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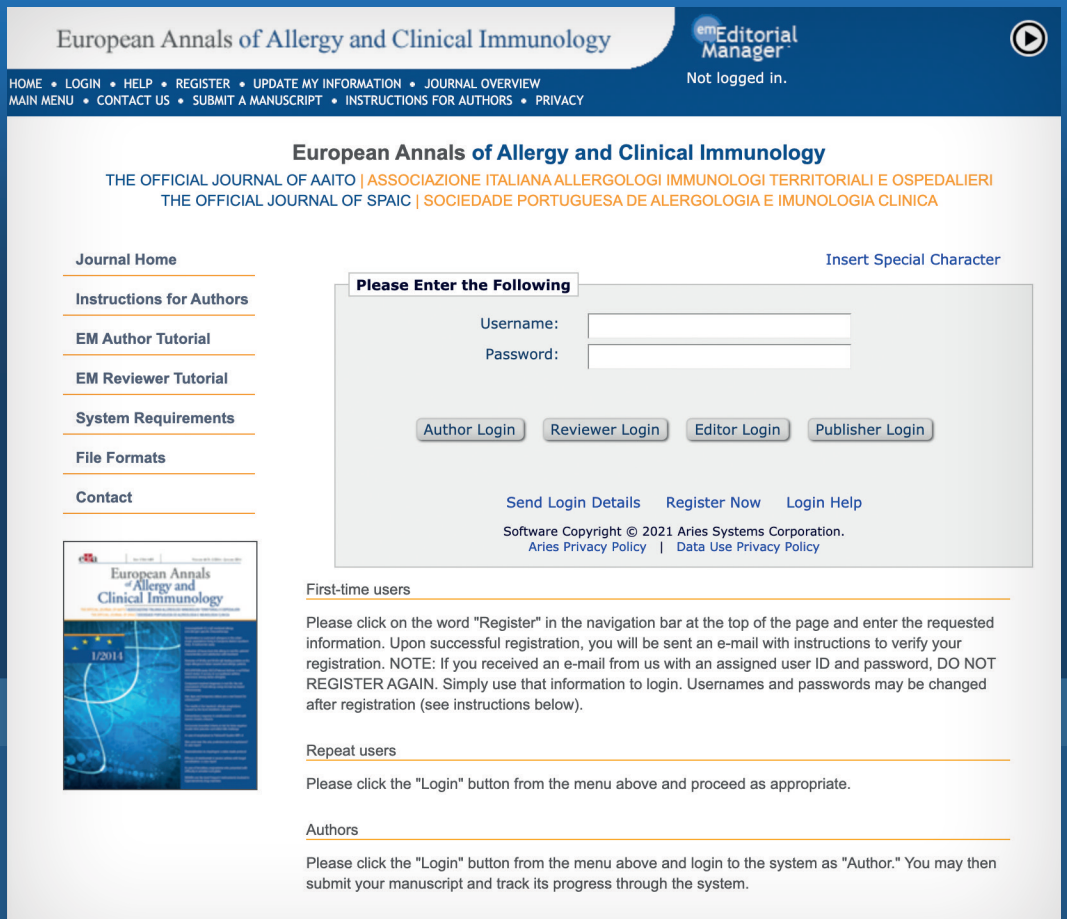
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Table of Contents

Review

Probiotics, prebiotics and food allergy: a review 99
Joana Filipe Ribeiro, Cláudia Pedrosa

Original articles

Association of asthma risk factors and the prevalence of the disease in a population of Brazil 111
Sabrina T. Reis, Patrícia Candido, Amir Zeide Charruf,
Renata Maximiano Meiga, Poliana Romão, Alexandre Teruya,
Eunice Higuchi, Katia Ramos Moreira Leite, Victor Srougi

Factors effecting natural course of egg allergy 116
Handan Duman Şenol, Mehmet Geyik, Ezgi Topyildiz,
Ayşe Aygün, Figen Gülen, Esen Demir

Predicting the outcome of the buckwheat oral challenge test: a first evaluation assuming a single serving of boiled buckwheat noodles 121
Kenta Horimukai, Misako Kinoshita, Noriko Takahata

Evaluation of pain-alleviating strategies during allergy shots (subcutaneous immunotherapy): a randomized controlled pilot study 128
Jennifer Pfieffer, Kristine Wehmeier, Karen Gee, Tracy DeSanto, Ejaz Yousef

Case report

Dupilumab to induce tolerance to SLIT-Melocotón®. 137
Maria Soledad Zamarro Parra, Yulia Petryk Petryk, Soledad San Roman Sirvent,
Cristina Navarro Garrido, Ana Isabel Escudero Pastor, Juan Carlos Miralles López,
Antonio Carbonell Martínez

Letter to the Editor

Atopic status and thyroid autoimmunity do not predict omalizumab response in severe chronic spontaneous urticaria patients 141
Riccardo Asero

REVIEW

Eur Ann Allergy Clin Immunol Vol 56, N.3, 99-110, 2024

Joana Filipe Ribeiro[1], Cláudia Pedrosa[2]

Probiotics, prebiotics and food allergy: a review

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Key words

Probiotics; prebiotics; food allergy; dysbiosis; microbiota.

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Impact statement

Probiotics and prebiotics are potential therapeutic interventions in managing cow's milk and peanut allergy. Oligosaccharides from breast milk show promising benefits in the prevention of atopic dermatitis, food allergy and asthma.

Summary

Background. *The prevalence of food allergy (FA) has increased, a possible consequence of intestinal dysbiosis, environmental or genetic factors. Currently, no formal indications exist for probiotic or prebiotic supplementation in FA. This review aims to analyze the role of probiotics and prebiotics in the prevention and treatment of FA.* ***Methods.*** *A PubMed/Medline search was carried out on articles published between 2011 and 2021 with the following query: ("Food Hypersensitivity"[Mesh]) AND (("Probiotics"[Mesh]) OR ("Prebiotics"[Mesh])). Subsequently, the titles and abstracts were analyzed and selected according to established criteria. After full reading of these articles, 54 were included and a narrative review was performed.* ***Results.*** *The review was structured in the following sections: 1) Cow's Milk Proteins Allergy (CMA), 2) Food Allergy to Peanuts and 3) Prevention of Food Allergy. In CMA, studies indicate that extensively hydrolyzed casein formula supplemented with Lactobacillus Rhamnosus GG aids in acquiring tolerance to cow's milk proteins, resolving gastrointestinal symptoms and preventing of other allergic manifestations. In peanut oral immunotherapy (OI), supplementation with Lactobacillus Rhamnosus CGMCC 1.3724 appears to promote sustained desensitization. However, the evidence supporting probiotics for preventing food allergies lacks robustness. Current evidence supports the use of oligosaccharides from breast milk in the first months of life for preventing atopic dermatitis, FA and asthma.* ***Conclusions.*** *The potential of probiotics to be used as therapeutic adjuvants in CMA and peanut OI is promising. However, there is inconsistency regarding the type of probiotic, the dose and duration of supplementation.*

Introduction

In last decades, food allergy (FA) prevalence has increased, particularly in industrialized countries, affecting up to 10% of children. Nonetheless, some figures are based on parent-reported data, potentially leading to overestimations (1, 2). Concurrently, clinical symptoms have also become more severe and FA prevalence is extending to older age groups (3). As in other chronic diseases, FA is the result of an interplay between genetic predisposition and environmental influences. Several factors have been identified as contributing to FA, encompassing both non-modifiable (male gender, Asian and African ethnicities, genetics and atopic dermatitis) and modifiable (microbial exposure/increased hygiene, use of antibiotics, diet, obesity, urban lifestyle and the timing/route of food exposure) elements (4-6). Cow's milk allergy (CMA) and peanuts are among the most common food allergens, exhibiting geographical and age-related variations (7, 8). Some of these have a high rate of recovery during childhood, such as CMA, egg allergy, wheat allergy and soy allergy; in contrast allergy to nuts and fish often persist over time (9). Typically, the immune system maintains a state of tolerance towards ingested food antigens (10). However, in individuals with FA there is an immunological deviation characterized by the impairment of Treg cell activation and their

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replacement by antigen-specific TH2 cells, leading to IgE-mediated, non-IgE-mediated or mixed (IgE and cell-mediated) allergic responses (5, 11). The management of FA involves allergen avoidance, desensitization therapies and acute drug treatments, in the event of accidental ingestion (5).

The human gastrointestinal tract is colonized by a complex ecosystem of microorganisms, called the intestinal microbiota (IM). Its composition undergoes continuous changes influenced by factors such as the intestinal mucosa, regular diet, peri-partum factors, medication use and interactions with the host immune system (12, 13). Dysbiosis refers to an unbalanced alteration of the IM, characterized by decreased microbial diversity and an overgrowth of proteobacteria, which has implications for shaping food tolerance (12, 14, 15). This implies that the IM plays a crucial role in programming the developing immune system in the early months of life, and the increased prevalence of allergies may be linked to intestinal dysbiosis during infancy (16, 17).

Probiotics are formed by strictly selected live microorganisms that, when administered in adequate amounts, confer a benefit in the health condition of the receiver (18). These microorganisms have a modulatory effect on IM, colonizing and suppressing the action of pathogens, as well as in metabolic control, with a regulatory effect on cholesterol absorption and glucose metabolism (19). Another impact is the immunomodulation of IM, with the induction and maintenance of immunological tolerance by 1) promoting Th1 cell production and Treg cell development; 2) supressing Th2 and IgE production (19-21).

Prebiotics are non-digestible food components that promote the growth and activity of a limited number of bacteria at the colonic level and modify the composition and activity of the IM to confer benefits to the host (22-24). The most commonly used prebiotics are non-digestible carbohydrates, such as fructooligosaccharides (FOS) and galactooligosaccharides (GOS) (25). The rationale for the use of probiotics and prebiotics in food allergy is grounded in their potential to modulate the gut microbiota, regulate the immune system response, strengthen the gut barrier to reduce the translocation of allergenic proteins and other molecules into the bloodstream and reduce inflammation, all while maintaining a favorable safety profile.

In summary, FA is a complex disease caused by an immunological imbalance and therapeutic options are still limited. The increasing prevalence of FA highlights the need for further research to evaluate the potential role of probiotics and prebiotics in the prevention and treatment of this condition. Currently, there are no recommendations from scientific societies endorsing the use of a particular strain of probiotic or prebiotic for the prevention and treatment of FA (26, 27). Nevertheless, selected strains of *Lactobacillus* and *Bifidobacterium* have been investigated in this context. Notably, a recent systematic review as provided evidence supporting the potential benefits of probiotics, as they have been shown to promote immunomodulation, reduce clinical symptoms and may contribute to the management of children with FA (28). A recent review addressing probiotics supplementation in confirmed CMA, demonstrated that it could be beneficial for early acquisition of tolerance to cow's milk protein in affected individuals (29). Conversely, a distinct review focusing on the supplementation of probiotics and prebiotics in allergies concluded that they may serve as adjuncts in preventing atopic dermatitis but not other forms of allergic diseases. Furthermore, the effects of probiotics and prebiotics on the treatment of allergic diseases remain a topic of controversy (30).

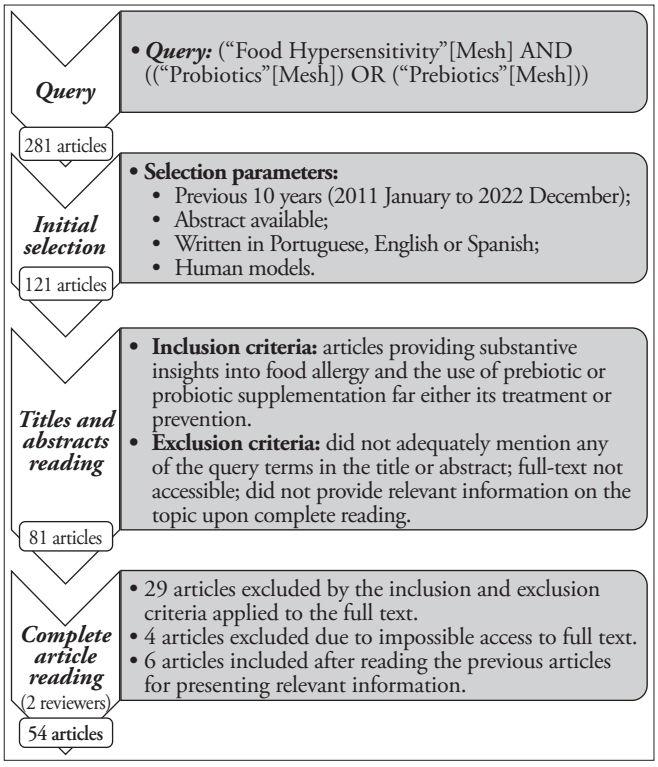
This article is a narrative review that aims to evaluate the existing literature on the use of probiotics and prebiotics in FA.

Methods

In this narrative review, the PubMed/Medline database was used and the search was conducted using the following query: ("Food Hypersensitivity"[Mesh]) AND (("Probiotics"[Mesh]) OR ("Prebiotics"[Mesh])).

To ensure the selection of current and relevant literature (31), articles published in the last 10 years (2011 January to 2022 December, inclusive), whose abstract was available for reading, written in Portuguese, English or Spanish and whose studies were in

***Figure 1** - Selection diagram of the articles used for the preparation of this narrative review.*



human models were included. The article typology did not constitute an exclusion factor. After this initial selection, articles were selected if they provided insights into FA and the use of prebiotic or probiotic supplementation for either its treatment or prevention. Exclusion criteria included articles that did not adequately mention any of the query terms in the title or abstract and those whose full text was not possible to access. Articles were also excluded after reading them completely, when they did not present relevant information on the topic. Six articles were included that were not in the initial selection, but were referenced in the articles read, as they presented relevant information related to the topic. In the end, 54 articles were included in this narrative review and an evaluation was carried out by two reviewers to ensure the relevance of the selected literature (**figure 1**).

Results

Immune tolerance is the most important therapeutic target in FA and is modulated by immune and non-immune mechanisms. Intestinal dysbiosis seems to contribute to the development of allergic diseases, as IM and its metabolites play an important role in immune tolerance (6, 26). However, it is still not clear that maintaining IM balance will induce food tolerance (16). Therefore, it is relevant to better understand the possible role of probiotics and prebiotics in the pathogenesis of FA.

The majority of studies carried out with prebiotics and probiotics are in CMA and peanut allergy. Other studies investigating fish and shellfish allergy, have not yielded clear beneficial results (32, 33). Therefore, the article is divided into tree topics for better clarification and comprehension: 1) Cow's Milk Proteins Allergy (**table I**); 2) Food Allergy to Peanuts (**table II**); 3) Prevention of Food Allergy (**table III**).

Cow's milk proteins allergy

CMA has an important economic and social impact. Elimination diets and extensively hydrolyzed milk formulas are the first line treatments. In severe cases, it may be necessary to use amino acids milk formulas (29, 34). **Table I** presents the results of 16 articles regarding probiotics in CMA.

The use of extensively hydrolyzed casein formula (EHCF) supplemented with *Lactobacillus rhamnosus* GG (LGG) in IgE-mediated and non-IgE mediated CMA has been proved to be more effective in preventing other allergic manifestations than the formula alone (35-38). In addition to this beneficial effect on the prevention of other atopic manifestations, there is also a modulation of tolerance to cow's milk proteins (CMP), which is earlier in children treated with EHCF and LGG when compared to children treated with EHCF alone within a period of 36 months (35, 37, 39, 40). Tolerance to CMP at

Table I *- Summary of probiotics and prebiotics and their impact in cow's milk allergy.*

Supplement	Article	Sample / Intervention / Duration / Dose	Outcomes	Main results
Probiotics				
Lactobacillus rhamnosus GG	Canani RB *et al.* 2013 (Prospective Cohort Study) (41)	n = 260 children with CMA / EHCF *vs* EHCF + LGG *vs* hydrolyzed rice formula *vs* SF *vs* amino acid-based formula / 12 months.	Rate of acquisition of milk tolerance.	EHCF accelerates tolerance acquisition in children with CMA when compared with other dietetic choices, this effect is augmented by LGG.
	Canani RB *et al.* 2016 (RCT) (35)	n = 220 patients with CMA / EHCF *vs* EHCF + LGG / 36 months.	Primary: occurrence of other allergic manifestations in CMA; Secondary outcome: acquisition of tolerance at 12, 24 and 36 months-old.	EHCF + LGG reduces the incidence of other allergic manifestations. EHCF + LGG accelerates the development of oral tolerance in children with IgE-mediated CMA.
	Canani RB, Sangwan N *et al.* 2016 (RCT) (42)	n = 39 (healthy children: 20; children with CMA: 19) / EHCF with *vs* without LGG.	Gut microbiota evaluation from fecal samples of 4 groups: (i) Healthy controls; (ii) CMA infants before treatment; (iii) CMA patients after EHCF alone; (iv) CMA patients after EHCF + LGG.	EHCF + LGG promotes tolerance in infants with CMA, in part, by influencing the strain-level bacterial community structure of the infant gut. *Blautia, Roseburia* and *Coprococcus* were significantly enriched following treatment with EHCF + LGG, but only Oscillospira was significantly different between infants that became tolerant and those that remained allergic. Most tolerant infants showed a significant increase in fecal butyrate levels.

Supplement	Article	Sample / Intervention / Duration / Dose	Outcomes	Main results
	Guest JF *et al.* 2018 (RCT) (45)	n = 220 children with CMA / EHCF + LGG *vs* EHCF alone *vs* AAF / 36 months.	Cost-effectiveness of EHCF + LGG *vs* EHCF alone or AAF in treating CMA in the US, from the perspective of third-party insurers and from parents.	The probability of developing tolerance to cow's milk was higher in EHCF + LGG *vs* EHCF alone or AAF. Infants fed with EHCF+LGG are expected to utilize fewer healthcare resources. Initial management of CMA with EHCF + LGG was a cost-effective strategy when compared to an eHCF alone or AAF.
	Guest JF *et al.* 2019 (Retrospective Cohort Study) (38)	n = 940 children with CMA / EHCF + LGG *vs* EHWF / 24 months.	Management of CMA and preventing other allergic manifestations.	First-line management of newly diagnosed CMA infants with EHCF + LGG appears to be more clinically effective than EHWF and may slow down the allergic march.
	Paparo L *et al.* 2019 (RCT) (39)	n = 20 children with CMA / EHCF + LGG *vs* SF / 12 months.	Evaluation of epigenetic mechanisms in CMA children (FoxP3 methylation rate; FoxP3 expression in $CD4^+$ T cells; IL-4, IL-5, IL-10, IFN-γ methylation rate, expression and serum concentration; miRNAs expression).	At 6 and 12 months, EHCF + LGG group showed a significant increase in FoxP3 demethylation *vs* SF group. EHCF+LGG group presented a higher increase in IL-4 and IL-5 and a higher reduction in IL-10 and IFN-γ DNA methylation rate *vs* SF group. A different modulation of miR-155, -146a, -128 and -193a expression was observed in EHCF + LGG group. Dietary intervention could exert a different epigenetic modulation on the immune system in CMA children.
	Guest JF Singh H 2019 (RCT) (40)	n = 220 children with CMA / EHCF + LGG *vs* EHCF / 36 months.	Cost-effectiveness of EHCF + LGG *vs* EHCF alone as first-line dietary management.	First-line management with EHCF+LGG instead of EHCF improves outcome, releases healthcare resources for alternative use, reduces the cost of patient management and thereby affords a cost-effective dietetic strategy.
	Nocerino R *et al.* 2019 (Prospective nonrandomized trial) (43)	n = 30 (healthy children: 110; children with CMA in the 1st year of life: 220) / EHCF alone *vs* EHCF + LGG *vs* healthy controls / 5 years and 4 months.	Occurrence of functional gastrointestinal disorders (FGIDs) later in life of children with CMA.	Increased risk for FGIDs in children with CMA, suggesting that EHCF + LGG could reduce this risk
	Basturk A *et al.*, 2020 (RCT) (53)	n = 106 children with CMA / Probiotic group: LGG (5 drops/day; LGG 1×10^9 CFU) + milk free diet (EHCF or breast milk of a mother on milk-free diet) *vs* placebo group: milk free diet / 4 weeks.	Symptoms (diarrhea, vomiting, mucousy or bloody stool, abdominal pain or distension, constipation, dermatitis and restiveness) recorded at the beginning and weekly during the study; Symptoms improvement between groups.	A significant improvement in symptoms (bloody stool, diarrhea, restiveness, abdominal distension, mucousy stool and vomiting) of infants receiving LGG + cow's milk-free diet was observed.
	Nocerino, *et al.* 2021 (Prospective Cohort Study) (37)	n = 365 patients with CMA / EHCF + LGG *vs* rice hydrolyzed formula *vs* soy formula *vs* EHWD *vs* amino acid-based formula / 36 months	Occurrence of other atopic manifestations and the time of immune tolerance acquisition.	EHCF + LGG for CMA treatment is associated with lower incidence of atopic manifestations. The 36-month immune tolerance acquisition rate was greater in the EHCF + LGG.

