric Allergy and Clinical Immunology confirmed the search methods and evaluation items of this review on April 19, 2019.

Results

Selection process

The selection process for the articles is shown in [Figure 1](#). We identified 559 articles from the PubMed® database and 361 articles from the Ichushi-Web database. After title and abstract reviews, we assessed the full text of each of the remaining 76 articles (52 and 24 from the PubMed® and Ichushi-Web databases, respectively) for eligibility. Of the 76 articles, we excluded five articles due to duplication and 31 that were determined to contain irrelevant studies after evaluating the contents of the full text. Overall, 40 articles were included in this study ([Fig. 1](#)). The articles included in our systematic review are listed in the [Supplementary Table 1](#).

Study characteristics

The number of patients who avoided complete elimination of CM (O-1) was described in 17 articles, SAEs (O-2) in 22 articles, AEs (O-3) in 22 articles, QOL (O-4) in only one article, and immunological tests (O-5) in three articles. The outcomes of each patient before and after the OFC were compared.

Regarding the OFC methods described in the articles, the intake intervals varied from 15 to 60 min. Raw milk was the most common food used in the OFC, although the total dose of raw milk varied from 3 to 200 ml, followed by yogurt, lactic acid bacteria beverages, and processed foods containing CM. All facilities in the articles included in this study reported OFC results using the open method.

The subjects receiving CM OFC varied among the articles and included patients with: immediate reactions and confirmed allergen-specific IgE to CM, immediate reactions or confirmed allergen-specific IgE to CM, history of positive CM OFC results, moderate reactions to CM, immediate reactions to CM or infantile atopic dermatitis, and patients with immediate reactions or history of positive CM OFC results. The severity of CM allergies ranged from mild to severe.

Results of individual outcomes

O-1 number of patients able to avoid complete elimination of CM

A total of 17 articles reported on the number of patients who avoided complete elimination of CM, including six case-control studies (#2, 5, 9, 10, 21, 36); one cross-sectional study (#38); six case series studies (#1, 27, 32, 33, 35, 37); and four case reports (#15, 28, 29, 34). In total, 48% (407/856) of patients had negative OFC results, and the average negative rate for CM OFC was 51%.

The dietary guidance given to patients based on the OFC results was different among the reports. In six articles (#1, 5, 9, 28, 29, 34), CM intake was permitted only when the OFC was negative.