Supplement	Article	Sample / Intervention / Duration / Dose	Outcomes	Main results
***Lactobacillus rhamnosus* ŁOCK 0900, ŁOCK 0908 and *Lactobacillus casei* ŁOCK 0918**	Cukrowska B *et al.* 2021 (Multicenter randomized placebo-controlled trial) (46)	n = 151 children < 2 years of age with atopic dermatitis and CMA / Milk-free diet + mixture of three probiotic strains containing 1 × 10^9 CFU of selected bacteria (50% of *Lactobacillus casei* ŁOCK 0919, 25% of *Lactobacillus rhamnosus* ŁOCK 0908, 25% of *Lactobacillus rhamnosus* ŁOCK 0900) *vs* milk free diet alone / 12 months follow-up.	Primary: atopic dermatitis severity and changes in the proportion of children with clinical improvement *vs* no improvement *vs* deterioration. Secondary outcomes: levels of total serum IgE and the presence of allergen-specific IgE.	The probiotic strains are safe and induce beneficial effects in allergen sensitized patients. Supplementation of the children's diet with the probiotic preparation for 3 months resulted in a significant improvement in atopic dermatitis symptom severity.
***Bifidobacterium breve* C50 and *Streptococcus thermophilus* 065**	Morisset M *et al.* 2011 (RCT) (47)	n = 129 infants with high risk of atopy / non-hydrolyzed fermented infant formula with HKBBST *vs* standard infant formula / 24 months.	Primary: Effect of HKBBST milk on the incidence of CMA and cow's milk sensitization; Secondary: effect of HKBBST milk on the incidence of sensitization and/or allergy to other allergens and the incidence of allergic symptoms during the study period.	HKBBST milk did not alter the proportion of CMA. HKBBST decreased the proportion of positive skin prick tests to cow's milk, and the incidence of digestive and respiratory potentially allergic adverse events at 12 months, and that of respiratory PAAEs at 24 months. Fermented milks may represent a new dietetic strategy to promote oral tolerance to cow's milk.
***L. casei* CRL431 and *B. lactis* Bb-12**	Dupont C *et al.* 2015 (RCT) (48)	n = 119 infants with CMA / EHCF *vs* EHCF + *L. casei* CRL431 and *B. lactis* Bb-12 / 7 months.	Assess the tolerance and hypo-allergenicity of the EHCF along with its safety for growth in infants fed with EHCF.	EHCF + *L. casei* CRL431 and *B. lactis* Bb-12 did not improve tolerance in children with CMA. EHCF is safe, hypo-allergenic and nutritionally suitable for infants with CMA.
Probiotics + Prebiotics				
***Bifidobacterium breve M16-V*, inulin and oligofructose**	Sorensen K *et al.* 2021 (Retrospective matched cohort study) (49)	n = 148 infants with CMA / AAF-S *vs* AAF.	Baseline characteristics, clinical symptoms, infections, healthcare usage.	AAF-S was associated with fewer symptoms, infections, medication prescriptions and healthcare contacts *vs* AAF. Infants prescribed AAF-S had a significantly higher probability of achieving asymptomatic management without HAF. AAF-S showed potential cost-savings of £452.18/infant.
	Chatchatee P *et al.* 2022 (RCT) (50)	n = 169 infants with CMA / AAF-S (n = 80) *vs* AAF (n = 89) / 12 months; age-appropriate diet advised by clinician.	CM tolerance by food challenge.	At 12 and 24 months, respectively, 49% and 62% of subjects were CM tolerant (AAF-S 45% and 64%; AAF 52% and 59%), and not differ significantly between groups. No difference in adverse events. Fewer hospitalization due to infections in the AAF-S group (9% *vs* 20%)
Prebiotics				
2' fucosyl-lactose and lacto-N-neotetraose	Nowak-Wegrzyn A *et al.* 2019 (Prospective Nonrandomized Trial) (52)	n = 67 children with CMA / whey-based EHF with 2'Fland LNnT ("Test") *vs* EHF without HMO ("Control") / 100% whey-based EHF with HMO 2'FL (1.0g/L) and LNnT (0.5 g/L).	Hypoallergenicity evaluation, symptoms and adverse events.	Test formula was tolerated on the modified intention to treat (98.4%) and on the per-protocol (98.4%) analysis, meeting the clinical hypoallergenicity criteria.

AAF: amino acid formula; AAF-S: amino acid formula with symbiotics; CMA: cow's milk allergy; EHCF: extensively hydrolyzed casein formula; EHWF: extensively hydrolyzed whey formula; HAF: hypoallergenic formula; HKBBST: heat-killed Bifidobacterium breve C50 and Streptococcus thermophilus 065; HMO: human milk oligosaccharides; LNnT: lacto-N-neotetraose; RCT: Randomized Control Trial; SF: soy formula; 2'FL: 2'fucosyl-lactose.

Table II *- Summary of probiotics and their impact, when combined with specific immunotherapy, in peanut allergy treatment.*

Supplement	Article	Sample / Intervention / Duration / Dose	Outcomes	Main results
Probiotics				
***Lactobacillus rhamnosus* CGMCC 1.3724 (LR CGMCC)**	Tang ML *et al.* 2015 (RCT) (57)	n = 62 children with peanut allergy / PPOIT *vs* placebo / 18 months / LR CGMCC at dose of 2×10^{10} CFU and POIT once daily according to protocol.	Primary: induction of sustained unresponsiveness 2 to 5 weeks after discontinuation of treatment Secondary: desensitization, peanut skin prick test, and specific IgE and specific IgG4 measurements.	Significant sustained unresponsiveness (PPOIT: 82.1% *vs* placebo: 3.6%), desensitization (PPOIT: 89.7% *vs* placebo: 7.1%), reduced responses in peanut skin prick test and peanut-specific IgE levels and increased IgG4 in PPOIT group. PPOIT group reported higher adverse events.
	Hsiao KC *et al.* 2017 (follow-up RCT) (58)	n = 48 / PPOIT *vs* placebo / 4 years after treatment cessation.	Assess long-term outcomes in peanut intake and adverse reactions to this ingestion.	Patient previously treated with PPOIT were significantly more likely to have continued eating peanut; PPOIT (n = 4) and placebo (n = 6) participants reported allergic reactions to peanut. PPOIT provides long-lasting clinical benefit and persistent suppression of the allergic immune response to peanut.
	Galvin AD *et al.* 2018 (follow-up RCT) (60)	n = 51 / PPOIT *vs* placebo / 12 months after treatment cessation.	FAQLQ-PF and FAIM scores.	Patient previously treated with PPOIT showed significant improvement in FAQLQ-PF and FAIM scales at 3 and 12 months post-treatment.
***Lactobacillus rhamnosus* ATCC 53103**	Loke P *et al.* 2022 (RCT) (61)	n = 201 children with peanut allergy / PPOIT *vs* placebo probiotic + POIT *vs* placebo / 18 months / POIT: titration until 2000 mg daily; LR ATCC: 2 × 1010 CFU daily dose of the LR ATCC.	Primary: sustained unresponsiveness to peanut protein for 8 weeks; Safety endpoints: adverse events during the treatment and the 12-month post-treatment period.	Sustained unresponsiveness was significantly higher in the PPOIT (46%) and POIT (51%) groups *vs* placebo (5%), with no difference between PPOIT and POIT. Addition of a probiotic did not improve efficacy of POIT but might offer safety benefits.

CFU: colony-forming units; FAIM: Food Allergy Independent Measure; FAQLQ-PF: Food Allergy Quality of Life Questionnaire; POIT: peanut oral immunotherapy; PPOIT: Probiotic (*Lactobacillus rhamnosus* CGMCC 1.3724) and peanut oral immunotherapy; RCT: Randomized Control Trial.

12 months in children with CMA was also found to be higher in those treated with EHCF supplemented with LGG compared to those supplemented with EHCF alone or with other formulas such as rice, soy or amino acid formula (41). The addition of LGG to EHCF leads to an enrichment of IM in certain strains of bacteria, associated with the production and increased levels of fecal butyrate. Butyrate has been identified as a regulator of the functional epithelial barrier and, as such, a facilitator of oral tolerance induction (42). Nocerino *et al.* also demonstrated that children with CMA have an increased risk of developing functional gastrointestinal diseases, likely due to intestinal dysbiosis. This study also suggested that the temporary use of EHCF supplemented with LGG might reduce this risk when used in 4-6-year-old children with a past history of CMA. Several mechanisms may be responsible for this effect, such as the modulation of the IM structure and function, with an increase in butyrate production, and its interaction with epigenetic mechanisms, the immune system and gastrointestinal tract (43). Thus, LGG associated with EHCF appears to contribute to a favorable intestinal homeostasis, adjusting the microbial, metabolic and immune profiles of the intestinal environment (44). LGG supplementation is associated with a complex intestinal mucosal response, positively modulating the immune system (41). Additionally, the use of EHCF with LGG seems to be a beneficial and cost-effective strategy compared to EHCF alone or with amino acid formulas (40, 45).

Different probiotics have also been investigated in the treatment of FA. In a study, including children with CMA, the administration of a probiotic preparation containing a mixture of *Lactobacillus rhamnosus* ŁOCK 0900, *Lactobacillus rhamnosus* ŁOCK 0908 and *Lactobacillus casei* ŁOCK 0918 has found to be safe and effective, inducing a significant decrease in the severity of symptoms in sensitized patients (46). Moriset *et al.* found that in children, with high risk of atopy, a non-hydrolyzed milk formula containing *Bifidobacterium breve* C50 and *Streptococcus thermophilus* 065, consumed from birth until one year old, did not result in a lower incidence of CMA, but did result in less sensitization in skin prick tests for milk.

Table III - *Summary of probiotics and prebiotics and their impact in preventing food allergy.*

Supplement	Article	Sample / Intervention / Duration / Dose	Aims and outcomes	Main results
		Probiotics		
Bifidobacterium breve **M-16V (Bb M-16V)**	Ezaki S *et al.* 2012 (Retrospective cohort study) (72)	n = 30 / Bb M-16V supplementation (n = 18) *vs* no supplementation (n = 12) / From small intestine surgery until full enteral feeding / 1 × 10^9 UFC of Bb M-16V in a package of 1 g suspended in 2mL of sterilized water, 0.5 mL was administered enterally 3 times/day.	Evaluate the preventive effects of probiotics on CMA in newborns that underwent small intestine surgery.	CMA was induced in newborns after small intestine surgery, and it is possible that the disruption of intestinal flora plays a role. Administration of Bb M-16V can reduce the incidence of CMA after small intestine surgery.
Bifidobacterium longum **(BL999) and** ***Lactobacillus rhamnosus*** **(LR)**	Loo EX *et al.* 2014 (RCT) (66)	n = 220 infants at risk for allergy / Cow´s milk supplemented with BL999 and LR *vs* cow´s milk not supplemented since birth until 6 months-old / 5 years.	Determine if early-life supplementation with probiotics has a long-term effect on allergic outcomes.	Supplementation of probiotics did not prevent allergic diseases, namely food allergy, asthma, allergic rhinitis, eczema and sensitization to inhalant allergens.
		Probiotics + Prebiotics		
Mixture of probiotics and prebiotics *(Lactobacillus Rhamnosus* GG (LGG) + *Lactobacillus rhamnosus (*LR) ATCC 53103 + LR LC705 + *Bifidobacterium breve* Bb99 + *Propionibacterium freudenreichii ssp. shermanii JS* + Galacto-oligosaccharides*)*	Peldan PS *et al.* 2020 (RCT double-blind) (69)	n = 1,223 pregnant women and fetuses with a high allergy risk / Probiotics *vs* placebo since 36 weeks pregnant until delivery and their offspring with the same mixture of probiotics and a prebiotic since birth until 6 months-old / 13 years / Mother's probiotic group: LGG and LR ATCC 53103 (5 × 10^9 CFU) + *LR LC705* (5 × 10^9 CFU) + *B. breve* Bb99 (2 × 10^8 CFU) + *Propionibacterium freudenreichii ssp. shermanii JS* (2 × 10^9 CFU); Children probiotic group: same probiotics + Galacto-oligosaccharide (0.8 g).	Evaluate the prevalence of IgE sensitization up to 13 years in high-risk atopy children.	No significant difference in the prevalence of IgE sensitization to any of the tested allergens was found at 2.5 and 13 years of follow-up. At 13 years, IgE sensitization to cat and/or dog dander was more common in the probiotic *vs* placebo group.
		Prebiotics		
6'-sialyllactose + 2'-fucosyllactose (2´FL)	Zehra S *et al.* 2018 (Experimental study) (74)	n = 24 of human colonic cell lines seeded per well and cultured for 72 h / Well plates with HMOs (n = 12) *vs* well plates without HMOs (n = 12) / Incubation for 24h at 37 °C then stored at -20 °C until analysis.	Understanding the mechanisms underlying the beneficial effects of HMO on intestinal epithelial cell responses associated with allergy and inflammation.	Modulation of Ag-IgE complex activation of human epithelial cells may have important implications for food-allergy. Structurally different oligosaccharides have distinct biological activities.

BL999: *Bifidobacterium longum*; CFU: colony-forming units; CMA: Cow´s milk allergy; HMOs: Human Milk Oligosaccharides; IgE: immunoglobulin E; LR: *Lactobacillus rhamnosus*; RCT: Randomized Control Trial; SCFAs: short-chain fatty acid; 2´FL: 2'-fucosyllactose; 6´SL: 6'-sialyllactose.

However, this combination of probiotics with a non-hydrolyzed milk formula decreased the incidence of respiratory and gastrointestinal allergic events during the first months of life, even after the formula was discontinued (47). In contrast, Dupont *et al.* found that supplementation of an EHCF with a combination of two probiotics, *Lactobacillus casei* CRL431 and *Bifidobacterium lactis* BB-12, did not improve the acquisition of tolerance in children with CMA (48).

Regarding the use of prebiotics and probiotics in combination, Sorensen *et al.* described that the use of amino acid formulas supplemented with the probiotic *Bifidobacterium breve* M16-V and prebiotics (inulin and oligofructose) in CMA was associated with fewer

symptoms, infections, pharmacological prescriptions and health services utilization compared to the use of amino acid formulas without supplementation. Furthermore, this strategy has also been shown to have a beneficial economic impact (49). Chatchatee *et al.* also evaluated the use of an amino acid-based formula including synbiotics (prebiotic oligosaccharides, oligofructose, inulin, and probiotic *Bifidobacterium breve* M-16V) in infants with confirmed IgE-mediated CMA. Their goal was to compare the development of tolerance to cow's milk and safety of this combination *vs* the administration of an amino acid-based formula alone. They found that at 12 and 24 months, the acquisition of tolerance was not different between groups. As Sorensen *et al*., they found that during this intervention the group receiving synbiotics required less hospitalizations due to infectious diseases (50).

Dairy formulas supplemented with GOS and FOS increase the number of bifidobacteria in the IM. In preclinical studies, breast milk oligosaccharides (HMO) have been shown to attenuate allergic responses, making the prevention and treatment of CMA a potential area of research and future studies (51). In addition to FOS and GOS, a hypoallergenic effect of EHCF supplementation with 2 HMOs (2-fucosyl, lactose and lacto-n-neotetraose) has also been described in infants with CMA, when compared to EHCF alone (52).

Non-IgE mediated cow's milk proteins allergy

The pathogenesis of non-IgE mediated food allergies, such as eosinophilic esophagitis, food protein-induced enterocolitis syndrome, or proctocolitis, differs from that of IgE mediated allergies. Therefore, the rationale for potential benefits cannot be directly compared.

Qamer *et al*. demonstrated that, in presumed CMA, probiotic supplementation was not associated with a faster resolution of hematochezia when compared with placebo. However, in confirmed CMA, probiotic supplementation revealed a higher rate of acquisition of cow's milk protein (CLP) tolerance at 3 years when compared with the use of formula without probiotic supplementation (29).

Studies have also shown that LGG supplementation of EHCF is more effective in treating gastrointestinal symptoms in children with CMA and in decreasing intestinal permeability, decreasing fecal calprotectin levels and reducing the presence of occult blood in children's feces (38, 41, 53). In a case series described by Martin *et al.* infants aged 1-3 months who were clinically diagnosed with allergic proctocolitis saw complete symptom resolution with the administration of LGG probiotic alone, without requiring any dietary restrictions. These cases underscore the potential role of IM in the development of food allergies, and further research is warranted to elucidate the pathogenesis of allergic proctocolitis (54).

Food allergy to peanuts

Peanut allergy ranges from mild exacerbations to severe anaphylactic episodes, persisting throughout an individual's lifetime. Currently, no effective long-term treatment is available (55, 56). This section focuses on the use of pro/prebiotics in association with immunotherapy.

Recent studies have demonstrated the promise of specific oral immunotherapy (OI) as a treatment for peanut allergy (55, 57). Additionally, the combination of recombinant allergens with certain strains of probiotics has been shown to be a safe and immunologically effective strategy, given the modulating properties of probiotics in the immune system. Probiotic supplementation is carried with the goal of improving peanut desensitization and oral tolerance (55). The four main studies concerning supplementation of probiotics in association to OI are described in **table II**. Tang *et al.* performed the first randomized clinical trial of a combination therapy of OI for peanut and the probiotic *Lactobacillus rhamnosus* CGMCC 1.3724 (LR CGMCC) (57). This was also the first placebo-controlled trial to perform a double-blind oral challenge after a period of peanut food avoidance in allergy patients. They concluded that the use of OI plus LR CGMCC was highly effective, with 7 out of 9 treated children achieving possible sustained desensitization over time (57). Additionally, the use of OI plus LR CGMCC was also associated with a lower sensitization in skin prick tests, a decrease in the value of specific IgE and an increase in specific IgG4, suggesting a modulation of the allergic response to peanut (57). Subsequently, the same working group confirmed the efficacy of the combination therapy (OI plus LR CGMCC) and maintenance of peanut desensitization 4 years after discontinuation of treatment in most cases (58). In order to clarify the advantage and contribution of the probiotic in relation to OI, a study is being developed which compares the following intervention groups: 1) placebo; 2) combined therapy (OI plus LR CGMCC); and 3) OI alone (56). The group is also developing a similar study, but with OI for egg with the same probiotic (LR CGMCC), in order to induce desensitization in patients with egg allergy (59). Regarding quality of life, Galvin *et al.* proved that the use of OI and LR CGMCC was well tolerated and did not have a negative impact on the quality of life reported by parents, or on psychological well-being. In contrast, there appears to be an improvement in the quality of life reported by parents in cases of sustained response to treatment (60).

Another *Lactobacillus* – *Lactobacillus rhamnosus* ATCC 53103 (LR ATCC) – have been studied by Loke *et al.* and they found that both OI plus LR ATCC and OI alone were effective at inducing sustained unresponsiveness, with no significant differences between groups. Besides this, they found that addition of LR ATCC might offer a safety benefit compared with OI alone, with less adverse reactions, particularly gastrointestinal symptoms and in preschool children (61).

Prevention of food allergy

Studies reveal a lack of robust scientific evidence for the effectiveness in preventing FA with supplementation of specific strains of

probiotics in pregnant or breastfeeding women or in children with a high-risk atopy (18, 62-66). **Table III** comprises the four main articles found in the literature concerning prevention in food allergy.
Regarding supplementation during pregnancy, Ogrodowczyk *et al*. evaluated the associations between offspring's immunological markers (specific IgE profile and cytokine content) and maternal intake of special diets. They found that gestational probiotic supplementation yielded ambiguous results, likely due to variations in probiotic strains, doses, reasons, duration of use, and the route of administration. Gestational probiotic supplementation did not alleviate the severity of allergies in offspring, as indicated by high levels of total IgE and cytokines (67). Instead, when considering supplementation of pregnant/ breastfeeding women and newborns, a systematic review and meta-analysis conducted by Zhang *et al.* in 2016, reported that prenatal and postnatal administration of probiotics to mothers and newborns, could reduce the risk of atopy and food hypersensitivity, particularly in families at high risk of atopy. Despite this, the authors acknowledged the need for further studies to determine the optimal probiotic strain, dose and duration of therapy, as well as studies with longer follow-up periods (68). In this regard, a double-blind randomized clinical trial by Peldan *et al.* involving 1,233 pregnant women (whose fetuses were at high atopic risk) and their offspring, found that supplementation with a mixture of probiotics from 36 weeks of gestational age to birth and infants supplemented with the same mixture of probiotics and a prebiotic from 0 to 6 months did not affect the prevalence of sensitization to allergens up to age 13. Nevertheless, there was a tendency towards sensitization to aeroallergens in the probiotic-supplemented group at age 13 (69).

Discussion and conclusions

No studies have reported the effect of supplementation with specific strains of probiotics during pregnancy or lactation as a primary prevention of CMA (70, 71). However, the effect of mixtures of probiotics and prebiotics to increase IM diversity has been shown to reduce the risk of necrotizing enterocolitis in preterm neonates and may have similar benefits for the prevention of FA (51). Additionally, probiotic supplementation in newborns with short bowel syndrome, after intestinal resection surgery, seems to reduce the incidence of CMA in this population (72).
The prebiotic role of dietary oligosaccharides can be compared to that of HMOs. Clinical trials have demonstrated that dietary intervention with oligosaccharides in the first months of life can prevent atopic dermatitis, FA and asthma (73). Breast milk is considered the ideal diet for the first 6 months of life. However, in the absence of breastfeeding, milk formulas with the addition of certain HMOs have been shown to have a health benefit. Different oligosaccharides have different biological activities. Zehra *et al.* found that 6`SL and 2`FL HMOs modulate the Ag-IgE activation complex of human epithelial cells, which may have implications for FA (74).
Several studies advocated the need for further research to clarify the presence or absence of intestinal dysbiosis in patients with FA and to evaluate the role of different probiotics in modulating IM, its function and composition (6, 75, 76). Goldberg *et al*. in 2020, demonstrated that gut microbiota composition of allergic patients was significantly different compared to age-matched controls. In individuals with FA, IM was less diverse and less abundant in bacterium producing short chain fatty acids (SCFA). Consequently, the feces of these patients had decreased concentrations of SCFA, which may play a role in the allergic cascade. Furthermore, he demonstrated that each FA is associated with a different IM composition (77).
Also, Nowak-Węgrzyn *et al.* reported that interventions focused on correcting the alterations present in the IM of children with allergies, through supplementation with probiotics, may have potential application in the prevention and treatment of FA (36).
The safety and tolerability of probiotic and prebiotic supplementation has been well established in previous studies, with no reported adverse effects (78). However, further research is needed to fully understand the role of these interventions in the prevention of FA (62).
Concluding, in recent years, numerous studies have been conducted to investigate the potential influence of microbiota, probiotics and prebiotics supplementation on the prevention and treatment of FA. However, the results of these studies have been contradictory and inconsistent. This lack of consistency arises from the wide range of probiotics and prebiotics used in different studies, as well as the varying age groups that have been studied. To date, scientific societies have not issued formal recommendations for the use of probiotics or prebiotics in the treatment or prevention of FA.
Despite this, some studies have yielded promising results suggesting that probiotics may serve as therapeutic adjuvants in the management of CMA and peanut-induced allergies. The differences in the composition and diversity of IM in children with FA may also support the role of intestinal dysbiosis as a potentiator of allergies and the need to balance and promote intestinal homeostasis, through the supplementation with probiotics and prebiotics.
In the future, studies under strict methodological protocols are needed, in order to clarify the specific types of probiotics and prebiotics, their optimal dosage, therapeutic regimens and routes of administration.

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JFR: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, validation visualization, writing – original draft, writing – review &

editing. CP: conceptualization, data curation, project administration, resources, software, supervision, validation, visualization, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

References

1. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. J Allergy Clin Immunol. 2011;127(3):668-76.e1-2. doi: 10.1016/j.jaci.2011.01.039.
2. Loh W, Tang MLK. The Epidemiology of Food Allergy in the Global Context. Int J Environ Res Public Health. 2018;15(9):2043. doi: 10.3390/ijerph15092043.
3. NIAID-Sponsored Expert Panel. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1-58. doi: 10.1016/j.jaci.2010.10.007.
4. du Toit G, Tsakok T, Lack S, Lack G. Prevention of food allergy. J Allergy Clin Immunol. 2016;137(4):998-1010. doi: 10.1016/j.jaci.2016.02.005.
5. Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol. 2018;141(1):41-58. doi: 10.1016/j.jaci.2017.11.003.
6. Aitoro R, Paparo L, Amoroso A, Costanzo M, Cosenza L, Granata V, et al. Gut microbiota as a target for preventive and therapeutic intervention against food allergy. Nutrients. 2017;9(7):672. doi: 10.3390/nu9070672.
7. Leung ASY, Wong GWK, Tang MLK. Food allergy in the developing world. J Allergy Clin Immunol. 2018;141(1):76-8.e1. doi: 10.1016/j.jaci.2017.11.008.
8. 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(8):992-1007. doi: 10.1111/all.12423.
9. Savage J, Sicherer S, Wood R. The Natural History of Food Allergy. J Allergy Clin Immunol Pract. 2016;4(2):196-203; quiz 204. doi: 10.1016/j.jaip.2015.11.024.
10. Tordesillas L, Berin MC, Sampson HA. Immunology of food allergy. Immunity. 2017;47(1):32-50. doi: 10.1016/j.immuni.2017.07.004.
11. Chu DK, Llop-Guevara A, Walker TD, Flader K, Goncharova S, Boudreau JE, et al. IL-33, but not thymic stromal lymphopoietin or IL-25, is central to mite and peanut allergic sensitization. J Allergy Clin Immunol. 2013;131(1):187-200.e1-8. doi: 10.1016/j.jaci.2012.08.002.
12. Weiss GA, Thierry H. Mechanisms and consequences of intestinal dysbiosis. Cell Mol Life Sci. 2017; 74(16):2959-77. doi: 10.1007/s00018-017-2509-x.
13. Canani RB, Paparo L, Nocerino R, Di Scala C, Della Gatta G, Maddalena Y, et al. Gut microbiome as target for innovative strategies against food allergy. Front Immunol. 2019;10:191. doi: 10.3389/fimmu.2019.00191.
14. Stefka AT, Feehley T, Tripathi P, Qiu J, McCoy K, Mazmanian SK, et al. Commensal bacteria protect against food allergen sensitization. Proc Natl Acad Sci U S A. 2014;111(36):13145-50. doi: 10.1073/pnas.1412008111.
15. Rivas MN, Burton OT, Wise P, Zhang YQ, Hobson SA, Lloret MG, et al. A microbiota signature associated with experimental food allergy promotes allergic sensitization and anaphylaxis. J Allergy Clin Immunol. 2013;131(1):201-12. doi: 10.1016/j.jaci.2012.10.026.
16. Shu SA, Yuen AW, Woo E, Chu KH, Kwan HS, Yang GX. Microbiota and food allergy. Clin Rev Allergy Immunol. 2019;57(1):83-97. doi: 10.1007/s12016-018-8723-y.
17. Cukrowska B. Microbial and nutritional programming—the importance of the microbiome and early exposure to potential food allergens in the development of allergies. Nutrients. 2018;10(10):1541. doi: 10.3390/nu10101541.
18. Fiocchi A, Pawankar R, Cuello-Garcia C, Ahn K, Al-Hammadi S, Agarwal A, et al. World Allergy Organization-McMaster University guidelines for allergic disease prevention (GLAD-P): probiotics. World Allergy Organ J. 2015;8(1):4. doi: 10.1186/s40413-015-0055-2.
19. Markowiak P, Śliżewska K. Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients. 2017;9(9):1021. doi: 10.3390/nu9091021.
20. Isolauri E, Sütas Y, Kankaanpää P, Arvilommi H, Salminen S. Probiotics: effects on immunity. Am J Clin Nutr. 2001;73(2):444s-50s. doi: 10.1093/ajcn/73.2.444s.
21. Borchers AT, Selmi C, Meyers FJ, Keen CL, Gershwin ME. Probiotics and immunity. J Gastroenterol. 2009;44(1):26-46. doi: 10.1007/s00535-008-2296-0.
22. Agostoni C, Axelsson I, Goulet O, Koletzko B, Michaelsen KF, Puntis JW, Rigo J, Shamir R, Szajewska H, Turck D; ESPGHAN Committee on Nutrition. Prebiotic oligosaccharides in dietetic products for infants: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2004;39(5):465-73. doi: 10.1097/00005176-200411000-00003.
23. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr. 1995;125(6):1401-12. doi: 10.1093/jn/125.6.1401.
24. Gibson GR, Probert HM, Van Loo J, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. Nutr Res Rev. 2004;17(2):259-75. doi: 10.1079/NRR200479.
25. Cuello-Garcia CA, Fiocchi A, Pawankar R, Yepes-Nuñez JJ, Morgano GP, Zhang Y, et al. World Allergy Organization-McMaster University guidelines for allergic disease prevention (GLAD-P): prebiotics. World Allergy Organ J. 2016;9(1):10. doi: 10.1186/s40413-016-0102-7.
26. Paparo L, Nocerino R, Di Scala C, Della Gatta G, Di Costanzo M, Buono A, et al. Targeting Food Allergy with Probiotics. Adv Exp Med Biol. 2019;1125:57-68. doi: 10.1007/5584_2018_316.
27. Koletzko S. Probiotics and Prebiotics for Prevention of Food Allergy: Indications and Recommendations by Societies and Institutions. J Pediatr Gastroenterol Nutr. 2016;63 Suppl 1:S9-S10. doi: 10.1097/MPG.0000000000001220.
28. Santos SCD, Konstantyner T, Cocco RR. Effects of probiotics in the treatment of food hypersensitivity in children: a systematic review. Allergol Immunopathol (Madr). 2020 Jan-Feb;48(1):95-104. doi: 10.1016/j.aller.2019.04.009.
29. Qamer S, Deshmukh M, Patole S. Probiotics for cow's milk protein allergy: a systematic review of randomized controlled trials.

Eur J Pediatr. 2019;178(8):1139-49. doi: 10.1007/s00431-019-03397-6.
30. Fiocchi A, Cabana MD, Mennini M. Current Use of Probiotics and Prebiotics in Allergy. J Allergy Clin Immunol Pract. 2022;10(9):2219-42. doi: 10.1016/j.jaip.2022.06.038.
31. Cunningham M, Azcarate-Peril MA, Barnard A, Benoit V, Grimaldi R, Guyonnet D, et al. Shaping the Future of Probiotics and Prebiotics. Trends Microbiol. 2021;29(8):667-85. doi: 10.1016/j.tim.2021.01.003.
32. El-Qutob D. Shrimp allergy: beyond avoidance diet. Eur Ann Allergy Clin Immunol. 2017 Nov;49(6):252-256. doi: 10.23822/EurAnnACI.1764-1489.16.
33. Fu L, Wang C, Wang Y. Seafood allergen-induced hypersensitivity at the microbiota-mucosal site: Implications for prospective probiotic use in allergic response regulation. Crit Rev Food Sci Nutr. 2018;58(9):1512-25. doi: 10.1080/10408398.2016.1269719.
34. Parekh H, Bahna SL. Infant Formulas for Food Allergy Treatment and Prevention. Pediatr Ann. 2016;45(4):e150-6. doi: 10.3928/00904481-20160225-01.
35. Berni Canani R, Di Costanzo M, Bedogni G, Amoroso A, Cosenza L, Di Scala C, et al. Extensively hydrolyzed casein formula containing Lactobacillus rhamnosus GG reduces the occurrence of other allergic manifestations in children with cow's milk allergy: 3-year randomized controlled trial. J Allergy Clin Immunol. 2017;139(6):1906-13.e4. doi: 10.1016/j.jaci.2016.10.050.
36. Nowak-Węgrzyn A, Chatchatee P. Mechanisms of Tolerance Induction. Ann Nutr Metab. 2017;70 Suppl 2:7-24. doi: 10.1159/000457915.
37. Nocerino R, Bedogni G, Carucci L, Cosenza L, Cozzolino T, Paparo L, et al. The Impact of Formula Choice for the Management of Pediatric Cow's Milk Allergy on the Occurrence of Other Allergic Manifestations: The Atopic March Cohort Study. J Pediatr. 2021;232:183-191.e3. doi: 10.1016/j.jpeds.2021.01.059.
38. Guest JF, Fuller GW. Effectiveness of using an extensively hydrolyzed casein formula supplemented with Lactobacillus rhamnosus GG compared with an extensively hydrolysed whey formula in managing cow's milk protein allergic infants. J Comp Eff Res. 2019;8(15):1317-26. doi: 10.2217/cer-2019-0088.
39. Paparo L, Nocerino R, Bruno C, Di Scala C, Cosenza L, Bedogni G, et al. Randomized controlled trial on the influence of dietary intervention on epigenetic mechanisms in children with cow's milk allergy: the EPICMA study. Sci Rep. 2019;9(1):2828. doi: 10.1038/s41598-019-38738-w.
40. Guest JF, Singh H. Cost-effectiveness of using an extensively hydrolyzed casein formula supplemented with Lactobacillus rhamnosus GG in managing IgE-mediated cow's milk protein allergy in the UK. Curr Med Res Opin. 2019;35(10):1677-85. doi: 10.1080/03007995.2019.1612339.
41. Canani RB, Nocerino R, Terrin G, Frediani T, Lucarelli S, Cosenza L, et al. Formula selection for management of children with cow's milk allergy influences the rate of acquisition of tolerance: a prospective multicenter study. J Pediatr. 2013;163(3):771-7.e1. doi: 10.1016/j.jpeds.2013.03.008.
42. Berni Canani R, Sangwan N, Stefka AT, Nocerino R, Paparo L, Aitoro R, et al. Lactobacillus rhamnosus GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants. ISME J. 2016;10(3):742-50. doi: 10.1038/ismej.2015.151.
43. Nocerino R, Di Costanzo M, Bedogni G, Cosenza L, Maddalena Y, Di Scala C, et al. Dietary Treatment with Extensively Hydrolyzed Casein Formula Containing the Probiotic Lactobacillus rhamnosus GG Prevents the Occurrence of Functional Gastrointestinal Disorders in Children with Cow's Milk Allergy. J Pediatr. 2019;213:137-142.e2. doi: 10.1016/j.jpeds.2019.06.004.
44. Guadamuro L, Diaz M, Jiménez S, Molinos-Norniella C, Pérez-Solis D, Rodríguez JM, et al. Fecal Changes Following Introduction of Milk in Infants With Outgrowing Non-IgE Cow's Milk Protein Allergy Are Influenced by Previous Consumption of the Probiotic LGG. Front Immunol. 2019;10:1819. doi: 10.3389/fimmu.2019.01819.
45. Guest JF, Kobayashi RH, Mehta V, Neidich G. Cost-effectiveness of using an extensively hydrolyzed casein formula containing Lactobacillus rhamnosus GG in managing infants with cow's milk allergy in the US. Curr Med Res Opin. 2018;34(9):1539-48. doi: 10.1080/03007995.2017.1400962.
46. Cukrowska B, Ceregra A, Maciorkowska E, Surowska B, Zegadło-Mylik MA, Konopka E, Trojanowska I, et al. The Effectiveness of Probiotic Lactobacillus rhamnosus and Lactobacillus casei Strains in Children with Atopic Dermatitis and Cow's Milk Protein Allergy: A Multicenter, Randomized, Double Blind, Placebo Controlled Study. Nutrients. 2021;13(4):1169. doi: 10.3390/nu13041169.
47. Morisset M, Aubert-Jacquin C, Soulaines P, Moneret-Vautrin DA, Dupont C. A non-hydrolyzed, fermented milk formula reduces digestive and respiratory events in infants at high risk of allergy. Eur J Clin Nutr. 2011;65(2):175-83. doi: 10.1038/ejcn.2010.250.
48. Dupont C, Hol J, Nieuwenhuis EE; Cow's Milk Allergy Modified by Elimination and Lactobacilli study group. An extensively hydrolysed casein-based formula for infants with cows' milk protein allergy: tolerance/hypo-allergenicity and growth catch-up. Br J Nutr. 2015;113(7):1102-12. doi: 10.1017/S000711451500015X.
49. Sorensen K, Cawood AL, Cooke LH, Acosta-Mena D, Stratton RJ. The Use of an Amino Acid Formula Containing Synbiotics in Infants with Cow's Milk Protein Allergy-Effect on Clinical Outcomes. Nutrients. 2021;13(7):2205. doi: 10.3390/nu13072205.
50. Chatchatee P, Nowak-Wegrzyn A, Lange L, Benjaponpitak S, Chong KW, Sangsupawanich P, et al. PRESTO study team. Tolerance development in cow's milk-allergic infants receiving amino acid-based formula: A randomized controlled trial. J Allergy Clin Immunol. 2022;149(2):650-8.e5. doi: 10.1016/j.jaci.2021.06.025.
51. Zepeda-Ortega B, Goh A, Xepapadaki P, Sprikkelman A, Nicolaou N, Hernandez REH, et al. Strategies and Future Opportunities for the Prevention, Diagnosis, and Management of Cow Milk Allergy. Front Immunol. 2021;12:608372. doi: 10.3389/fimmu.2021.608372.
52. Nowak-Wegrzyn A, Czerkies L, Reyes K, Collins B, Heine RG. Confirmed Hypoallergenicity of a Novel Whey-Based Extensively Hydrolyzed Infant Formula Containing Two Human Milk Oligosaccharides. Nutrients. 2019;11(7):1447. doi: 10.3390/nu11071447.
53. Basturk A, Isik İ, Atalay A, Yılmaz A. Investigation of the Efficacy of Lactobacillus rhamnosus GG in Infants With Cow's Milk Protein Allergy: a Randomised Double-Blind Placebo-Controlled Trial. Probiotics Antimicrob Proteins. 2020;12(1):138-43. doi: 10.1007/s12602-019-9516-1.
54. Martin VJ, Shreffler WG, Yuan Q. Presumed Allergic Proctocolitis Resolves with Probiotic Monotherapy: A Report of 4 Cases. Am J Case Rep. 2016;17:621-4. doi: 10.12659/ajcr.898490.
55. Joo Chan C, Richardo T, Lim RLH. Current Trend in Immunotherapy for Peanut Allergy. Int Rev Immunol. 2018;37(6):279-90. doi: 10.1080/08830185.2018.1509967.