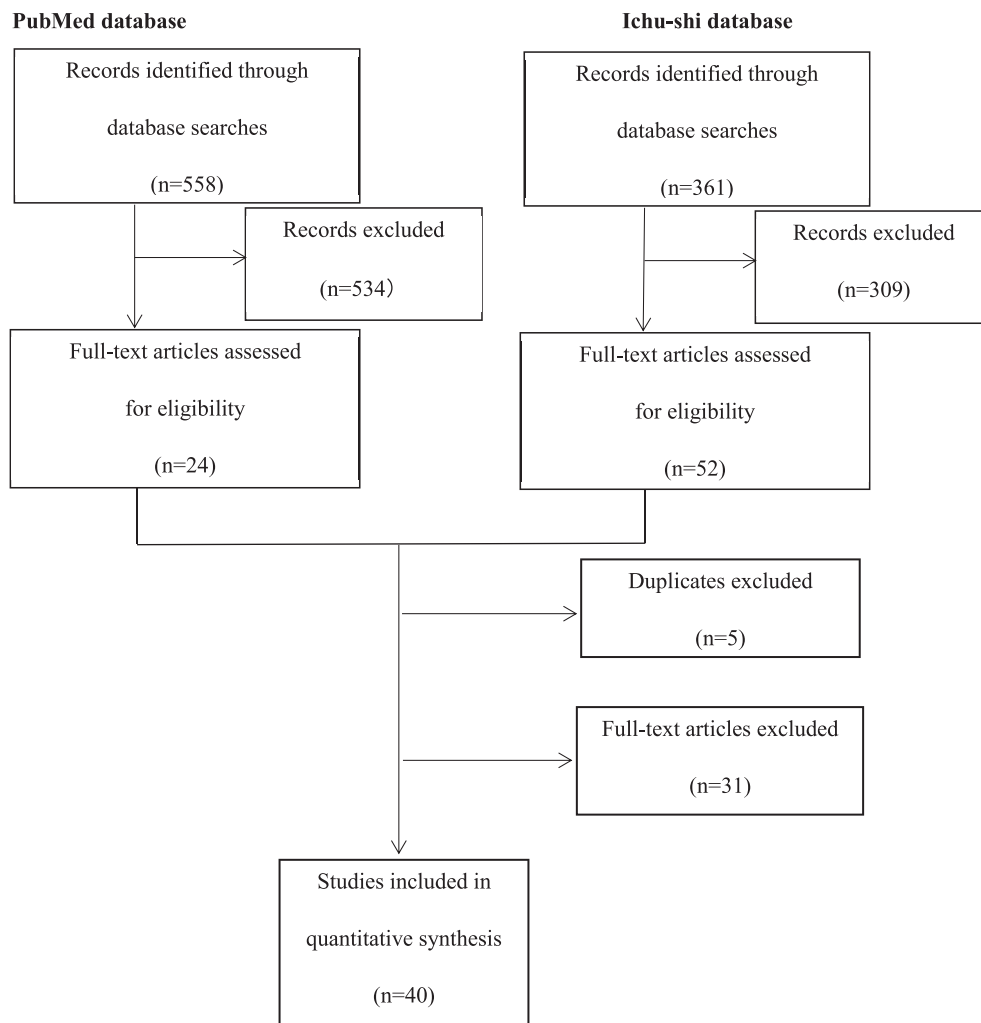


Fig. 1. Flow diagram for indexing the articles on the oral food challenge against cow's milk allergy.

However, in nine articles (#2, 9, 21, 27, 33, 35–38), the intake of CM within the upper limit was permitted even if the OFC was positive. The percentage of patients who avoided complete elimination of CM and the mean value of all reports were 66% (565/856) and 68%, respectively.

O-2 number of patients with SAEs

SAEs were reported in 22 articles, including one RCT (#18); two case controls (#7, 9); 16 case series studies (#1, 2, 4–6, 9, 22, 24–27, 31, 32, 35, 36, 40); and three case reports (#28, 29, 34). Of the 22 articles, 10 (#1, 5–7, 18, 24, 29, 31, 32, and 35) defined each level of severity. AEs, not SAEs, were reported in 386 (55.3%) of 698 patients. The only RCT (#18) among the 22 articles was a study comparing the symptom-suppressing effects of CM OFC that included the administration of supatast tosilate and ketotifen and was not a comparative study of OFC and non-OFC groups. Neither of the two articles (#7, 9) were case–control studies comparing the OFC and non-OFC groups.

No cases were reported in the included articles that met our definition of a SAE. According to 19 articles (#1, 2, 5–7, 9, 10, 14, 15, 22, 25–29, 31–34), 57 of 1252 cases (4.5%) required an intramuscular adrenaline injection as the result of an OFC. Some cases were also treated with infusions, which might be included under the SAE category of “extension of hospital stay.”

O-3 number of patients with AEs

The presence or absence of AEs was reported in a total of 31 articles: one RCT (#18); three case–control studies (#7, 9, 20); 23 case series studies (#1, 2, 4–6, 10–14, 18, 22, 24–27, 30–33, 35–36, 40); and four case reports (#28–29, #34, #36). Since AEs in this study were defined as any events that occurred during CM OFC, all positive symptoms, including mild or severe, during CM OFC were considered AEs.

Among the 1891 cases in the 31 articles, 1016 (53.7%) patients experienced AEs. After excluding nine articles (#15, 18, 28–31, 34, 36, 40) in which all subjects had a history of positive CM OFC, 893 of 1768 (50.5%) had AEs.

O-4 improvement of QOL

Only one case series study (#22) has evaluated QOL after CM OFC, and reported the results of OFCs using doses of processed dairy products equivalent to 25 ml of CM. They interpreted QOL as improved because patients with negative OFC could include a wider range of foods in their diets, including CM. No study has directly evaluated changes in QOL before and after CM OFC.