56. Chebar Lozinsky A, Loke P, Orsini F, O'Sullivan M, L Prescott S, Gold MS, et al. Study protocol of a multicentre, randomised, controlled trial evaluating the effectiveness of probiotic and peanut oral immunotherapy (PPOIT) in inducing desensitisation or tolerance in children with peanut allergy compared with oral immunotherapy (OIT) alone and with placebo (the PPOIT-003 study). BMJ Open. 2020;10(9):e035871. doi: 10.1136/bmjopen-2019-035871.
57. Tang ML, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, et al. Administration of a probiotic with peanut oral immunotherapy: A randomized trial. J Allergy Clin Immunol. 2015;135(3):737-44.e8. doi: 10.1016/j.jaci.2014.11.034.
58. Hsiao KC, Ponsonby AL, Axelrad C, Pitkin S, Tang MLK; PPOIT Study Team. Long-term clinical and immunological effects of probiotic and peanut oral immunotherapy after treatment cessation: 4-year follow-up of a randomised, double-blind, placebo-controlled trial. Lancet Child Adolesc Health. 2017;1(2):97-105. doi: 10.1016/S2352-4642(17)30041-X.
59. Loke P, Chebar Lozinsky A, Orsini F, Wong LS, Leung AS, Tham EH, et al. Study protocol of a phase 2, dual-centre, randomised, controlled trial evaluating the effectiveness of probiotic and egg oral immunotherapy at inducing desensitisation or sustained unresponsiveness (remission) in participants with egg allergy compared with placebo (Probiotic Egg Allergen Oral Immunotherapy for Treatment of Egg Allergy: PEAT study). BMJ Open. 2021;11(7):e044331. doi: 10.1136/bmjopen-2020-044331.
60. Dunn Galvin A, McMahon S, Ponsonby AL, Hsiao KC, Tang MLK; PPOIT study team. The longitudinal impact of probiotic and peanut oral immunotherapy on health-related quality of life. Allergy. 2018;73(3):560-8. doi: 10.1111/all.13330326.
61. Loke P, Orsini F, Lozinsky AC, Gold M, O'Sullivan MD, Quinn P, et al. Probiotic peanut oral immunotherapy versus oral immunotherapy and placebo in children with peanut allergy in Australia (PPOIT-003): a multicentre, randomised, phase 2b trial. Lancet Child Adolesc Health. 2022;6(3):171-84. doi: 10.1016/S2352-4642(22)00006-2.
62. de Silva D, Halken S, Singh C, Muraro A, Angier E, Arasi S, et al. Preventing food allergy in infancy and childhood: Systematic review of randomised controlled trials. Pediatr Allergy Immunol. 2020;31(7):813-26. doi: 10.1111/pai.13273.
63. Chinthrajah RS, Hernandez JD, Boyd SD, Galli SJ, Nadeau KC. Molecular and cellular mechanisms of food allergy and food tolerance. J Allergy Clin Immunol. 2016;137(4):984-97. doi: 10.1016/j.jaci.2016.02.004.
64. Waserman S. Doctor, can we prevent food allergy and eczema in our baby? Curr Opin Allergy Clin Immunol. 2016;16(3):265-71. doi: 10.1097/ACI.0000000000000267.
65. Kong XY, Yang Y, Guan J, Wang RZ. Probiotics' preventive effect on pediatric food allergy: a meta-analysis of randomized controlled trials. Chin Med Sci J. 2014;29(3):144-7. doi: 10.1016/s1001-9294(14)60059-6.
66. Loo EX, Llanora GV, Lu Q, Aw MM, Lee BW, Shek LP. Supplementation with probiotics in the first 6 months of life did not protect against eczema and allergy in at-risk Asian infants: a 5-year follow-up. Int Arch Allergy Immunol. 2014;163(1):25-8. doi: 10.1159/000356338.
67. Ogrodowczyk AM, Zakrzewska M, Romaszko E, Wróblewska B. Gestational Dysfunction-Driven Diets and Probiotic Supplementation Correlate with the Profile of Allergen-Specific Antibodies in the Serum of Allergy Sufferers. Nutrients. 2020;12(8):2381. doi: 10.3390/nu12082381.
68. Zhang GQ, Hu HJ, Liu CY, Zhang Q, Shakya S, Li ZY. Probiotics for Prevention of Atopy and Food Hypersensitivity in Early Childhood: A PRISMA-Compliant Systematic Review and Meta-Analysis of Randomized Controlled Trials. Medicine (Baltimore). 2016;95(8):e2562. doi: 10.1097/MD.0000000000002562.
69. Peldan PS, Kukkonen AK, Savilahti E, Kuitunen M. Perinatal Probiotic Mixture and Development of Allergic Sensitization up to 13 Years of Age. Int Arch Allergy Immunol. 2020;181(4):270-7. doi: 10.1159/000504915.
70. Heine RG. Food Allergy Prevention and Treatment by Targeted Nutrition. Ann Nutr Metab. 2018;72 Suppl 3:33-45. doi: 10.1159/000487380.
71. D'Auria E, Salvatore S, Pozzi E, Mantegazza C, Sartorio MUA, Pensabene L. Cow's Milk Allergy: Immunomodulation by Dietary Intervention. Nutrients. 2019;11(6):1399. doi: 10.3390/nu11061399.
72. Ezaki S, Itoh K, Kunikata T, Suzuki K, Sobajima H, Tamura M. Prophylactic probiotics reduce cow's milk protein intolerance in neonates after small intestine surgery and antibiotic treatment presenting symptoms that mimics postoperative infection. Allergol Int. 2012;61(1):107-13. doi: 10.2332/allergolint.11-OA-0305.
73. Jeurink PV, van Esch BC, Rijnierse A, Garssen J, Knippels LM. Mechanisms underlying immune effects of dietary oligosaccharides. Am J Clin Nutr. 2013;98(2):572S-7S. doi: 10.3945/ajcn.112.038596.
74. Zehra S, Khambati I, Vierhout M, Mian MF, Buck R, Forsythe P. Human Milk Oligosaccharides Attenuate Antigen-Antibody Complex Induced Chemokine Release from Human Intestinal Epithelial Cell Lines. J Food Sci. 2018;83(2):499-508. doi: 10.1111/1750-3841.14039.
75. Fiocchi A, Pecora V, Dahdah L. Probiotics, Prebiotics & Food allergy Prevention: Clinical Data in Children. J Pediatr Gastroenterol Nutr. 2016;63 Suppl 1:S14-7. doi: 10.1097/MPG.0000000000001220.
76. Rachid R, Chatila TA. The role of the gut microbiota in food allergy. Curr Opin Pediatr. 2016;28(6):748-53. doi: 10.1097/MOP.0000000000000427.
77. Goldberg MR, Mor H, Neriya DM, Magzal F, Muller E, Appel MY, et al. Microbial signature in IgE-mediated food allergies. Genome Med. 2020 27;12(1):92. doi: 10.1186/s13073-020-00789-4.
78. van den Nieuwboer M, Brummer RJ, Guarner F, Morelli L, Cabana M, Claassen E. Safety of probiotics and synbiotics in children under 18 years of age. Benef Microbes. 2015;6(5):615-30. doi: 10.3920/BM2014.0157.

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Association of asthma risk factors and the prevalence of the disease in a population of Brazil

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Impact statement
The presence of some clinical characteristics, such as sedentarism, overweight, and obesity, may be associated with the prevalence of asthma in an adult population in southeastern Brazil.

Summary
Background. *Asthma, a chronic lower airway disease, affects all age groups worldwide. Its prevalence varies globally, with Brazil estimating over 10% affected. Risk factors include obesity, sedentary lifestyle, smoking, and environmental exposures. Understanding these factors is crucial for effective prevention strategies. The aim of our study was to evaluate the association between the previously described asthma risk factors and the prevalence of asthma in a population of Brazilian adults.* ***Methods.*** *A population-based cross-sectional study was conducted using data collected from 7,891 patients. All patients in the database > 18 years of age were included. The following variables were collected from the health plan database: age, body mass index, smoking status, alcohol consumption, sedentary lifestyle, heart disease, hypertension, diabetes, and asthma diagnosis. The frequency of the collected variables was compared between patients with or without an asthma diagnosis, and logistic regression was performed.* ***Results.*** *Of our total sample (7,891 patients), 150 (1.9%) had asthma. The mean age of patients with asthma was 39.4 years. 1.4% of normal weight patients had the diagnosis of asthma, while 2.4% of overweight and 2.2% of obese patients had the diagnosis. Multivariate analysis demonstrated that a sedentary lifestyle and overweight and obesity were independently associated with asthma prevalence Odds Ratio (OR) [95% confidence interval]: (1.61 [1.16-2.22] and 1.25 [1.03-1.52] respectively).* ***Conclusions.*** *Our data provide evidence that some clinical characteristics, such as sedentarism, overweight, and obesity, may be related to the prevalence of asthma in an adult population in southeastern Brazil. Such factors could be modified and better understood through multidisciplinary research and health programs that evaluate the risk factors for asthma in large populations.*

Introduction

Asthma is a common clinical syndrome that affects all age groups. It is considered a heterogeneous chronic disease of the lower airways characterized by chronic inflammation and hyper-reactivity of the airways leading to various respiratory symptoms (1). The prevalence of asthma has increased in recent years throughout the world, and its severity and mortality of asthma vary globally (2). In Brazil it is estimated that asthma affects more than 10% of the population (3, 4). Many risk factors have been associated with asthma, and the differences in distributions of these risk factors may explain the variations in its prevalence. Approximately 38% of current adult asthmatics in the United States are also obese, a known risk factor for asthma (5). Sed-

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entary time is the time spent in any seated or reclining posture during wake time, which is associated with harmful health consequences, such as obesity (6). Although previous data have confirmed the association between sedentary time and obesity, studies exploring sedentarism and asthma development are scarce. Moreover, in the U.S., about 17% of asthmatics adults smoke, a prevalence comparable to that found in healthy subjects, even though cigarette smoke is known to be a trigger for asthma attacks (7) and a risk factor for childhood asthma onset (8).
The diagnosis of asthma is based on anamnesis, clinical examination, and pulmonary function tests. It should be founded on the presence of one or more characteristic symptoms, such as dyspnea, wheezing, chest tightness, and cough, particularly at night and in the morning on awakening. Asthma results from an interaction between genetics, environmental exposure, and other specific factors that lead to symptoms' development and maintenance. Genetic, immunological, and environmental factors can affect the risk of developing asthma (1, 9, 10). Epidemiological studies have shown that environmental factors such as smoking and exposure to air pollution can increase the risk of developing asthma. In addition, atopy, stress, obesity, lifestyle, and dietary patterns are associated with asthma in genetically susceptible people (11, 12).
As previously mentioned, the prevalence of asthma differs according to the geographic region of the individuals studied, and a better understanding of the risk factors associated with asthma is needed. And this knowledge can be used to develop primary prevention strategies that effectively reduce asthma's prevalence. Therefore, the objective of our study was to evaluate the association between the previously described asthma risk factors and the prevalence of asthma in a population of Brazilian adults.

Materials and methods

A population-based cross-sectional study was conducted using data collected from 7,891 patients. All patients in the database > 18 years of age who are part of the Life Health plan and are followed up in a private referral hospital in São Paulo, Brazil, were included. Variables were collected from the Life Health plan's physical and electronic medical record database. We used the entire population from the hospital database and did not perform a sample size calculation because of this.
The following variables were collected from the Life Health plan database: age, body mass index, smoking (smoker/ex-smokers or non-smoker), alcohol consumption, sedentary lifestyle, heart disease, hypertension, diabetes, and asthma diagnosis. The frequency of the variables collected was compared between patients with or without the medical diagnosis of asthma. This study was submitted and approved by the research Ethics Committee of Moriah Hospital under protocol 5.269.059 and conducted according to Helsinki declaration.
Clinical variables were defined according to the medical-diagnostic data in the medical records. Patients were classified as hypertensive if their blood pressure was above the recommended optimal levels of 140/85 in non-diabetic patients or 140/80 in diabetic patients on two or more subsequent outpatient measurements, requiring medications to control blood pressure. According to the database, patients were classified as smokers/ex-smokers, those who smoke currently or for at least five years, and non-smokers, those who never smoked. To evaluate obesity, the patients were classified as having normal weight (BMI: 18.5-24.9), overweight (BMI: 25-29.9) and obese (BMI: > 30), according to BMI classes. A sedentary lifestyle was considered as performing physical activity < 2 times per week.
The results of the numerical variables that follow a normal distribution are presented as mean and standard deviation. Non-numerical variables are expressed as proportions/percentages. The chi-square test was used to compare categorical variables, the Mann-Whitney U test was used to compare numerical variables with nonparametric distribution. Logistic regression was used for the identification of significant factors associated with asthma. To build our statistical model, first, bivariate logistic models were used to estimate the strength of association between individual predictors and the prevalence of asthma, variables with significance level of P-value < 0.1 were selected for the statistical model. A multivariable logistic regression model was then used to identify the independent risk factors associated with the disease. In logistic regression, backward elimination was used to select variables to be maintained in the final model, using 5% as criterion for statistical significance of associations. The quality of the fit was measured by the Hosmer-Lemeshow test. SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data, and P-values less than 0.05 were considered statistically significant.

Results

Of our total sample (7,891 patients), 150 (1.9%) had asthma at the time of inclusion. The mean age of the patients with asthma was 39.4 years (± 13.36) and for the patients without asthma was 38.2 (± 27.00). The difference in age between the two groups was not statistically significant (p = 0.627).
Data on smoking, sedentarism, obesity, hypertension, and diabetes are shown in **table I**. Hundred ninety-six patients reported being smokers (2.5%), while 7,695 were non-smokers (97.5%). When associated with the diagnosis of asthma, we found that 4.1% of the patients who smoked had the disease, while for the non-smokers, only 1.8% had asthma (p = 0.024).
Regarding sedentarism, 3,122 patients reported being sedentary (39.6%), whereas 4,769 (60.4%) patients reported physical activity at least two times per week. When analyzing the relation between sedentarism and asthma, we found that 78 (2.5%) seden-

Table I *- Comparison between asthma and smoking, sedentarism, overweight and obesity, hypertension, prediabetes and diabetes.*

	Asthma n (%)		P-value
	No	Yes	
Smoking			
No	7553 (97.6)	142 (94.7)	**0.024***
Yes	188 (2.4)	8 (5.3)	
Sedentarism			
No	4697 (60.7)	72 (48.0)	**0.002***
Yes	3044 (39.3)	78 (52.0)	
Overweight and obesity			
No	3497 (45.2)	49 (32.7)	
Overweight	2046 (26.4)	51 (34.0)	**0.008***
Obesity	2198 (28.4)	50 (33.3)	
Hypertension			
No	6644 (85.8)	126 (84.0)	0.525
Yes	1097 (14.2)	24 (16.0)	
Prediabetes and diabetes			
No	7273 (94.0)	146 (97.3)	
Prediabetes	54 (0.7)	0	0.200
Diabetes	414 (5.3)	4 (2.7)	

*Chi-square test.

tary patients had asthma, while 72 (1.5%) non-sedentary patients had the disease (p = 0.002).

In our sample, 3,546 (44.9%) patients had normal weight, 2,097 (26.6%) were overweight, and 2,248 (28.5%) were obese. We found that 49 (1.4%) patients with normal weight had a diagnosis of asthma, while 51 (2.4%) overweight and 50 (2.2%) obese patients had the diagnosis (p = 0.008).

Hypertension and diabetes were present in 14.2% and 5.3% of the cohort. When we evaluated whether the presence of diabetes and hypertension was associated with asthma, we found no statistically significant differences between groups.

Table II *- Logistic regression analysis of risk variables smoking, sedentarism, overweight and obesity for asthma.*

Variables	Odds ratio	95%CI	P-value
Smoking	2.05	0.99-4.26	**0.053**
Sedentarism	1.61	1.16-2.22	**0.004**
Overweight and obesity	1.25	1.03-1.52	**0.02**

A multivariate analysis was performed, including smoking, sedentarism, and BMI variables, and we found that sedentarism, overweight, and obesity were independently associated with asthma (**table II**), Odds Ratio (OR) [95% confidence interval]: 1.61 [1.16-2.22]; p = 0.004 and 1.25 [1.03-1.52]; p = 0.02 respectively). Smoking was not independently associated OR [95% confidence interval]: 2.05 [0.99-4.26]; p = 0.053).

Discussion and conclusions

The prevalence of asthma varies significantly in different regions of the world. Prevalence trends are best estimated by surveying large samples in the same area using validated methods. The European Community Respiratory Health Survey (ECRHS) and the International Study of Asthma and Allergy in Children (ISAAC) are the two most extensive global asthma assessments (13, 14). According to the results of these surveys, the highest asthma rates were found in higher-income countries. Despite therapeutic advances, the continued increase in the prevalence of asthma suggests that the specific causes of asthma are still poorly understood. As with prevalence data, studying of risk factors in asthma has proved difficult because many factors are related (15).

Modern lifestyle may explain variations in the prevalence of asthma in urban areas in developing countries (16). In Latin America, asthma prevalence has been associated with changes in lifestyle and environment of the population in urban areas in recent decades, which play an essential role in asthma or related phenotypes (17, 18). This cross-sectional study showed a high prevalence of sedentarism and overweight/obesity in patients with asthma in a southeastern Brazilian population. Few previous cross-sectional studies related obesity to asthma (19, 20).

Obesity is associated with increased prevalence and incidence of asthma. However, this association has been inconsistently reported in genders, across different races, and among age groups (21). The study results' heterogeneity highlights this association's complexity, including different asthma definitions and study designs. Despite these limitations, it is a consensus that weight gain and obesity adversely affect respiratory health (21).

In a previous meta-analysis of 7 longitudinal cohort studies by Beuther and Sutherland, there was a dose-response effect between increasing BMI and asthma incidence. Compared to normal weight, a BMI ≥ 25 was associated with an OR of 1.5 for having asthma (95%CI 1.2-1.6), whereas the OR for a BMI > 30 was 1.9 (95%CI 1.4-2.6) (5).

There are many mechanisms by which obesity could potentially worsen asthma, including its effects on pulmonary physiology. Increasing weight can affect lung physiology, including reducing respiratory system compliance, primarily due to fatty tissue deposits around the chest and abdominal wall. This could result in reduced total lung capacity and low expiratory reserve volume.

Therefore, airway closure occurs at or above functional residual capacity in the dependent lung zones, which can lead to significant ventilation/perfusion mismatching (22).

Not every obese asthmatic has an increase in asthma severity suggests that other non-mechanical factors are involved. It has been previously proposed that obesity, as a chronic systemic inflammatory disorder, could affect asthma by enhancing airway inflammation (23). In a study by Desai *et al*. obesity was associated with increased sub-mucosal eosinophils and greater IL-5 levels. This phenomenon in obese asthmatics may be due to altered eosinophil survival or clearance or a functional change in eosinophil response to cytokines or chemokines. Moreover, obesity has increased airway neutrophilia (24). So, we can postulate that obesity-mediated changes in airway inflammation are more consistent with a non-predominant Th-2 phenotype and potentially a more Th-1 polarized immune response (25).

In our study, we also found a high prevalence of sedentarism in patients with asthma. Evidence in the literature supports this finding, but most epidemiological studies analyzed this association in pediatric and adolescent populations (23, 26, 27). A few studies demonstrated that obesity might be a confounding factor to asthma due to the low prevalence of physical activity and high prevalence of sedentarism in the same population, rather than having a cause-effect relation (28, 29). A longitudinal study demonstrated that excessive screen time during childhood predicts low cardiorespiratory fitness levels in adolescence (30).

In our study, we identified that smoking seems to have some relationship with the prevalence of asthma. According to the literature, the prevalence of active smoking in adults with asthma is similar to that in the general population. However, smoking-related asthma is associated with poorer disease control, impaired response to drug therapy, accelerated decline in lung function, and increased rate of health care utilization (31).

Although epidemiological studies indicate that many other factors are likely associated with the development of asthma, the relationships are not considered causal due to inadequate evidence and inconsistent results from recent studies. This may highlight that sufficient data and exact mechanisms of causality still need further studies (11).

The methodological limitations of our study include its cross-sectional design and the use of retrospective data. In addition, we restricted the analysis to a population seen in a private hospital. We cannot conclude its generalizability until the results are replicated in other populations and geographic regions. The clinical characteristics associated with asthma prevalence that we discuss here may change over the years according to the population's lifestyle. This may involve a range of influences determined by cultural, economic, environmental, and other factors (17, 32). We addressed asthma in a population with a shared history, culture, and geography and selected clinical characteristics based on the asthma literature and our database. In addition, although we collected detailed information related to asthma risk factors, other data such as environmental air sampling and seasonal or geographic data were unavailable.

Indeed, this study has the inherited drawbacks of its retrospective nature. However, the prevalence of risk factors for asthma was never analyzed in such a large Brazilian population.

In conclusion our data provide evidence that the presence of some clinical characteristics, such as sedentarism, overweight, and obesity, may be associated with the prevalence of asthma in an adult population in southeastern Brazil. Such factors could be modified and better understood through multidisciplinary research and health programs that evaluate the risk factors for asthma in large populations.

Fundings

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Contributions

STR, AZC, RMM, VS: conceptualization, validation. STR, formal analysis. STR, PC, PR: investigation. STR, PC, AZC, RMM, VS: methodology. STR, VS, AT, EH: project administration. STR, AZC, RMM, KRML, VS: supervision. STR, PC, PR, KRML, VS: visualization. STR, PC: writing – original draft. PR, VS: writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

References

1. Cevhertas L, Ogulur I, Maurer DJ, Burla D, Ding M, Jansen K, et al. Advances and recent developments in asthma in 2020. Allergy. 2020;75(12):3124-46. doi: 10.1111/all.14607.
2. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald JM, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008;31(1):143-78. doi: 10.1183/09031936.00138707.
3. IV Diretizes Brasileiras para o Manejo da Asma. J bras pneumol. 2006;32:S447-74. doi: 10.1590/S1806-37132006001100002.
4. DATASUS. Ministério da Saúde 2022. Available at: https://datasus.saude.gov.br/. Last access date: 02/09/2022.
5. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med. 2007;175(7):661-6. doi: 10.1164/rccm.200611-1717OC.
6. Liou YM, Liou TH, Chang LC. Obesity among adolescents: sedentary leisure time and sleeping as determinants. J Adv Nurs. 2010;66(6):1246-56. doi: 10.1111/j.1365-2648.2010.05293.x.
7. Analysis performed by the American Lung Association Epidemiology and Statistics Unit using SPSS software. 2021. Available at: https://www.cdc.gov/mmwr/volumes/70/ss/ss7005a1.htm?s_cid=ss7005a1_w.