O-5 immunological changes

Three articles, including one case series study (#36) and two case reports (#28, 34), evaluated immunological changes. All of

them only reported changes in allergen-specific IgE, not IgG4, SPT, basophil activation test results, or regulatory T cells. One case series study (#36) reported that there was no significant change in milk-specific IgE levels before and after CM OFC. And, there was uniformity in the timing of the inspections in this study. Two case reports (#28, 34) showed that milk-specific IgE levels increased and decreased, respectively, after CM OFC.

We could not evaluate the immunological changes before and after CM OFC because only three articles were selected and their results were inconsistent.

Risk of bias across studies

The risk of bias summary for each outcome is presented in Table 3. Most of the articles selected in this study were case-control studies, case series studies, and case reports comparing patient outcomes before and after CM OFC. The only RCT (#18) was not a comparative study of the OFC and non-OFC groups described above. All OFC were performed using the open method; hence, we considered that there was a performance bias and a detection bias. The selection bias was small because the subjects had various milk allergy severities; however, there were inconsistencies due to differences in the subjects, the amount of CM used in the OFC, the food used in the OFC, and the severity of CM allergies. The attrition bias was considered small, as none of the articles were evaluated prospectively. Publication bias may exist in reports of post-CM OFC nutritional guidance and oral immunotherapy. Indirectness was indicated for QOL, since QOL was not directly evaluated, and processed dairy products were used in the CM OFC instead of raw milk. There was also a performance bias and detection bias because the subjects, OFC practitioners, and QOL evaluators were not blinded. For immunological changes, there was inconsistency, since the results of milk-specific IgE tests before and after CM OFC differed from article to article.

Discussion

In this study, we systematically reviewed for Japanese patients who were diagnosed with or were suspected of having IgE-dependent CM allergy to determine whether CM OFC is effective for avoiding complete elimination of CM. Our systematic review showed that CM OFC may be useful for avoiding the complete elimination of CM.

This systematic review revealed that the overall percentage of negative CM OFC was relatively high (48%). Among all patients receiving CM OFC, the percentage who were able to avoid complete elimination of CM was 66%. Even if the results of a CM OFC is positive, it is possible that many patients could avoid complete elimination of CM after being instructed on the safe intake amount of CM based on the results of their CM OFC. In Japan, “minimum avoidance of causative foods” is the principal strategy in food allergy management.²² Although eliminating causative foods is typically the principal treatment, a CM elimination diet also has nutritional consequences,^{26,27} and caution should be emphasized on avoiding eliminating these foods excessively.

Recently, various studies have shown that ingestion of food allergens, starting with small, gradually increasing doses, can cause desensitization, which consists of raising the threshold of reactivity to the food while ingesting the food.²⁸ Oral immunotherapy is one of the treatment options that increases doses beyond the threshold when immune tolerance to food cannot be expected naturally. However, oral immunotherapy for CM allergy is problematic because of the many AEs that can occur, and the success rate is lower than that of hen's egg allergy.^{29,30} In the Japanese guideline, the challenge test dose is set in steps according to the severity of the disease. By setting the OFC in stages, the negativity rate and safety of the OFC increases. Furthermore, shifting from complete avoidance to partial intake of milk by conducting an OFC, enables better management of these children.³¹ Therefore, we consider that it may be beneficial to introduce limited quantities of CM at a younger age to avoid completely eliminating it, and then increasing the quantity of CM provided, with time, to enhance the safe range of CM that can be ingested.

AEs occurred in 51% of the CM OFC, which is a fairly high rate. However, in this study, AE was defined as all positive results induced by a CM OFC, including mild symptoms. We considered that this result (51% AEs) was reasonable because the OFCs were conducted to confirm the presence or absence of allergic symptoms. Furthermore, unlike accidental ingestion, OFC can be performed relatively safely if the challenging volume is controlled. Perhaps because of this, there were no cases of SAEs, and there were no deaths or serious sequelae. However, we classified the cases of infusion as AEs not SAEs. This may have led to an underestimation. On the other hand, the intramuscular injection of adrenaline was used in 4.5% of all reported CM OFC that described treatment for allergic reactions. According to the report of a systematic review of hen's egg OFC conducted at the same time as this

Table 3
Assessment of evidence for each outcome.