8. Booalayan H, Abdualrasool M, Al-Shanfari S, Boujarwa A, Al-Mukaimi A, Alkandery O, et al. Exposure to environmental tobacco smoke and prevalence of asthma among adolescents in a middle eastern country. BMC Public Health. 2020;20(1):1210. doi: 10.1186/s12889-020-09245-9.
9. Busse WW, Lemanske RF. Asthma. N Engl J Med. 2001;344(5):350-62. doi: 10.1056/NEJM200102013440507.
10. Cookson W. The alliance of genes and environment in asthma and allergy. Nature. 1999;402(6760 Suppl):B5-11. doi: 10.1038/35037002.
11. Ding G, Ji R, Bao Y. Risk and protective factors for the development of childhood asthma. Paediatr Respir Rev. 2015;16(2):133-9. doi: 10.1016/j.prrv.2014.07.004.
12. Toskala E, Kennedy DW. Asthma risk factors. Int Forum Allergy Rhinol. 2015;5 Suppl 1:S11-6. doi: 10.1002/alr.21557.
13. Pearce N, Aït-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax. 2007;62(9):758-66. doi: 10.1136/thx.2006.070169.
14. Janson C, Anto J, Burney P, Chinn S, de Marco R, Heinrich J, et al. The European Community Respiratory Health Survey: what are the main results so far? European Community Respiratory Health Survey II. Eur Respir J. 2001;18(3):598-611. doi: 10.1183/09031936.01.00205801.
15. Kuruvilla ME, Vanijcharoenkarn K, Shih JA, Lee FE. Epidemiology and risk factors for asthma. Respir Med. 2019 Mar;149:16-22. doi: 10.1016/j.rmed.2019.01.014.
16. Murrison LB, Brandt EB, Myers JB, Hershey GKK. Environmental exposures and mechanisms in allergy and asthma development. J Clin Invest. 2019;129(4):1504-15. doi: 10.1172/JCI124612.
17. Rodriguez A, Vaca MG, Chico ME, Rodrigues LC, Barreto ML, Cooper PJ. Lifestyle domains as determinants of wheeze prevalence in urban and rural schoolchildren in Ecuador: cross sectional analysis. Environ Health. 2015;14:15. doi: 10.1186/1476-069X-14-15.
18. Le Moual N, Jacquemin B, Varraso R, Dumas O, Kauffmann F, Nadif R. Environment and asthma in adults. Presse Med. 2013;42(9 Pt 2):e317-33. doi: 10.1016/j.lpm.2013.06.010.
19. Chen Y, Rennie D, Cormier Y, Dosman J. Sex specificity of asthma associated with objectively measured body mass index and waist circumference: the Humboldt study. Chest. 2005;128(4):3048-54. doi: 10.1378/chest.128.4.3048.
20. Appleton SL, Adams RJ, Wilson DH, Taylor AW, Ruffin RE, Team NWAHS. Central obesity is associated with nonatopic but not atopic asthma in a representative population sample. J Allergy Clin Immunol. 2006;118(6):1284-91. doi: 10.1016/j.jaci.2006.08.011.
21. Baffi CW, Winnica DE, Holguin F. Asthma and obesity: mechanisms and clinical implications. Asthma Res Pract. 2015;1:1. doi: 10.1186/s40733-015-0001-7.
22. Holguin F, Cribbs S, Fitzpatrick AM, Ingram RH Jr, Jackson AC. A deep breath bronchoconstricts obese asthmatics. J Asthma. 2010;47(1):55-60. doi: 10.3109/02770900903318330.
23. Sutherland ER, Goleva E, King TS, Lehman E, Stevens AD, Jackson LP, et al. Cluster analysis of obesity and asthma phenotypes. PLoS One. 2012;7(5):e36631. doi: 10.1371/journal.pone.0036631.
24. Desai D, Newby C, Symon FA, Haldar P, Shah S, Gupta S, et al. Elevated sputum interleukin-5 and submucosal eosinophilia in obese individuals with severe asthma. Am J Respir Crit Care Med. 2013;188(6):657-63. doi: 10.1164/rccm.201208-1470OC.
25. Rastogi D, Canfield SM, Andrade A, Isasi CR, Hall CB, Rubinstein A, et al. Obesity-associated asthma in children: a distinct entity. Chest. 2012;141(4):895-905. doi: 10.1378/chest.11-0930.
26. Vale S, Soares-Miranda L, Santos R, Moreira C, Marques A, Santos P, et al. Influence of cardiorespiratory fitness and parental lifestyle on adolescents' abdominal obesity. Ann Hum Biol. 2011;38(5):531-6. doi: 10.3109/03014460.2011.590529.
27. Moliner-Urdiales D, Ruiz JR, Ortega FB, Rey-Lopez JP, Vicente-Rodriguez G, España-Romero V, et al. Association of objectively assessed physical activity with total and central body fat in Spanish adolescents; the HELENA Study. Int J Obes (Lond). 2009;33(10):1126-35. doi: 10.1038/ijo.2009.139.
28. Sandercock GR, Ogunleye AA. Screen time and passive school travel as independent predictors of cardiorespiratory fitness in youth. Prev Med. 2012;54(5):319-22. doi: 10.1016/j.ypmed.2012.03.007.
29. Tremblay MS, LeBlanc AG, Kho ME, Saunders TJ, Larouche R, Colley RC, et al. Systematic review of sedentary behaviour and health indicators in school-aged children and youth. Int J Behav Nutr Phys Act. 2011;8:98. doi: 10.1186/1479-5868-8-98.
30. Aggio D, Ogunleye AA, Voss C, Sandercock GR. Temporal relationships between screen-time and physical activity with cardiorespiratory fitness in English schoolchildren: a 2-year longitudinal study. Prev Med. 2012;55(1):37-9. doi: 10.1016/j.ypmed.2012.04.012.
31. Bakakos P, Kostikas K, Loukides S. Smoking asthma phenotype: diagnostic and management challenges. Curr Opin Pulm Med. 2016;22(1):53-8. doi: 10.1097/MCP.0000000000000221.
32. Rodriguez A, Vaca M, Oviedo G, Erazo S, Chico ME, Teles C, et al. Urbanisation is associated with prevalence of childhood asthma in diverse, small rural communities in Ecuador. Thorax. 2011;66(12):1043-50. doi: 10.1136/thoraxjnl-2011-200225.

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Factors effecting natural course of egg allergy

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Key words

Egg allergy; egg specific IgE; skin prick test induration; persistence; tolerance.

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Impact statement

Anaphylaxis as onset symptom or during oral food challenge could predict persistence of egg allergy.

Summary

Background. *There is limited data about the natural course of egg allergy in the literature. We aimed to analyze the factors that can affect the tolerance or persistence of egg allergy.* ***Methods.*** *A total number of 126 IgE-mediated egg allergic patient who had data about tolerance gaining were included in the study. Demographic and laboratory data were recorded retrospectively. Kaplan-Meier curves was used for estimation of resolution and the factors related to resolution by Cox regression model.* ***Results.*** *Among 126 patients, 81 (64.2%) had gained tolerance with a median survival time of 48 months (min: 12-max: 121). Tolerance was gained in 22.2% (n = 28) of these patients in the first 2 years of life, in 46.8% (n = 49) in 2-6 years, 3.1% (n = 4) between 7-12 years. In univariate analysis, baseline sIgE level was < 8.2 (Hazard ratio: 2.193; 95%CI 1.309-3.674; p = 0.003), no history of anaphylaxis (at initiation or during OFC) (Hazard ratio: 11.292; 95%CI 2.766-46.090; p = 0.001) and baseline egg SPT < 11 mm (Hazard ratio: 2.906; 95%CI 1.424-5.930, p = 0.003) were found to be related to earlier resolution of egg allergy. In multivariate analysis, only anaphylaxis was significantly related to later resolution (Hazard ratio: 6.547; 95%CI 15.80-27.434; p = 0.01).* ***Conclusions.*** *Higher levels of egg sIgE, skin prick test induration and anaphylaxis at onset or during oral food challenge, can give hint about persistence of egg allergy.*

Introduction

Hen's egg allergy is one of the most seen allergens during childhood. Its prevalence ranges between 1%-2% (1). Egg was reported to be the most seen allergen at children with anaphylaxis under one year old and 35% of children with atopic dermatitis especially boys with severe form of eczema (2, 3).

Although most of the children gain tolerance until school age, recent studies showed that egg allergy may persist into adolescence. Savage *et al.* (4) reported 12% of the children gained tolerance by age of 6 and 68% by age 16. In another study, 49% of the children outgrow egg allergy by 6 years old (5). It is hard to predict whether the allergy persists or resolves naturally. History of severe reaction or anaphylaxis, reaction at low level of food ingestion, high specific IgE levels (by skin prick test or immunoassay), comorbidity of another allergic disease is reported to be predictors of persistence egg allergy (4, 5).

Elimination diets are the gold standard management plan in all food allergic patients. As egg is an important source of protein and a common ingredient in many foods, questions about resolution of egg allergy are the point of interest. In this study it is aimed to identify the risk factors for persistence of egg allergy after 6 years by clinical and laboratory parameters.

Materials and methods

The records of a total number of 204 patients with a history of egg allergy, attending from January 2019 to January 2022 were analyzed retrospectively. Patients with no sensitization (9 patients), non-IgE reactions (23 patients) and patients with IgE reactions who had no data about tolerance were excluded from the study. Thus, 126 patients' data was evaluated. The diagnosis of egg allergy was confirmed by prick to prick test (≥ 3 mm larger than negative control) and/or specific IgE positiv-

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ity (> 0.35 kU/L) with a clear clinical history (early reactions as hives, angioedema, dyspnea, cough, vomiting, *etc*., within 2 hours of egg ingestion), or a positive oral food challenge to boiled egg. Negative oral food challenge to boiled egg in the follow-up or consumption of egg at home without any reaction for the last one month was accepted as resolution of egg allergy. Clinical characteristics (age, age at diagnosis, symptoms, comorbid allergic diseases and food allergy, history of family atopy, prematurity) and laboratory data (total IgE level, eosinophil count and percentage, skin prick test and oral food challenge test results) were recorded from the patient file and hospital registry system.

The study was approved by the local Ethics Committee of Ege University (Ethics number: E-99166796-050.06.04- 291753) and conducted in accordance with declaration of Helsinki. The informed consent was obtained from all parents/guardians.

Table I *- Demographic properties of the patients.*

Variables	
Numerosity	n = 126 (%)
Gender (F/M)	44/82
Age at symptom onset Median (IQR) (min-max)	4 (4) (2-10)
Atopic dermatitis	80 (63.4)
Concomitant food allergy	81 (64.2)
Family atopy history	39 (31)
Initial symptom	
Anaphylaxis	9 (7.1)
Skin	110 (87.3)
Gastrointestinal	15 (11.9)
Respiratory	9 (7.1)

Statistical analyses

Data were evaluated using the Statistical Package for Social Sciences 25.0 (SPSS for Windows 25.0, Inc., Chicago, IL, USA). Analysis included descriptive statistics (means, standard deviation), comparison of the means of quantitative data for dual groups using the Student t-test, paired t-test, chi square test and Mann-Whitney-U test. P-value < 0.05 was considered significant. Receiver operating characteristic curve analysis for sIgE and skin prick test induration was used for distinguishing patients with resolution or persistence of egg allergy. Kaplan-Meier curves was used for estimation of resolution and the factors related to resolution by Cox regression model.

Results

A total number of 126 patients were enrolled to the study. The median age at symptom onset was 4 months (IQR:4) (2-6). Forty-four (34.9%) of the patients were female. Among them

Figure 1 *- Cumulative survival for all patients.*

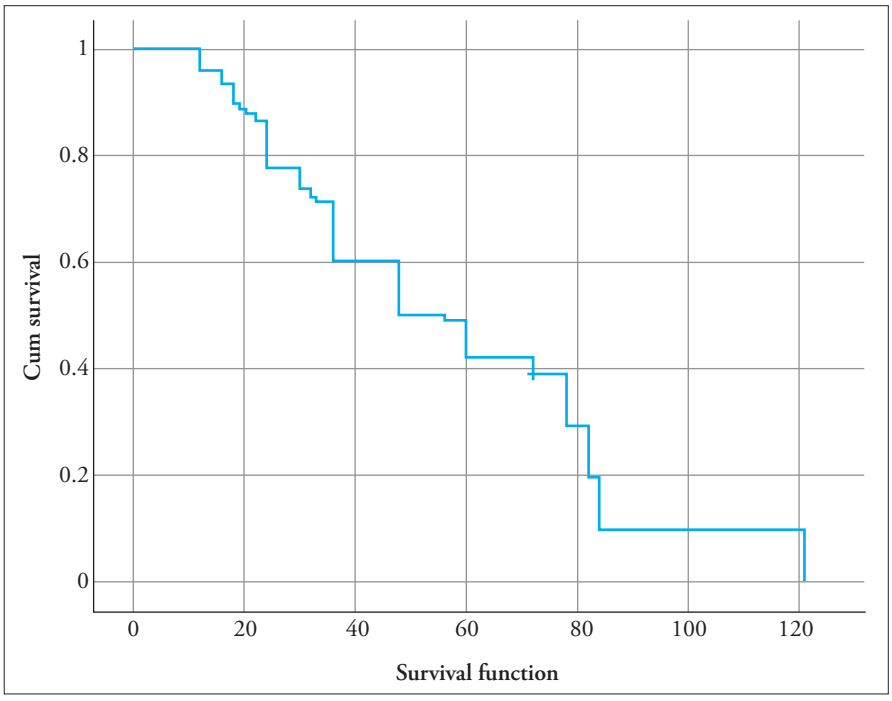


Table II *- Characteristics of patients who outgrown egg allergy and persistence.*

	Tolerance n = 81 (%)	**Persistence n = 45 (%)**	**P-value**
Sex (F/M)	28/53	16/29	0.91
Family history of atopy	28(37.3)	11(25.0)	0.16
Concomitant food allergy	52(64.1)	29(64.4)	0.74
Atopic dermatitis	56(69.1)	24(53.3)	0.07
Prematurity	5(7.2)	3(6.8)	0.93
Initial symptom			
Skin	77 (95.1)	33 (73.3)	0.01
Respiratory	5 (6.2)	4 (8.9)	0.72
Gastrointestinal	8 (9.9)	7 (15.6)	0.34
Anaphylaxis	2 (2.5)	7 (15.6)	0.01
Age at symptom onset	4 (3.25) (1.0-20.0)	5.5 (4.0) (1.0-13.0)	0.91
Symptom onset before 6 months	11 (14.9)	6 (14.3)	0.93
Symptom during OFC	6 (18.8)	46 (82.1)	< 0.01
Skin	10 (17.9)	21 (67.7)	< 0.01
Respiratory	0 (0.0)	14 (43.8)	< 0.01
Gastrointestinal	1 (1.8)	8 (25.0)	< 0.01
Anaphylaxis	1 (1.8)	15 (46.9)	< 0.01
Egg specific IgE (kU/L) Median (IQR) (min-max)	4.91 (10.3) (0.58-280)	11.0 (37.5) (0.48-100)	0.01
Skin prick test induration mm	8.0 (5.0) (3.0-45.0)	10 (7.25) (4.0-35.0)	0.01
Total IgE	199.0 (433.9) (8.0-3963.0)	304.0 (531.1) (17.4-3321.0)	0.37
Eosinophil count %	4.46 (5.14) (0.0-21.0)	6.18 (7.46) (0.8-19.6)	0.14

80 (63.4%) had atopic dermatitis and 81 (64.2%) had another food allergy, with cow's milk (n = 72) (57.1%) being the most common. Nine (7.1%) of the patients had history of anaphylaxis with egg. The most common symptom at home was skin related (87.3%). Demographic data are shown in **table I**.

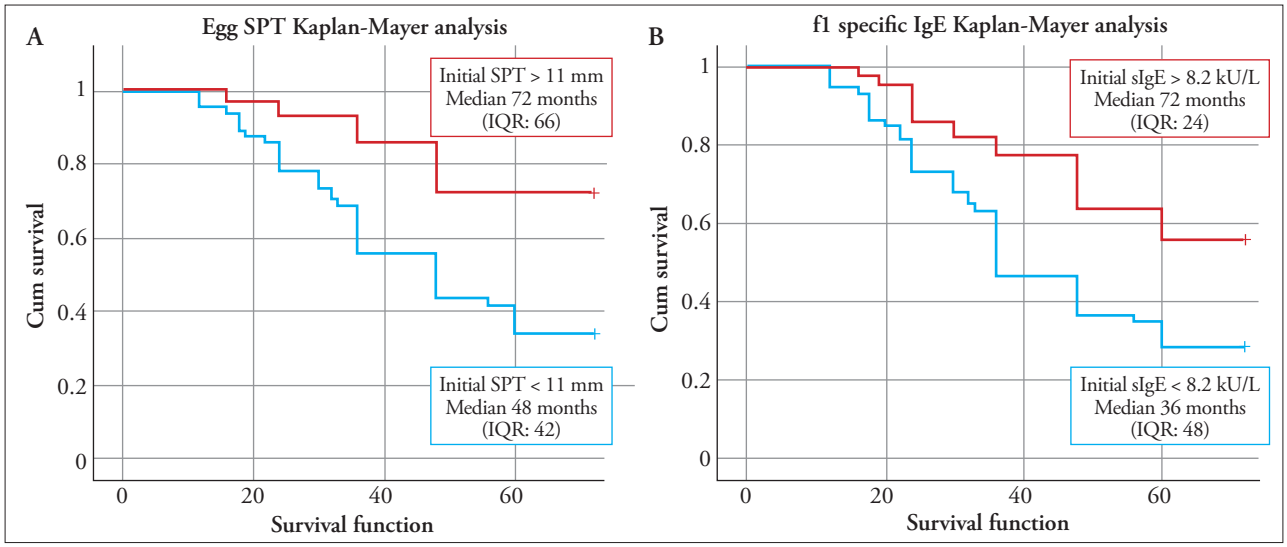
The median egg specific IgE level was 6.13 (IQR:17.6) (min: 0.48-max: 280), median SPT induration was 9 mm (6.0) (3.0-45.0). A total of 88 oral food challenge (OFC) with boiled egg was performed. Sixteen (12.6%) patients experienced anaphylaxis during OFC. The most seen reaction was skin related (24.6%).

The number of the children who had outgrown egg allergy was 81 (64.2%). The median survival time was 48 months (12-121). Tolerance was gained in 22.2% (n = 28) of these patients in the first 2 years of life, in 46.8% (n = 49) in 2-6 years, 3.1% (n = 4) between 7-12 years. Twenty-four months cumulative disease survival probability was 77.7%, 50% at 48 months, 42% at 60 months and 38.8% at 72 months (**figure 1**). Skin symptom and anaphylaxis at home was more common in patients who had not gained tolerance (p = 0.01, p = 0.01, respectively). Egg oral immunotherapy was applied to 9 (7.1%) of the patients whose allergy persisted. Egg specific IgE and skin prick test induration diameter were higher in the persistence group too (p < 0.01, p < 0.01, respectively). **Table II** shows the comparison of the patients who outgrown allergy or not.

ROC-curve analysis for skin prick test induration and baseline specific IgE level was used for distinguishing patients who had persistence or outgrown egg allergy at the age of 2 and 6. For 2 years the highest sensitivity and specificity was 3.6 kU/L (AUC: 0.629; p = 0.024) for sIgE and 5.5 mm (AUC: 0.671; p = 0.002) for SPT; for patients with 6 years 8.2 kU/L (AUC: 0.629; p = 0.024) for sIgE and 11 mm (AUC: 0.671; p = 0.002) for SPT. The tolerance was developed over a longer period for patients with SPT > 11 mm (median 72 monhs *versus* 48 months) and also for patinets with sIgE > 8.2 kU/L (median 72 months *versus* 36 months) according to Kaplan-Meiyer Analysis (p < 0.01 and p < 0.01, respectively Log-Rank, Mantel-Cox regression) (**figure 2**).

Cox-regression analysis was used to determine the factors for resolution of egg allergy for a duration of 72 months. In univariate analysis, baseline sIgE level < 8.2 (Hazard ratio: 2.193; 95%CI 1.309-3.674; p = 0.003), no history of anaphylaxis (at initiation or during OFC) (Hazard ratio: 11.292; 95%CI 2.766-46.090; p = 0.001) and baseline egg SPT < 11 mm (Haz-

Figure 2 *- Kaplan Meiyer Analysis for* ***(A)*** *egg sIgE;* ***(B)*** *SPT.*



P-value < 0.01.

ard ratio: 2.906; 95%CI 1.424-5.930; p = 0.003) were found to be related to earlier resolution of egg allergy. In multivariate analysis only anaphylaxis was significantly related to later resolution (Hazard ratio: 6.547; 95%CI 15.80-27.434; p = 0.01).

Discussion and conclusions

In this study 64.2% of the children achieved tolerance to boiled egg with a cumulative tolerance probability 50% at 48 months. Initial egg sIgE level < 8.2 kU/L, skin prick test induration < 11 mm and no history of anaphylaxis at home or during OFC were significantly associated with earlier resolution of egg allergy.

Ngai *et al.* (6) reported egg allergy resolved at 71% of Chinese children with a median of 36 months. Boyana-Martinez *et al.* (7) followed 58 patients prospectively until egg tolerance developed. Half of the children tolerated egg at 35 months of follow-up, and 66% after 5 years. A systematic review reported a resolution rate of 68% by the age 16 years (4). In contrast, in HealthNuts population-based study, 5,276 children had been followed prospectively and resolution occurred at 89% of the egg allergic children (n = 471) by 6 years old (8). In our study 64.2% of 126 patients achieved tolerance (61.1% by 6 years old), only four (3.1%) of the patients gained resolution after 6 years old.

Little is known about the prognostic factors that can show tolerance to any food. Presence of other food allergies and atopic diseases, high egg specific IgE/SPT wheal size levels, respiratory and multisystem symptoms are found to be associated with persistent egg allergy (7, 9). Arik Yilmaz *et al.* (10) reported that initial egg sIgE level 6.2 kU/L could distinguish tolerance or persistence at the age of 6. Another study also found baseline sIgE level and initial symptoms to be independent predictors for resolution (6). Schrier *et al.* (5) also published elevated egg sIgE levels were related to persistent egg allergy. We found a cut of level of initial sIgE 3.6 for two years and 8.2 kU/L for six years to distinguish persistence and tolerance. It could be said that as the initial sIgE level is higher, the resolution time of allergy will be later. We found the same result for skin prick test induration as for 2 years 5.5 mm, for 6 years 11 mm. A recent study indicated the wheal size at SPT at one year old, was not a good predictor of egg allergy persistence at 6 years old (8). Ngai *et al.*

Table III *- Factors with earlier resolution of egg allergy before 6 years.*

	Hazard Ratio (95%CI)	P-value
Gender	0.938 (0.578-1.521)	0.794
IgE	1.000 (0.999-1.000)	0.297
Eosinophil %	0.967 (0.915-1.022)	0.240
Egg sIgE	0.999 (0.985-1.005)	0.293
F1< 8.2 Ku/L	2.193 (1.309-3.674)	0.003
Concomitant food allergy	0.880 (0.529-1.464)	0.623
SPT induration < 11 mm	2.906 (1.424-5.930)	0.003
SPT induration	0.927 (0.870-0.987)	0.018
Atopic dermatitis	0.520 (0.308-0.879)	0.015
Anaphylaxis at initiation or during OFC	11.292 (2.766-46.090)	0.001

(6) reported skin prick test wheal size > 6 mm was associated with later resolution.

In a recent study egg was found to be the most common allergen causing anaphylaxis < 12 months of children (2). Nine of our patients had history of anaphylaxis and 16 had anaphylaxis during OFC. Three of the patients had anaphylaxis both at home and during OFC. In accordance with the literature the resolution was delayed in children with anaphylaxis in our study. In a recent study presence of atopic dermatitis, peanut and wheat allergy were predictors for persistence (2). Peters *et al*. (8) also found early-onset severe eczema was associated with persistence. We found no risk for persistence in patients with atopic dermatitis. This may be the reason of higher rate of atopic dermatitis among our patients (63.5%). The rate is lower in the literature. Samady *et al*. (11) evaluated 38,408 children and found 0.9% had egg allergy. Among these patients with egg allergy 19.0% had atopic dermatitis.

Limitations

One of limitation of our study is its retrospective design. We could not reach all the laboratory data. Second limitation is that we could only investigate standard serum egg-specific IgE levels. Recent developments in component resolved diagnosis technology can be more informative both for diagnosis and to predict development of tolerance. Dang *et al*. (12) reported Gal-d 1 sensitization increased the risk of persistent egg allergy by 2.5-fold and all four egg allergens (Gal-d 1, 2, 3, 4) by 4-fold.

In conclusion, this study showed that egg tolerance was achieved at 64.2% of the patients. Skin prick test induration < 11 mm or sIgE < 8.2 kU/L could predict achievement of tolerance at the age of 6. Anaphylaxis at home or during OFC was the only associated factor with persistent egg allergy.

Fundings

None.

Contributions

HDS: conceptualization, data curation, formal analysis, writing - original draft. MG: conceptualization, methodology, project administration, resources. ET: formal analysis, validation, visualization, writing - original draft. FG, AA, ED: data curation, formal analysis, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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References

1. Keil T, McBride D, Grimshaw K, Niggemann B, Xepapadaki P, Zannikos K, et al. The multinational birth cohort of EuroPrevall: background, aims and methods. Allergy. 2010;65(4):482-90. doi: 10.1111/j.1398-9995.2009.02171.x.
2. Samady W, Trainor J, Smith B, Gupta R. Food induced anaphylaxis in infants and children. Ann Allergy Asthma Immunol. 2018;121(3):360-5. doi: 10.1016/j.anai.2018.05.025.
3. Celakovská J, Ettlerová K, Ettler K, Vaněčková J. Egg allergy in patients over 14 years old suffering from atopic eczema. Int J Dermatol. 2011;50(7):811-8. doi: 10.1111/j.1365-4632.2010.04780.x.
4. Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. J Allergy Clin Immunol. 2007;120(6):1413-7. doi: 10.1016/j.jaci.2007.09.040.
5. Sicherer SH, Wood RA, Vickery BP, Jones SM, Liu AH, Fleischer DM, et al. The natural history of egg allergy in an observational cohort. J Allergy Clin Immunol. 2014;133(2):492-9. doi: 10.1016/j.jaci.2013.12.1041.
6. Ngai NA, Leung ASY, Leung JCH, Chan OM, Leung TF. Identification of predictors for persistence of immediate-type egg allergy in Chinese children. Asia Pac Allergy. 2021;11(4):e41. doi: 10.5415/apallergy.2021.11.e41.
7. 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(2):304-9. doi: 10.1067/mai.2002.126081.
8. Peters RL, Guarnieri I, Tang MLK, Lowe AJ, Dharmage SC, Perrett KP, et al. The natural history of peanut and egg allergy in children up to age 6 years in the HealthNuts population-based longitudinal study. J Allergy Clin Immunol. 2022;150(3):657-65.e13. doi: 10.1016/j.jaci.2022.04.008.
9. Sampson HA, Berin MC, Plaut M, Sicherer SH, Jones S, Burks AW, et al. The Consortium for Food Allergy Research (CoFAR): The first generation. J Allergy Clin Immunol. 2019;143(2):486-93. doi: 10.1016/j.jaci.2018.12.989.
10. Arik Yilmaz E, Cavkaytar O, Buyuktiryaki B, Sekerel BE, Soyer O, Sackesen C. Factors associated with the course of egg allergy in children. Ann Allergy Asthma Immunol. 2015;115(5):434-8.e1. doi: 10.1016/j.anai.2015.08.012.
11. Samady W, Warren C, Wang J, Das R, Gupta RS. Egg Allergy in US Children. J Allergy Clin Immunol Pract. 2020;8(9):3066-73.e6. doi: 10.1016/j.anai.2015.08.012.
12. Dang TD, Peters RL, Koplin JJ, Dharmage SC, Gurrin LC, Ponsonby AL, et al. Egg allergen specific IgE diversity predicts resolution of egg allergy in the population cohort HealthNuts. Allergy. 2019;74(2):318-26. doi: 10.1111/all.13572.

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Predicting the outcome of the buckwheat oral challenge test: a first evaluation assuming a single serving of boiled buckwheat noodles

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Key words

Child; buckwheat hypersensitivity; oral challenge test.

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Impact statement

Buckwheat-specific IgE levels poorly predict food challenge outcomes despite increased serving size; prior buckwheat-induced symptoms strongly correlate with positive challenges, emphasizing patient history's importance.

Summary

Background. *Global increase in buckwheat consumption has led to a surge in buckwheat allergy reports. However, studies scrutinizing the predictive accuracy of buckwheat-specific immunoglobulin E (IgE) antibody levels in correlation with symptom manifestation remain limited. A critical concern is the discrepancy between the total buckwheat amount featured in prior studies and the quantity consumed per occasion. We aimed to determine open Oral Food Challenge (OFC) positivity rates with buckwheat, using a single serving of boiled buckwheat noodles, and assess the predictability of positive responses using buckwheat-specific IgE levels.* ***Methods.*** *Patients aged 20 years or younger, suspected of buckwheat allergy, were subjected to an OFC involving consumption of 100 g (4,800 mg of protein) of boiled buckwheat noodles for those under six years, and 200 g (9,600 mg of protein) for those six years or older. The predictive accuracy of the OFC, corresponding with buckwheat-specific IgE antibody levels, was evaluated using Receiver Operating Characteristic (ROC) analysis.* ***Results.*** *Our study involved 80 patients who undertook a buckwheat OFC. Among these, 14 (17.5%) tested positive for a buckwheat allergy, with 3 (3.8%) developing anaphylaxis. The comparative analysis of buckwheat-specific IgE antibody levels did not offer a reliable predictive measure for OFC outcomes. However, a past history of symptom manifestation following buckwheat consumption was significantly correlated with a positive OFC.* ***Conclusions.*** *Forecasting OFC outcomes based on buckwheat-specific IgE antibody levels poses a challenge, even when taking into account the total quantity of buckwheat that can be consumed in a single occasion.*

Introduction

Buckwheat is a widely cultivated and consumed crop that is used as a primary ingredient in various traditional dishes worldwide. It has gained popularity in the European market due to its nutritional value and suitability for gluten-free products (1, 2). In Italy, however, buckwheat allergies account for approximately 7% of all identified food allergies (3). This finding is supported by a separate clinical study that reported buckwheat allergies in approximately 3.6% of patients evaluated at 18 allergy clinics across Italy (4).

Therefore, accurate diagnosis of buckwheat allergy has become increasingly crucial. However, the largest study conducted to date, involving 419 individuals with suspected buckwheat allergy, demonstrated a low predictive accuracy for symptom onset during a buckwheat oral food challenge (OFC) when using buckwheat-specific IgE antibody levels (5). Additionally, previous studies used a single serving size of boiled buckwheat noodles that was relatively low, ranging from 64 to 80 g (equivalent to 3,072 to 3,840 mg of buckwheat protein). This suggests the need for a study to investigate the rate of symptomatic positivity with a higher total serving size (5-8). In this research,

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we conducted a buckwheat OFC with a serving size of 100 grams (equivalent to 4,800 mg of protein) for subjects under 6 years of age and 200 grams (equivalent to 9,600 mg of protein) for those aged 6 and above, aiming to investigate the positive predictive accuracy of buckwheat-specific IgE antibody levels. This study represents the first cross-sectional case series where the total serving size of buckwheat was set higher than in previous studies.

Materials and methods

Study design, ethics statement and informed consent

In this cross-sectional study, we administered open OFC to patients under 20 years of age suspected of buckwheat allergy. The amount of boiled buckwheat noodles typically consumed in Japan (100 g for children under six years of age, and 200 g for those over six) was employed for the OFC. We retrospectively evaluated the accuracy of predicting symptom development during OFC based on buckwheat-specific IgE antibody levels, using data obtained from electronic medical records.

We ensured the stringent observance of ethical standards in the course of the study. Parents or guardians were thoroughly briefed, both verbally and in writing, about potential risks associated with OFC. Written informed consent was acquired from the parents or legal guardians of all subjects. The study protocol received approval from the Ethics Review Committee of Jikei University Hospital (approval number 35-027 [11648])). The study was conducted in adherence to the ethical guidelines for life science and medical research involving human subjects as stipulated by Japanese standards. Moreover, we ensured full compliance with the principles enshrined in the Declaration of Helsinki throughout the study.

Objectives

The study, conducted at the Department of Pediatrics, The Jikei University Katsushika Medical Center in Tokyo, from January 1, 2012, to April 30, 2023, aimed to assess OFC in patients under 20 years of age suspected of buckwheat allergy. The inclusion criteria were patients with a history of buckwheat-related symptoms or a positive buckwheat-specific IgE antibody level, and no prior consumption of buckwheat. Patients who underwent an oral boiled buckwheat noodles challenge of 100 g for those under six years of age, and 200 g for those over six, were considered for the total buckwheat load. Those scheduled for a lower total load were excluded.

Total immunoglobulin E (IgE) levels and serum-specific IgE antibody titers

We utilized the ImmunoCAP assay system (Thermo Fisher Scientific, Uppsala, Sweden) to measure total immunoglobulin E (IgE) levels and serum-specific IgE antibody titers. For this study, we used buckwheat-specific IgE antibody measurements taken within one year, both preceding and following the OFC. Specific IgE antibody titers below 0.1 UA/mL were recorded as 0.09 UA/mL, and those above 100 UA/mL as 101 UA/mL. Notably, in January 2013, the lower limit of accuracy for the commercial ImmunoCAP assay system in Japan was revised from 0.35 UA/mL to 0.1 UA/mL. Consequently, for consistency, buckwheat-specific IgE antibody levels less than 0.35 UA/mL measured before January 2013 were adjusted to 0.09 UA/mL in our study.

OFC

The boiled buckwheat noodles OFC was conducted by administering buckwheat in specific fractions. For a total load of 100 g of boiled buckwheat noodles (buckwheat protein equivalent 4,800 mg), subjects consumed buckwheat in three divided servings of 10 g, 30 g, and 60 g at 30-minute intervals. For a total load of 200 g of boiled buckwheat noodles (buckwheat protein equivalent 9,600 mg), subjects ingested buckwheat in three divided servings of 25 g, 75 g, and 100 g. All patients underwent the oral challenge as inpatients and were monitored until the day following the test. Symptoms observed during the oral challenge were evaluated using a grading system based on the Sampson classification (9). All OFCs were performed in an inpatient setting and monitored through the next day.

Symptoms observed during the OFC were categorized into distinct groups: cutaneous symptoms (urticaria, erythema, pruritus), respiratory symptoms (cough, wheezing, hoarseness, dyspnea), gastrointestinal symptoms (vomiting, diarrhea, prolonged abdominal pain), cardiovascular symptoms (hypotension), and neurological symptoms (confusion).

If a positive result was determined by the OFC physician, patients under seven years of age were treated with antihistamines like fexofenadine or epinastine, while patients over seven were administered loratadine. The variation in types of antihistamines administered based on age was due to changes in, or limited availability of, the drugs employed at our institution. In addition, based on the specific pharmacotherapy available at the hospital, inhaled beta-adrenergic agonists (such as salbutamol), corticosteroids (prednisolone), and intramuscular epinephrine into the lateral thigh muscle were administered as needed. The final determination of whether the OFC results were positive, negative, pending, or indicative of anaphylaxis was made by the physician. “Pending” referred to cases where there were no clear objective clinical symptoms, making it difficult to render a positive determination. The details of the OFC were retrospectively confirmed from the medical records.

Endpoints

The primary endpoints of the study were as follows: the proportion of patients who tested positive for OFC with a total boiled

buckwheat noodles load of 100 g (< 6 years) and 200 g (≥ 6 years), sensitivity and specificity based on buckwheat-specific antibody levels, and the area under the curve (AUC) for the receiver operating characteristic (ROC) analysis.

Statistical analysis

Continuous variables were summarized using medians and interquartile ranges (IQRs), whereas nominal variables were represented as numbers and percentages. For the comparison of nominal variables, we applied Fisher's exact test, and for continuous variables, the Mann-Whitney U test was employed. We used the ordinary logarithm to transform Total IgE values and specific IgE antibody titers logarithmically. We considered a P-value less than 0.05 as indicative of statistical significance. To assess the predictive performance of buckwheat-specific IgE antibody titers, we generated ROC curves and calculated AUC. We determined specificity and sensitivity based on the point on the ROC curve nearest to the upper-left corner. We conducted statistical analyses using IBM SPSS Statistics for Windows, Version 17.0 (IBM Corp., Armonk, New York, United States). Additionally, we employed the graphical interface for R, EZR version 1.60 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is affiliated with The R Foundation, to facilitate data analysis.

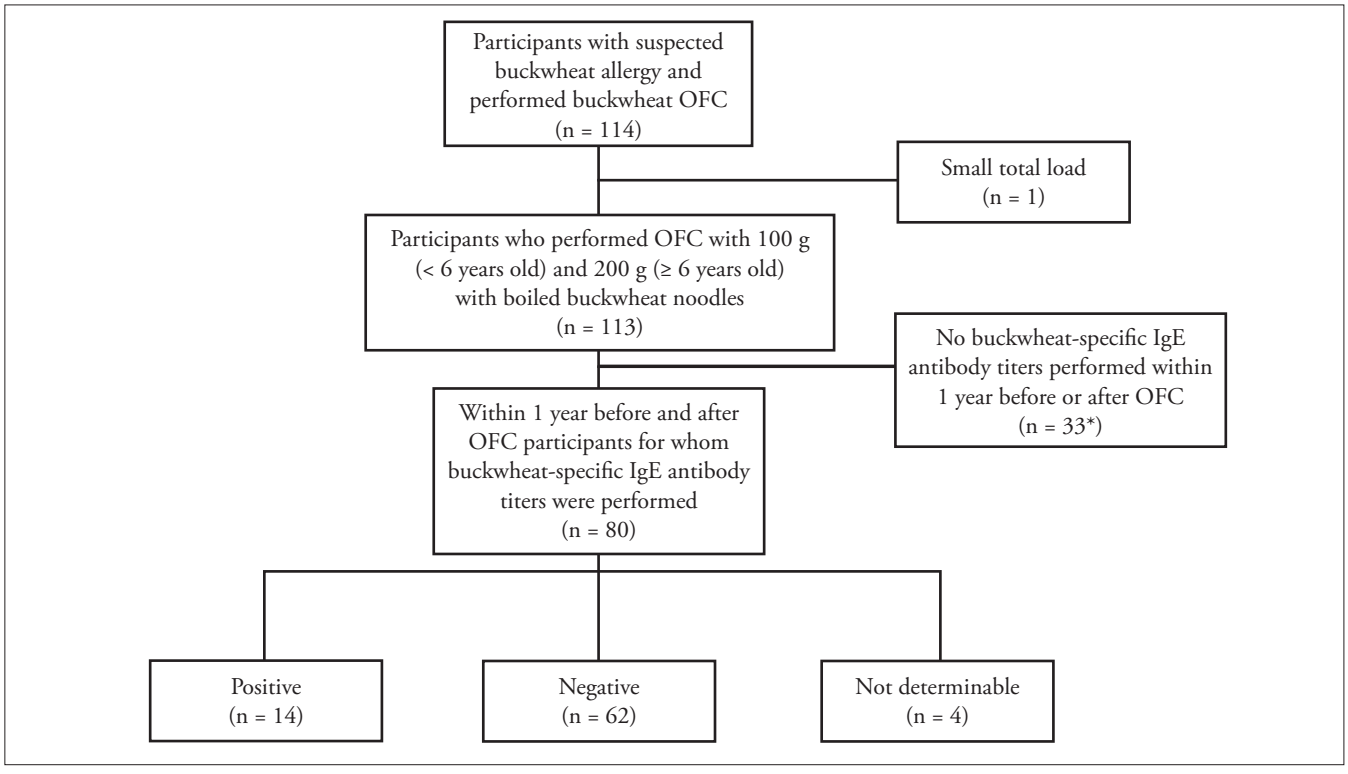
Results

Patient characteristics

Throughout the study period, 114 patients were set for a boiled buckwheat noodle OFC. Among these, 113 patients proceeded with the OFC, adhering to the total load designated in this study: 100 g for patients below the age of 6 and 200 g for those above 6 years old. Out of these patients, 80 had buckwheat-specific Immunoglobulin E (IgE) antibody titers measured within one year preceding or following the OFC (**figure 1**).

Therefore, 80 patients (56 males, constituting 70.0%) fulfilled the inclusion criteria for this study. The median age at the time of the OFC was 73 months (ranging between 23 to 203 months). At the time of the OFC, 11 (13.8%) had previous exposure to buckwheat consumption, 8 (10.0%) reported a history of symptoms triggered by buckwheat consumption, and 4 (5.0%) had experienced anaphylaxis following buckwheat exposure (**table I**).

Figure 1 *- Flowchart of this study*



*OFC: oral food challenge; *these subjects underwent buckwheat OFC and IgE antibody evaluations, but buckwheat-specific IgE wasn't assessed within a year of the OFC, largely because parents were wary of prior positive IgE findings and past buckwheat symptoms.*

Table I *- Patient characteristics (n = 80).*

Characteristics	Total
Sex	
Male	56 (70.0)
Female	24 (30.0)
Age (months)	73 [44.5-106.25]
History of symptom induction by buckwheat	8 (10.0)
History of anaphylaxis due to buckwheat	4 (5.0)
Current bronchial asthma	26 (32.5)
Buckwheat-specific IgE (UA/mL)	1.62 [0.66-3.98]
Total IgE (IU/mL)	829 [263-1,565]

Data are presented as n (%) or median [interquartile range]; IgE: immunoglobulin E.

OFC result

Of the participants, 14 subjects (17.5%) tested positive during the OFC, while 62 (77.5%) tested negative. A total of 4 (5.0%) showed minor symptoms, such as localized oral cavity itching, and were subsequently classified as inconclusive OFC results. 6 subjects (7.5%) showed symptoms before the maximum OFC dose: 100 g for children under 6 and 200 g for those 6 and older. Of these, 2 were positive at 25 g and 4 at 75 g.

Anaphylaxis was noted in three patients (3.8%), with one patient (1.3%) requiring an intramuscular adrenaline injection. In two cases, symptoms began to alleviate while the administration of adrenaline was under consideration, leading to the physician's decision against its use. There were no recorded cases of severity Grade 4 or higher.

Comparative analysis of OFC outcomes in positive and negative groups

OFC results were compared between 14 cases in the symptom-positive group and 62 cases in the negative group, excluding 4 cases with minor and difficult-to-identify symptoms (**table II**). In this study, the group with a history of symptom induction from previous buckwheat consumption had a significantly higher positive rate in the buckwheat OFC compared to those without such a history (28.6% *vs* 6.5%; p = 0.016).