Outcomes	Evidence assessment points	Evidence level
1. Number of patients who were able to avoid complete elimination of CM	1. Indirectness: weak 2. The risk of bias: performance, detection 3. Inconsistency: weak	C [†]
2. Number of patients with SAEs	1. Indirectness: weak 2. The risk of bias: performance, selection 3. Inconsistency: weak	C
3. Number of patients with AEs	1. Indirectness: weak 2. The risk of bias: performance, selection 3. Inconsistency: weak	C
4. Improvement of QOL	1. Indirectness: strong 2. The risk of bias: performance, detection 3. Inconsistency: strong	D [‡]
5. Immunological changes	1. Indirectness: strong 2. The risk of bias: implementation, detection, selection, reporting 3. Inconsistency: strong	D

AEs, adverse events; CM, cow's milk; QOL, quality of life; SAEs, serious adverse events.

[†] Low grade (low confidence that the evidence reflects the true effect and that further research is likely to change our confidence).

[‡] Insufficient grade (indicating that evidence is unavailable or too inadequate to draw a conclusion).

report, the incidence of AEs was 27% and the rate of intramuscular adrenaline use was 1.5%. We found that CM OFC was associated with a higher incidence of AEs and adrenaline use than with hen's egg OFC. Although pre-OFC risk assessment is important, the size of the SPT weals and allergen-specific IgE serum levels are not predictive of how severe the reaction will be when the result of the food challenge is positive.^{32,33} Keeping in mind that more severe symptoms will appear during CM OFC compared to hen's egg OFC, preparing medical devices and medicines for the treatment of AEs induced by CM OFC is of critical importance.

Most children with CM allergy are required to carry an adrenaline auto-injector at all times, as milk allergies have a high risk of inducing anaphylaxis.³⁴ Previous reports^{35,36} showed that this responsibility, in combination with dietary avoidance, has a deleterious effect on QOL for both the child and the caregiver. In this systematic review, we could not evaluate whether CM OFC could improve QOL because there were no articles that directly evaluated QOL before and after CM OFC. Hannah *et al.*³⁷ conducted a systematic review of QOL after OFC. Although not meta-analyzed, Hannah *et al.* showed that patients' QOL improved and the burden of food allergies was reduced after OFC. In Japan, further studies are needed to analyze the QOL improvement related to OFC.

We did not obtain sufficient evidence in this study regarding changes in immunological mechanisms after OFC. Since the immunological changes may be secondary effects of continuous allergen intake after OFC is instructed as a dietary guidance, the association between OFC and changes in immunological mechanisms should be evaluated accordingly.

The limitation of this study was that most of the articles were case series studies without controls or case reports, and there were no articles with high levels of evidence. There were also inconsistencies due to differences in nutritional guidance methods, subjects (such as age and reason for elimination of CM), purposes (i.e., the purpose of introducing oral immunotherapy and confirmation of resistance acquisition), amounts of CM used for the OFC, and severity of CM allergies.

In conclusion, our study suggests that CM OFC is useful for avoiding complete elimination of CM in the diets of Japanese patients with or suspected of having IgE-dependent CM allergy. However, CM OFC should be performed with great care due to the frequent occurrence of AEs.

Further prospective studies are needed to validate our results and analyze the QOL improvement related to CM OFC in Japan.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2021.09.001>.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

MM and YK performed quality assessments and data analysis, entered data, and were the primary authors of the article. YT, TN, and YH performed quality assessments and data analysis, entered data, and revised the manuscript. KYH, IO, YY, and

MF conceived and designed the study and critically revised the manuscript. ME provided overall supervision and critically revised the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary Table 1. List of articles included in systematic search