A Receiver Operating Characteristic (ROC) analysis of the buckwheat-specific IgE antibody titer, used for predicting OFC positivity, yielded an Area Under the Curve (AUC) of 0.543, which was deemed non-significant. A similar study was carried out utilizing the ratio of buckwheat-specific IgE antibody titer to total IgE titer. However, the AUC was 0.486, which also demonstrated a lack of significance (**figure 2**).

Association between past symptom induction during buckwheat consumption and outcomes of OFC

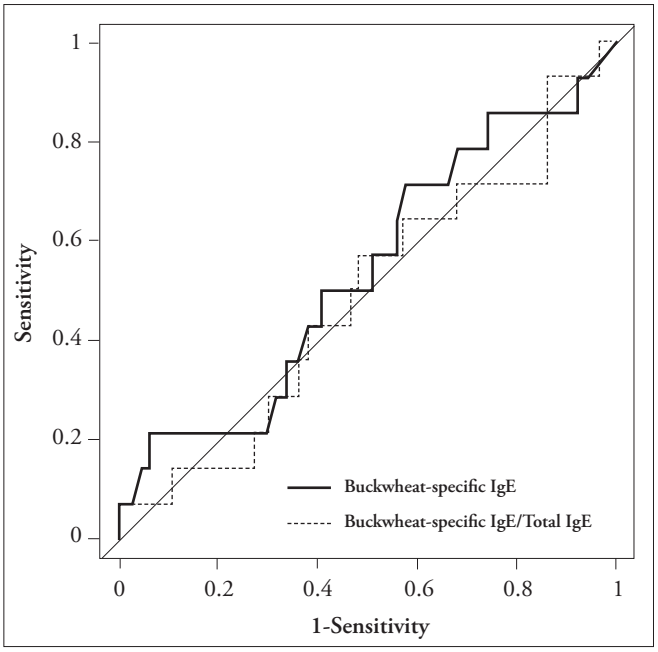
The OFC positivity rate for buckwheat was evaluated in eight individuals with a history of symptom onset following buckwheat consumption. Of these, 4 out of 8 patients who had previously experienced symptoms following buckwheat ingestion (50.0%), and 10 out of 72 subjects (13.9%) without such a history, tested positive for the buckwheat OFC. This difference was statistically significant (p = 0.028). Even when four subjects with inconclusive buckwheat OFC outcomes were excluded from the analysis, the significant difference persisted (p = 0.034).

Table II *- Comparison of patient characteristics and laboratory findings in positive versus negative buckwheat OFC (100 and 200 g of boiled buckwheat noodles in children < 6 and ≥ 6 years, respectively) results.*

Result of OFC	Positive (n = 14)	Negative (n = 62)	P-value
Sex			0.568
Male	11 (78.6)	44 (71.0)	
Female	3 (21.4)	18 (29.0)	
Age (months)	84.5 [51.75-137.50]	70.5 [43.0-102.25]	0.269
History of symptom induction by buckwheat	4 (28.6)	4 (6.5)	**0.016**
History of anaphylaxis due to buckwheat	2 (14.3)	2 (3.2)	0.096
Current bronchial asthma	3 (21.4)	22 (35.5)	0.315
Buckwheat-specific IgE (UA/mL)	1.81 [0.72-4.6275]	1.47 [0.620-3.927]	0.862
Total IgE (IU/mL)	650.5 [336.5-2,379.5]	862 [249-1,541.75]	0.615

Data are presented as n (%) or median [interquartile 25^{th}-75^{th} percentiles (range)]; OFC: oral food challenge; IgE: immunoglobulin E; $p < 0.05$ was considered statistically significant.

Figure 2 - *Receiver operating characteristic (ROC) curves for diagnostic accuracy of buckwheat allergy based on buckwheat-specific immunoglobulin E (IgE) antibody levels and the ratio of buckwheat-specific IgE/total IgE values.*



Comparison of groups with symptoms at below-planned vs planned total loads

Of 6 subjects positive for OFC at ≤ 75 g and 8 subjects at ≥ 100 g, the buckwheat-specific IgE antibody titers were 3.645 ± 5.085 UA/mL and 5.656 ± 9.557 UA/mL, respectively, with no significant difference (p = 0.622).

Discussion and conclusions

To our knowledge, this is the first investigation utilizing a typical single-serving amount of boiled buckwheat noodles for an OFC and evaluating the predictive accuracy of OFC outcomes based on buckwheat-specific IgE antibody titers. Buckwheat, a globally cultivated and consumed food, is a staple ingredient in various traditional cuisines worldwide. Its popularity extends beyond Asia, and it has seen growing acceptance in the European market due to its nutritional value and suitability for gluten-free products (1, 2, 10).

Hence, it is anticipated that both the frequency of buckwheat consumption and the quantity ingested per meal will increase. Previous studies on buckwheat OFCs have generally found that the total amount of boiled buckwheat noodles ranges from 64 to 80 g (equivalent to 3,072 to 3,840 mg of buckwheat protein – about 30 g to 40 g of buckwheat flour) (5-8). However, numerous cooking recipe websites from various regions commonly showcase buckwheat-based dishes, in which the total buckwheat content often surpasses the amounts used in previous research studies (11-14). In other words, a gap has developed between the total buckwheat load from previous studies and the total amount of buckwheat actually consumed at one time.

One obstacle to the widespread use of buckwheat OFC is the problem of total load. Clinical trials involving chicken eggs, milk and wheat suggest that as the cumulative intake during an OFC increases, so does the risk of symptom manifestation (15). In other words, even if a moderate dose (64-80 g of boiled buckwheat noodles) of OFC is negative, a single intake of an even higher dose (100-200 g of boiled buckwheat noodles) may cause concern for both patient and physician. As a result, there is a need for an OFC that corresponds with the quantity of buckwheat typically consumed in a single serving.

This study was conducted using a single serving of boiled buckwheat noodles. We administered an OFC with a total buckwheat intake of 100 g (equivalent to 4,800 mg of protein – about 50 g of buckwheat flour) for children under six years of age, and 200 g (equivalent to 9,600 mg of protein – about 100 g of buckwheat flour) for those older, resulting in a symptom induction rate of 17.5%. This outcome appears reasonable when compared to the largest cross-sectional study performed on 419 individuals, which reported a positive rate of 10.5% (5).

This study aligns with the results of previous studies in several ways. For example, it remains difficult to predict OFC positivity from buckwheat-specific IgE antibody titers, and a history of past symptom induction predicts OFC outcome. Previous studies have shown that patients whose symptoms were induced by ingestion of the target allergen in the past have a higher rate of symptom induction during OFC (16).

Our study diverges from previous findings in several respects. The incidence of anaphylaxis in our investigation was lower than in the previous study by Yanagida *et al.* (5). For instance, in Yanagida *et al.*'s study (5), 54.5% of patients who tested positive in the OFC developed anaphylaxis, whereas in our study, anaphylaxis occurred in only 21.4% of patients. The decision to administer OFC was made by an outpatient physician, which may have excluded patients with a history of anaphylaxis. Despite this, the incidence of anaphylaxis from buckwheat OFC, where buckwheat-specific IgE antibody titers is still estimated to be higher than in previous studies with various foods. For instance, a review of 6,377 open OFC cases conducted at 5 U.S. facilities estimated anaphylaxis to be 2% of the 14% positive rate for OFC (17). This study underscores the difficulty of predicting OFC symptom development based on buckwheat-specific IgE antibody titers in real-world scenarios. Moving forward, strategies to improve the accuracy of positive predictions for buckwheat OFC are needed. Kajita *et al.*, for example, reported an improvement in the accuracy of OFC

outcome prediction by considering the ratio of buckwheat-specific IgE antibody titer to the total IgE titer (8). However, our study did not replicate the effects reported by Kajita *et al*. They found that 27.0% of patients tested positive for OFC with approximately 80 g of boiled buckwheat noodles, which may be influenced by a higher rate of OFC positivity than in previous studies and our study.

This study has few limitations. First, the group in which the OFC was conducted was a cross-sectional study with a retrospective design, where the total load was predetermined by the outpatient physician. However, the study also encompassed cases with a history of anaphylaxis, and it was inferred that these groups were still at higher risk of inducing allergic symptoms. Thus, while bias may exist, its effect is minor and remains important as a result of OFC conducted in the real world.

Second, handling specific IgE antibody titers posed a challenge: as the accuracy of the lower limit for testing food-specific IgE antibody titers improved, the previous test group of less than 0.35 UA/mL was considered as 0.09 UA/mL. However, coincidentally, cases with buckwheat-specific IgE antibody titers less than 0.35 U_A/mL were not included in this study, meaning the results were not influenced by this factor.

Lastly, the number of cases was limited. However, this study is still considered valuable as it is the first to examine the total load set for the intake of one serving of buckwheat over a period of more than 10 years.

Given these circumstances, additional research on buckwheat components is necessary, as predicting buckwheat OFC results from buckwheat-specific IgE antibody titers remains challenging (18). For instance, the IgE antibody titers for Fag e3, Fag e 2, and Fag e 5 have been reported to significantly improve the accuracy of positive prediction of buckwheat allergy (7, 19).

In our study, these buckwheat component tests were not measured because it was not practical to use them routinely, but we believe they will become even more crucial in the future. Further research is desirable to establish a method for buckwheat OFC and a test with high predictive accuracy for symptom induction prior to OFC.

Fundings

None.

Contributions

KH: conceptualization, study design, sample collection, data analysis, writing – original draft. MK: data collection, writing – original draft. NT: study design, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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References

1. Zhou, M, Tang Y, Deng X, Ruan C, Kreft I, Tang Y, et al. Overview of buckwheat resources in the world. Buckwheat germplasm in the world. 2018;1-7. doi: 10.1016/B978-0-12-811006-5.00001-X.
2. Sofi SA, Ahmed N, Farooq A, Rafiq S, Zargar SM, Kamran F, et al. Nutritional and bioactive characteristics of buckwheat, and its potential for developing gluten-free products: An updated overview. Food Sci Nutr. 2022;11(5):2256-76. doi: 10.1002/fsn3.3166.
3. Heffler E, Nebiolo F, Asero R, Guida G, Badiu I, Pizzimenti S, et al. Clinical manifestations, co-sensitizations, and immunoblotting profiles of buckwheat-allergic patients. Allergy. 2011;66(2):264-70. doi: 10.1111/j.1398-9995.2010.02469.x.
4. Badiu I, Olivieri E, Montagni M, Guida G, Mietta S, Pizzimenti S, et al. Italian study on buckwheat allergy: prevalence and clinical features of buckwheat-sensitized patients in Italy. Int J Immunopathol Pharmacol. 2013;26(3):801-6. doi: 10.1177/039463201302600328.
5. Yanagida N, Sato S, Takahashi K, Nagakura KI, Ogura K, Asaumi T, et al. Reactions of Buckwheat-Hypersensitive Patients during Oral Food Challenge Are Rare, but Often Anaphylactic. Int Arch Allergy Immunol. 2017;172(2):116-22. doi: 10.1159/000456008.
6. Maruyama N, Sato S, Yanagida N, Cabanos C, Ito K, Borres MP, et al. Clinical utility of recombinant allergen components in diagnosing buckwheat allergy. J Allergy Clin Immunol Pract. 2016;4(2):322-3.e3. doi: 10.1016/j.jaip.
7. Yanagida N, Sato S, Maruyama N, Takahashi K, Nagakura KI, Ogura K, et al. Specific IgE for Fag e 3 Predicts Oral Buckwheat Food Challenge Test Results and Anaphylaxis: A Pilot Study. Int Arch Allergy Immunol. 2018;176(1):8-14. doi: 10.1159/000487135.
8. Kajita N, Yoshida K, Morikawa E, Hirao K, Yokoyama S, Narita M. Predictor of buckwheat allergy in children based on challenge test results: a retrospective observational study in Japan. Eur Ann Allergy Clin Immunol. 2022;54(4):183-8. doi: 10.23822/EurAnnACI.1764-1489.224.
9. Sampson HA. Anaphylaxis and emergency treatment. Pediatrics. 2003;111(6 Pt 3):1601-8.
10. Ohsawa R, Matsui K, Yasui Y. Current research and future prospects in common buckwheat (Fagopyrum esculentum). Breed Sci. 2020;70(1):1. doi: 10.1270/jsbbs.70.1.
11. Giallo Zafferano: Torta di grano saraceno. Available at: https://ricette.giallozafferano.it/Torta-di-grano-saraceno.html. [Italian]. Last access date: 06/06/2023.
12. Giallo Zafferano: Crostata di grano saraceno. Available at: https://ricette.giallozafferano.it/Crostata-di-grano-saraceno.html. [Italian]. Last access date: 06/06/2023.
13. Kwestia Amaku. Makaron Gryczany Z Grillowanym Łososiem. Available at: https://www.kwestiasmaku.com/przepis/makaron-gryczany-z-grillowanym-lososiem. [Polish]. Last access date: 06/06/2023.
14. Marmiton. Crêpes au Sarrasin farcies à l'oeuf, fromage et jambon. Available at: https://www.marmiton.org/recettes/recette_crepes-au-sarrasin-farcies-a-l-oeuf-fromage-et-jambon_71106.aspx. [French]. Last access date: 06/06/2023.

15. Yanagida N, Minoura T, Kitaoka S, Ebisawa M. A three-level stepwise oral food challenge for egg, milk, and wheat allergy. J Allergy Clin Immunol Pract. 2018;6(2):658-60.e10. doi: 10.1016/j.jaip.2017.06.029.
16. Miceli Sopo S, Gurnari G, Monaco S, Romano A, Liotti L, Cuomo B, et al. Predictive value of the number of adverse reaction episodes for the IgE-mediated food allergy diagnosis. Allergol Immunopathol (Madr). 2019;47(3):277-81. doi: 10.1016/j.aller.2018.10.006.
17. Akuete K, Guffey D, Israelsen RB, Broyles JM, Higgins LJ, Green TD, et al. Multicenter prevalence of anaphylaxis in clinic-based oral food challenges. Ann Allergy Asthma Immunol. 2017;119(4):339-48.e1. doi: 10.1016/j.anai.2017.07.028.
18. Satoh R, Jensen-Jarolim E, Teshima R. Understanding buckwheat allergies for the management of allergic reactions in humans and animals. Breed Sci. 2020;70(1):85-92. doi: 10.1270/jsbbs.19051.
19. Geiselhart S, Nagl C, Dubiela P, Pedersen AC, Bublin M, Radauer C, et al. Concomitant sensitization to legumin, Fag e 2 and Fag e 5 predicts buckwheat allergy. Clin Exp Allergy. 2018;48(2):217-24. doi: 10.1111/cea.13068.

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Evaluation of pain-alleviating strategies during allergy shots (subcutaneous immunotherapy): a randomized controlled pilot study

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Key words

Allergic pediatric patients; Buzzy device; pain interventions; ShotBlocker; subcutaneous immunotherapy.

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Impact statement

Evaluated distraction devices and ethyl chloride spray for reducing needle pain during SCIT in children. No significant differences found, suggesting need for further research due to small sample size.

Summary

Background. *Subcutaneous immunotherapy (SCIT) is a potential disease-modifying therapy effective for treatment of various allergic disorders. Pain and fear are common concerns of children, which can pose stress and result in negative experiences. The purpose of this study was to evaluate and compare the effectiveness of three marketed distraction devices and ethyl chloride spray (a routinely used topical anesthetic agent for painful procedures), the current clinical standard of care in reducing the perception of needle pain during SCIT administration in children.* ***Methods.*** *40 children, aged 4-17 years, receiving SCIT with use of one of three alternative pain therapies or with standard practice were enrolled. Participants were randomly assigned to one of the pain-modifying interventions. The three interventional groups were ShotBlocker® (Bionix, Toledo, OH, USA), Buzzy® I (Pain Care Labs, Atlanta, GA, USA) (vibration only), and Buzzy® II (vibration with ice). Control group was ethyl chloride spray. The study consisted of two visits during SCIT administration process.* ***Results.*** *Of these 40 children, 12 received the ShotBlocker, 8 received the Buzzy I, 11 received the Buzzy II, and 9 received ethyl chloride spray (control group).* ***Conclusions.*** *There were no significant differences found between each of the distraction devices and between the control group. Type II error/false negative finding cannot be ruled out because of a small sample. Therefore, we cannot conclude that no true difference exists between each distraction device and the control group simply because of occurrence of a non-significant P-value in our study.* ***Study registration.*** *Protocol ID: 1353562; ClinicalTrials.gov ID: NCT04181632.*

Introduction

Allergic diseases have reached epidemic proportions globally, affecting nearly 30% of the world's population (1). Subcutaneous immunotherapy (SCIT) is a potentially disease-modifying therapy that is effective for the treatment of patients with allergic diseases (2). Studies in general have found that allergen-specific immunotherapy is more effective than the standard of care including pharmacotherapy, and SCIT remains the gold standard of treatment (3). Pain and swelling are common adverse reactions of SCIT and can affect its tolerability in many children (4). Needle procedure-related fear may result in increased avoidance behavior and attempts to eliminate any possible exposure to needles (5). Thus, receiving repeated injections could develop into negative experiences for both child and legal guardian during SCIT administration and possibly affect compliance.

To determine the relevancy of this issue, we reviewed the charts of 150 current SCIT patients in our pediatric clinic and found 141 of them use at least one pain-relieving intervention (95%). This led us to believe that most SCIT pediatric patients desire pain relief during SCIT injections.

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The Buzzy® device (Pain Care Labs, Atlanta, GA, USA) and ShotBlocker® (Bionix, Toledo, OH, USA) are two non-pharmacological methods used during painful interventions (6) and for common needle-related medical procedures (4, 7). In these methods, according to the door control theory, the pain signals of the injection are blocked temporarily, and the "doors" leading to the central nervous system are closed (7). Studies and reviews evaluating pharmacological and nonpharmacological interventions for needle-related pain have increased considerably over the past decade (8); however, there are limited data on the comparative effectiveness in children receiving SCIT. The purpose of this study was to evaluate and compare these two marketed pain devices with ethyl chloride spray, a routinely used topical anesthetic agent for painful procedures, in reducing the perception of needle pain during SCIT administration in children.

Materials and methods

A randomized controlled pilot study included 40 participants aged 4 to 17 years presenting for SCIT administration in our clinic. The standardized dosage protocol outlined in the second and third updates of Allergen Immunotherapy: a Practice Parameter (9, 10) was used for environmental allergen and venom immunotherapy. As suggested in these updates, a consistent, uniform color-coded labeling system for dilutions was used. It consisted of the highest concentration (maintenance dose) labeled as a red vial, the next highest yellow, and then green and blue, respectively.

Patients were enrolled and randomly assigned to one of four color-coded study groups (three intervention/experimental groups and one comparison/control group). The study consisted of pain-reduction therapies received during one routine nurse visit for SCIT administration. This clinical trial was approved by our hospital's Institutional Review Board and conducted in accordance with the declaration of Helsinki.

Interventional groups

1. ShotBlocker #1-25 (red).
2. Buzzy I (vibration only) #26-50 (green).
3. Buzzy II (vibration with ice) #51-75 (blue).

Control group

4. Ethyl chloride/PainEase® spray (Gebauer Company, Cleveland, OH, USA) #76-100 (light blue).

Study procedures

Visit 1

Children aged 4 to 17 years presenting to the allergy clinic to receive SCIT were screened by the principal investigator or co-investigator for study inclusion and exclusion criteria. The investigator and the research coordinator provided the legal guardian and child with an overview of the study design, the risk and benefits assessment, and study requirements. Parents were advised that oral pain medication was an exclusion for the randomization visit. After obtaining legal guardian written consent and child assent, the child was considered enrolled in the study. A subject ID was assigned. A visible mark placed on the child's allergy injection chart indicated the child was ready to be randomized at their next routine allergy injection visit.

Inclusion criteria

- Children aged 4 to 17 years on SCIT.
- A minimum of three injections prior to enrollment at visit 1.
- Child accompanied by legal guardian.

Exclusion criteria

- Children with a known pain or sensory disorder.
- Developmental delay lacking necessary cognitive ability.
- Administration of any form of pain analgesic within 8 hours of randomization at visit 2.

Visit 2

The allergy nurse interviewed the legal guardian using a questionnaire that collected demographic, health, and treatment information. The principal investigator provided randomized subject assignments. Study staff were blinded to the envelopes containing the four group assignments that were coded by number and color. The subject was presented with a bag containing the envelopes and blindly selected one determining the distraction method to be utilized. The Wong-Baker FACES Pain Rating Scale is a validated tool utilized to assist in self-evaluation of pain in children aged 3 to 18 (11). The subject was introduced to the scale and asked to circle the face that most closely matched their current level of pre-injection pain.

Application of the distraction method

The nurse applied the assigned distraction method to the injection site per the manufacturer's guidelines before administering the first injection to the child. Immediately following the first SCIT injection, the child was asked to circle the face on the Wong-Baker FACES Pain Rating Scale that most closely matched their post-injection level of needle pain. The guardian circled the number on the Numeric Pain Rating Scale that most closely matched their perception of their child's post-injection needle pain level.