No.	Authors' names. Article title. <i>Journal Title</i> year;volume:pages.
#1	Yanagida N, Minoura T, Kitaoka S, Ebisawa M. A three-level stepwise oral food challenge for egg, milk, and wheat allergy. <i>J Allergy Clin Immunol Pract</i> 2018; 6 :658-60.
#2	Yanagida N, Minoura T, Kitaoka S. Butter Tolerance in Children Allergic to Cow's Milk. <i>Allergy Asthma Immunol Res</i> 2015; 7 :186-9.
#3	Ito K, Futamura M, Moverare R, Tanaka A, Kawabe T, Sakamoto T, et al. The usefulness of casein-specific IgE and IgG4 antibodies in cow's milk allergic children. <i>Clin Mol Allergy</i> 2012; 10 :1.
#4	Ito K, Futamura M, Takaoka Y, Morishita M, Nakanishi K, Sakamoto T. [Open food challenge with milk, egg white and wheat.] <i>[Jpn J Allergol]</i> 2008; 57 :1043-52. (in Japanese)
#5	Inuo C, Tanaka K, Nakajima Y, Yamawaki K, Matsubara T, Iwamoto H, et al. Tolerability of partially and extensively hydrolysed milk formulas in children with cow's milk allergy. <i>Asia Pac J Clin Nutr</i> 2019; 28 :49-56.
#6	Kawahara T, Tezuka J, Ninomiya T, Honjo S, Masumoto N, Nanishi M, et al. Risk prediction of severe reaction to oral challenge test of cow's milk. <i>Eur J Pediatr</i> 2019; 178 :181-8.
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#8	Yanagida N, Sato S, Asaumi T, Okada Y, Ogura K, Ebisawa M. A Single-Center, Case-Control Study of Low-Dose-Induction Oral Immunotherapy with Cow's Milk. <i>Int Arch Allergy Immunol</i> 2015; 168 :131-7.
#9	Okada Y, Yanagida N, Sato S, Ebisawa M. Better management of cow's milk allergy using a very low dose food challenge test: a retrospective study. <i>Allergol Int</i> 2015; 64 :272-6.
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#12	Tashiro M, Kuniyoshi Y, Hasegawa H, Yasuda S, Masuda Y, Ebisawa M. [Experience oral food challenge using dry food powder (single blind method).] <i>Medical Journal of Kensei Hospital</i> 2006; 29 :10-5. (in Japanese)
#13	Isozaki A, Shoda T, Kawano Y. [Clinical study of infant milk allergy.] <i>Medical Postgraduates</i> 2008; 46 :280-285. (in Japanese)
#14	Komata T, Shukuya A, Imai T, Tatimoto H, Ebisawa M. [Single blind food challenge using dried food powder-2nd Report.milk.] <i>[Jpn J Allergol]</i> 2009; 58 :779-89. (in Japanese)
#15	Inuo C, Ito N, Takamasu T, Kurihara K. [A case of oral milk immunotherapy.] <i>[Japanese Journal of Pediatrics]</i> 2010; 63 :999-1003. (in Japanese)
#16	Takaoka Y, Futamura M, Sakamoto T, Ito K. Analysis of the risk factors to persistent milk allergy.

	<i>[Jpn J Allergol]</i> 2010; 59 :1562-71.(in Japanese)
#17	Kawada Y. [Oral Food Challenge Test in the Private Outpatient Clinic.] <i>[Jpn J Pediatr Allergy Clin Immunol]</i> 2011; 25 :785-93. (in Japanese)
#18	Ito K. [Suppressive Effect of Supratast Tosylate on the Induced Symptoms of Oral Food Challenge Test.] <i>[The Allergy in Practice]</i> 2012; 32 :750-6. (in Japanese)
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#20	Kobayashi T, Kando N, Haneda Y, Yasui M, Maeda T, Umemura H, et al. [Diet instructions to consume the allergenic foods based on the results of an oral food challenge test.] <i>[Jpn J Pediatr Allergy Clin Immunol]</i> 2013; 27 :179-87. (in Japanese)
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#22	Yanagida N, Minoura T, Kidaoka S. [Milk and wheat food oral food challenge test using ready-made processed products] <i>[Japanese Journal of Pediatrics]</i> 2014; 67 :1699-1706. (in Japanese)
#23	Imai T, Yanagida N, Ogata M, Komata T, Tomikawa M, Ebisawa M. The Skin Prick Test is Not Useful in the Diagnosis of the Immediate Type Food Allergy Tolerance Acquisition. <i>Allergology Int</i> 2014; 63 :205-10.
#24	Yanagida N, Imai T, Sato S and Ebisawa M. [Study of methods of ingestion in oral food challenge tests.] <i>[Jpn J Pediatr Allergy Clin Immunol]</i> 2015; 29 :181-91. (in Japanese)
#25	Okayama Y, Hayashi T, Tomomori A, Ono S, Katayama T, Sugimoto S, et al. [Oral food challenge tests for children with food allergy in our outpatient clinic.] <i>[Jpn The Medical Journal of TSUYAMA Chuo Hospital]</i> 2015; 29 :9-14. (in Japanese)
#26	Yanagida N, Minoura T, Kitaoka S. [The Effect on Reduction of Eliminated Foods by Start of Stepwise Oral Food Challenge Test.] <i>[Jpn IRYO]</i> 2015; 69 :471-8. (in Japanese)
#27	Takei M, Yanagida N, Asaumi T, Sato S, Ebisawa M.[Oral lactose challenge tests for cow's milk allergy.] <i>[Jpn J Pediatr Allergy Clin Immunol]</i> 2015; 29 :649-54. (in Japanese)
#28	Meguro T, Shimomura M, Morishita H, Seto S, Kimura M. [A case of cow milk allergy developing urticarial rash after ingesting the first milk on the day of birth.] <i>[Jpn J Pediatr Allergy Clin Immunol]</i> 2016; 30 :178-83. (in Japanese)
#29	Yashiro A, Konishi T, Kidowaki S, Fujiki A, Isoda K, Fujiyo S, et al. [Clinical managements of the oral food challenge test among children with food allergy : a 3.5-year experience in a single institution.] <i>[Jpn Matsujinkai Medical Journal]</i> 2016; 55 :71-9. (in Japanese)
#30	Sugiura S, Sasaki K, Matsui T, Nakagawa T, Kando N, Ito K. Development of a prediction model for a severe reaction in cow's milk challenges. <i>Allergology International</i> 2018; 66 :493-5.
#31	Araki M, Hamahata Y, Usui M, Akashi M. [Use of multiple doses of adrenaline for food-induced anaphylaxis.] <i>[Jpn J Allergol]</i> 2018; 67 :751-8. (in Japanese)

#32	Kawahara T, Masumoto N, Tezuka J. [Risk factors for severe reactions in a low-dose oral food challenge in cow's milk.] [<i>Jpn J Pediatr Allergy Clin Immunol</i>]/2018; 32 :647-53. (in Japanese)
#33	Okura Y, Oshima Y, Yanazume N, Nawate M, Yoshioka M, Kobayashi I, et al. [The clinical benefit of an oral food challenge test in children under three years of age.] [<i>Jpn The medical journal of KKR Sapporo Medical Center</i>]/2017; 14 :26-32. (in Japanese)
#34	Hayashi R, Akamine Y, Ogawa E, Hashimoto K, Inamo Y. [A case of food allergy in a child who could stop an egg and wheat elimination diet using dietary guidance and oral food challenge test.] [<i>Journal of Nihon University Medical Association</i>]/2018; 77 :175-80. (in Japanese)
#35	Kusunoki T, Mukaida K, Inoue K, Nozaki F, Takeuchi J. [A "Feeding Approach" for patients on an elimination diet of egg, milk, and wheat by increasing the dose step by step from the safe intake level.] [<i>Jpn J Pediatr Allergy Clin Immunol</i>]/2018; 32 :762-71. (in Japanese)
#36	Inuzuka Y, Natsume O, Matsunaga M, Kato Y, Hakamata A, Mizoguchi Y, et al. [Evaluation of slow oral immunotherapy for food allergies in our hospital.] [<i>Japanese Journal of Pediatrics</i>]/2019; 72 :863-70. (in Japanese)
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