Data analysis

Quantitative component data collected and evaluated for this study included the following patient participant demographic information: age, race, and sex; randomized interventions used; diagnoses including allergic rhinitis, asthma, and atopic dermatitis; immunotherapy dose; antihistamine and pain medication

utilization; patient and parental pain scores; and any adverse reactions.

Quantitative component data collected for this study were entered into Microsoft Excel spreadsheets and analyzed using Excel functions. Target population demographic characteristics were analyzed using descriptive statistics by the principal investigator with the level of significance set at < 0.05.

All information collected as part of the evaluation of the impact of this study was aggregated data from the project participants and did not include any potential patient identifiers. Participant confidentiality was assured by coding participants using individual identification numbers for analysis activities occurring outside of the electronic health record. This information was stored in accordance with the policies and procedures of our organization's Institutional Review Board. The Excel files containing codified data without protected health information were stored in password-protected files at our hospital on a password-protected desktop computer in a locked office space accessible only by the principal investigator and study designees. The risks to patients participating in this project were no different from the risks of patients receiving standard care.

Continuous variables were summarized as median (range) and mean (standard deviation), while categorical variables were reported as frequency (percentage). Unadjusted comparisons of patient characteristics and outcomes between each distraction device and the control group were made using a Kruskal-Wallis rank sum test (continuous and ordinal variables) or Fisher's exact test (categorical variables). P-values less than 0.05 were considered statistically significant, and all statistical tests were two-sided. Statistical analyses were performed using R Statistical Software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 40 children who received SCIT were included in this randomized controlled pilot study. Of these 40 children, 12 received the ShotBlocker, 8 received the Buzzy I, 11 received the Buzzy II, and 9 received ethyl chloride spray (control group). Both the overall needle pain rating by the children after their allergy injection and the overall parental perception of needle pain are displayed by each of the four interventions (**figure 1**). The overall summary of patient characteristics is shown in **table I**. The median age overall was 13 years, and 62% of the patients were male.

Table II shows the comparison of patient characteristics between the ShotBlocker group and the control group. Similar-

Figure 1 *- Patient allergy shot pain scores.*

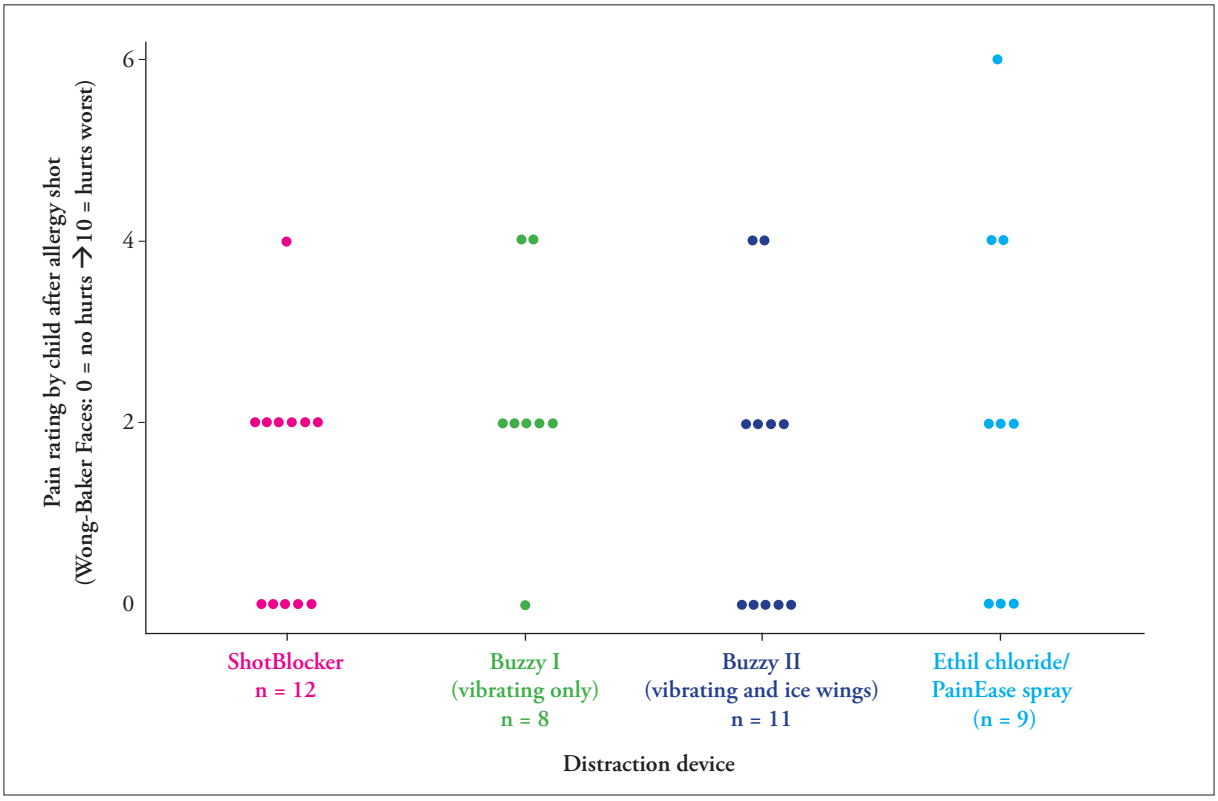


Table I *- Patient characteristics overall.*

Characteristic	Overall (n = 40)
Distraction device	
ShotBlocker	12 (30%)
Buzzy I (vibration only)	8 (20%)
Buzzy II (vibration and ice wings)	11 (28%)
Ethyl chloride/PainEase spray	9 (22%)
Age (years)	
Median (range)	13 (7-19)
Sex	
Male	25 (62%)
Female	15 (38%)
Race	
White	22 (55%)
Black	7 (18%)
Hispanic	6 (15%)
Mixed/other	5 (12%)
Asthma	11 (28%)
Atopic dermatitis	5 (12%)
Length of time receiving allergy shots (years)	
< 1 year	8 (20%)
1-2 years	19 (48%)
3-5 years	13 (32%)
Number of allergy shots received	
1-2	15 (38%)
3-4	20 (50%)
≥ 5	5 (12%)
Dosage for allergy shot (mL)	
< 0.5	15 (38%)
0.5	20 (50%)
> 0.5	5 (12%)
Type of allergy shot	
Environment	32 (80%)
Venom	8 (20%)
Has had symptoms after allergy shot	14 (35%)
Reaction type	
None	26 (65%)
Local	6 (15%)
Systemic	8 (20%)
Antihistamines	20 (50%)

ly, the comparison between the Buzzy I group and the control group is shown in **table III**, and the comparison between the Buzzy II group and the control group is shown in **table IV**. There were no significant differences found between any of the distraction devices and the control for age, sex, race, asthma, atopic dermatitis, length of time receiving allergy shots, number of allergy shots, vial color, allergy shot dosage, type of allergy shot, symptoms after allergy shot, reaction type, and antihistamine use.

Table V displays the pain outcomes comparison between the ShotBlocker and control groups, the Buzzy I and control groups, and the Buzzy II and control groups. While the mean pain ratings by both the children and the legal guardians were lower in two of the intervention groups (ShotBlocker and Buzzy II) compared with the standard care group (ethyl chloride spray), these differences were not significant (all $p > 0.34$).

Discussion and conclusions

Subcutaneous immunotherapy is an effective disease-modifying therapy for the treatment of allergic diseases. The injections may cause pain that could interfere with administration and possible adherence. This pilot study compared two distraction devices with a topical analgesic control group. To provide adequate power to compare devices, the goal was to enroll 100 children. The COVID-19 pandemic limited enrollment. Of the 48 patients enrolled, data were collected on 40 because of non-completion of visit 2. Our inclusion criteria required a minimum of three previous injection visits. Since the average length of SCIT for the enrollees was longer than 1 year, our cohort studied patients with established compliance. This pilot study suggested that the ShotBlocker resulted in the lowest mean child-reported pain score of 1.33, followed closely by the Buzzy II with a mean of 1.45 compared with 2.22 in the control group and 2.25 in the Buzzy I group. The same pattern was seen in the guardian scores.

Finally, we conducted a brief literature review of articles published on related topics to compare the results of this study with those existing in the medical literature (12-18). Although we identified several studies evaluating the pain-alleviating strategies used by various intramuscular injections, most of the studies (conducted in the last decade) compared with ours showed some degree of improvement in pain tolerance with the use of various distraction devices including Buzzy. We believe that the difference in their outcome *versus* ours was related to the following factors: 1) most of these studies examined the intramuscular injection *versus* the subcutaneous route in our study; 2) most of the reviewed studies were done on children receiving one to two immunizations *versus* a minimum of three subcutaneous immunotherapy injections; 3) although glycerin-related discomfort, burning, and pain sensation were not confounding factors in our study because of the similar glycerin concentration in all

injections, this could be a differentiating factor in comparison with non-glycerinated immunization injections.

Study limitations

First, considering the small sample size of our study, we cannot conclude that no true difference exists between each distraction device and the control group simply because of the occurrence of a non-significant P-value in our study. A type II error/false negative finding cannot be ruled out because of a small sample. Second, although our minimum age criterion for enrollment was 4 years, we were unable to enroll enough younger subjects because of parental/subject refusal to proceed because

Table II *- Patient characteristics by distraction device (ShotBlocker vs standard care).*

Characteristic	Ethyl chloride/PainEase spray (n = 9)	ShotBlocker (n = 12)	P-value
Age (years)			0.91
Median (range)	14 (8-17)	14 (8-19)	
Sex			0.66
Male	6 (67%)	6 (50%)	
Female	3 (33%)	6 (50%)	
Race			1.00
White	5 (56%)	6 (50%)	
Black	2 (22%)	3 (25%)	
Hispanic	1 (11%)	2 (17%)	
Mixed/other	1 (11%)	1 (8%)	
Asthma	2 (22%)	4 (33%)	0.66
Atopic dermatitis	1 (11%)	1 (8%)	1.00
Length of time receiving allergy shots (years)			0.056
< 1 year	2 (22%)	2 (17%)	
1-2 years	0 (0%)	8 (67%)	
3-5 years	7 (78%)	2 (17%)	
Number of allergy shots			0.90
1-2	4 (44%)	5 (42%)	
3-4	5 (56%)	7 (58%)	
Dosage for allergy shot (mL)			0.97
< 0.5	4 (44%)	4 (33%)	
0.5	3 (33%)	7 (58%)	
> 0.5	2 (22%)	1 (8%)	
Type of allergy shot			0.61
Environment	6 (67%)	10 (83%)	
Venom	3 (33%)	2 (17%)	
Has had symptoms after allergy shot	2 (22%)	4 (33%)	0.66
Reaction type			1.00
None	7 (78%)	8 (67%)	
Local	1 (11%)	2 (17%)	
Systemic	1 (11%)	2 (17%)	
Antihistamines	5 (56%)	6 (50%)	1.00

they did not want any pain-relieving methods or devices other than "what they were used to," *i.e.*, ethyl chloride spray. This led us to limit our subjects to those who were willing to accept all forms of methods/devices resulting in decreased sample size in the younger population.

In conclusion, to our knowledge, this is the first study that compared the efficacy of these pain-alleviating devices with ethyl chloride spray for children receiving SCIT. The data were inconclusive, so additional data collection including larger numbers of patients and perhaps an improved study design may be warranted. It may

Table III *- Patient characteristics by distraction device (Buzzy I vs standard care).*

Characteristic	Ethyl chloride/PainEase spray (n = 9)	Buzzy I (vibration only) (n = 8)	P-value
Age (years)			0.19
Median (range)	14 (8-17)	12 (7-14)	
Sex			1.00
Male	6 (67%)	5 (62%)	
Female	3 (33%)	3 (38%)	
Race			1.00
White	5 (56%)	4 (50%)	
Black	2 (22%)	2 (25%)	
Hispanic	1 (11%)	2 (25%)	
Mixed/other	1 (11%)	0 (0%)	
Asthma	2 (22%)	3 (38%)	0.62
Atopic dermatitis	1 (11%)	2 (25%)	0.58
Length of time receiving allergy shots (years)			0.055
< 1 year	2 (22%)	2 (25%)	
1-2 years	0 (0%)	5 (62%)	
3-5 years	7 (78%)	1 (12%)	
Number of allergy shots			0.13
1-2	4 (44%)	2 (25%)	
3-4	5 (56%)	3 (38%)	
≥ 5	0 (0%)	3 (38%)	
Dosage for allergy shot (mL)			0.80
< 0.5	4 (44%)	3 (38%)	
0.5	3 (33%)	3 (38%)	
> 0.5	2 (22%)	2 (25%)	
Type of allergy shot			1.00
Environment	6 (67%)	6 (75%)	
Venom	3 (33%)	2 (25%)	
Has had symptoms after allergy shot	2 (22%)	4 (50%)	0.34
Reaction type			0.49
None	7 (78%)	4 (50%)	
Local	1 (11%)	2 (25%)	
Systemic	1 (11%)	2 (25%)	
Antihistamines	5 (56%)	4 (50%)	1.00

Table IV *- Patient characteristics by distraction device (Buzzy II vs standard care).*

Characteristic	Ethyl chloride/PainEase spray (n = 9)	Buzzy II (vibration and ice wings) (n = 11)	P-value
Age (years)			0.82
Median (range)	14 (8-17)	13 (7-17)	
Sex			1.00
Male	6 (67%)	8 (73%)	
Female	3 (33%)	3 (27%)	
Race			0.62
White	5 (56%)	7 (64%)	
Black	2 (22%)	0 (0%)	
Hispanic	1 (11%)	1 (9%)	
Mixed/other	1 (11%)	3 (27%)	
Asthma	2 (22%)	2 (18%)	1.00
Atopic dermatitis	1 (11%)	1 (9%)	1.00
Length of time receiving allergy shots (years)			0.12
< 1 year	2 (22%)	2 (18%)	
1-2 years	0 (0%)	6 (55%)	
3-5 years	7 (78%)	3 (27%)	
Number of allergy shots			0.45
1-2	4 (44%)	4 (36%)	
3-4	5 (56%)	5 (45%)	
≥ 5	0 (0%)	2 (18%)	
Dosage for allergy shot (mL)			0.80
< 0.5	4 (44%)	4 (36%)	
0.5	3 (33%)	7 (64%)	
> 0.5	2 (22%)	0 (0%)	
Type of allergy shot			0.28
Environment	6 (67%)	10 (91%)	
Venom	3 (33%)	1 (9%)	
Has had symptoms after allergy shot	2 (22%)	4 (36%)	0.64
Reaction type			0.78
None	7 (78%)	7 (64%)	
Local	1 (11%)	1 (9%)	
Systemic	1 (11%)	3 (27%)	
Antihistamines	5 (56%)	5 (45%)	1.00

Table V *- Patient pain outcomes by distraction device.*

Pain outcome	Ethyl chloride/PainEase spray (n = 9)	ShotBlocker (n = 12)	P-value
Wong-Baker pain rating by child after shot			0.34
Median (range)	2 (0-6)	2 (0-4)	
Mean (SD)	2.22 (2.11)	1.33 (1.30)	
Parental perception of pain rating			0.53
Median (range)	2 (0-4)	1 (0-4)	
Mean (SD)	1.44 (1.33)	1.17 (1.19)	
Pain outcome	**Ethyl chloride/PainEase spray (n = 9)**	**Buzzy I (vibration only) (n = 8)**	**P-value**
Wong-Baker pain rating by child after shot			0.84
Median (range)	2 (0-6)	2 (0-4)	
Mean (SD)	2.22 (2.11)	2.25 (1.28)	
Parental perception of pain rating			0.48
Median (range)	2 (0-4)	2 (0-4)	
Mean (SD)	1.44 (1.33)	1.88 (1.46)	
Pain outcome	**Ethyl chloride/PainEase spray (n = 9)**	**Buzzy II (vibration and ice wings) (n = 11)**	**P-value**
Wong-Baker pain rating by child after shot			0.42
Median (range)	2 (0-6)	2 (0-4)	
Mean (SD)	2.22 (2.11)	1.45 (1.57)	
Parental perception of pain rating			0.63
Median (range)	2 (0-4)	1 (0-5)	
Mean (SD)	1.44 (1.33)	1.27 (1.49)	

be of value to compare the devices with a non-treatment control group, if participants were willing to refrain from pain relief. The data reported above indicate that the use of the ShotBlocker lowered pain perception in children compared with the other interventions. However, ShotBlocker, Buzzy I, and Buzzy II were non-inferior to ethyl chloride. Areas of additional study include the effect of allergen extract concentration and duration of SCIT on the efficacy of these distraction devices. Regardless, all studied interventions may be useful in counseling patients and families prior to and during SCIT administration for pain relief.

Fundings

None.

Contributions

EY: conceptualization, investigation, methodology, writing - review & editing. JP: data curation, investigation, methodology, project administration, supervision, writing - original draft. TD, KG, KW: data curation, investigation, methodology.

Conflict of interests

The authors declare that they have no conflict of interests.

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References

1. Pawankar R, Canonica GW, Holgate ST, Lockey RF. Allergic diseases and asthma: a major global health concern. Curr Opin Allergy Clin Immunol. 2012;12(1):39-41. doi: 10.1097/ACI.0b013e32834ec13b.

2. Ferreira C, Rezende I, Guilherme A, Lopes I. Allergen-specific subcutaneous immunotherapy-pain evaluation in pediatric age. Allergol Immunopathol (Madr). 2021;49(1):58-61. doi: 10.15586/aei.v49i1.17.
3. Durham SR, Penagos M. Sublingual or subcutaneous immunotherapy for allergic rhinitis? J Allergy Clin Immunol. 2016;137(2):339-49.e10. doi: 10.1016/j.jaci.2015.12.1298.
4. Alpern M, Ravi A, Park M, Hartz MF, Sogla C, Joshi AY. Improved tolerance of subcutaneous immunotherapy in pediatric patients through the use of comfort devices: a quality improvement project. J Allergy Clin Immunol. 2019;143(2):AB305. doi: 10.1016/j.jaci.2018.12.931.
5. Orenius T, Saila H, Mikola K, Ristolainen L. Fear of injections and needle phobia among children and adolescents: an overview of psychological, behavioral, and contextual factors. SAGE Open Nurs. 2018:4:2377960818759442. doi: 10.1177/2377960818759442.
6. Girgin BA, Aktaş E, Kılınç D, Gozen D. Let's prefer the pain reducing intervention, Buzzy or ShotBlocker: a randomized controlled trial. Dergisi. 2020;10(3):290-8. doi: 10.5222/buchd.2020.13007.
7. Canbulat Sahiner N, Turkmen AS, Acikgoz A, Simsek E, Kirel B. Effectiveness of two different methods for pain reduction during insulin injection in children with type 1 diabetes: Buzzy and ShotBlocker. Worldviews Evid Based Nurs. 2018;15(6):464-70. doi: 10.1111/wvn.12325.
8. Ballard A, Khadra C, Adler S, Trottier ED, Le May S. Efficacy of the Buzzy device for pain management during needle-related procedures: a systematic review and meta-analysis. Clin J Pain. 2019;35(6):532-43. doi: 10.1097/AJP.0000000000000690.
9. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Allergen immunotherapy: a practice parameter second update. J Allergy Clin Immunol. 2007;120(3 Suppl):S25-85. doi: 10.1016/j.jaci.2007.06.019.
10. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol. 2011;127(1 Suppl):S1-55. doi: 10.1016/j.jaci.2010.09.034.
11. Litcher-Kelly L, Martino SA, Broderick JE, Stone AA. A systematic review of measures used to assess chronic musculoskeletal pain in clinical and randomized controlled clinical trials. J Pain. 2007;8(12):906-13. doi: 10.1016/j.jpain.2007.06.009.
12. Canbulat Sahiner N, Inal S, Sevim Akbay A. The effect of combined stimulation of external cold and vibration during immunization on pain and anxiety levels in children. J Perianesth Nurs. 2015;30(3):228-35. doi: 10.1016/j.jopan.2014.05.011.
13. Taddio A, Shah V, McMurtry CM, MacDonald NE, Ipp M, Riddell RP, et al. Procedural and physical interventions for vaccine injections: systematic review of randomized controlled trials and quasi-randomized controlled trials. Clin J Pain. 2015;31(10 Suppl):S20-37. doi: 10.1097/AJP.0000000000000264.
14. Redfern RE, Chen JT, Sibrel S. Effects of thermomechanical stimulation during vaccination on anxiety, pain, and satisfaction in pediatric patients: a randomized controlled trial. J Pediatr Nurs. 2018;38:1-7. doi: 10.1016/j.pedn.2017.09.009.
15. Caglar S, Buyukyılmaz F, Cosansu G, Çağlayan S. Effectiveness of ShotBlocker for immunization pain in full-term neonates: a randomized controlled trial. J Perinat Neonatal Nurs. 2017;31(2):166-71. doi: 10.1097/JPN.0000000000000256.
16. Şıktaş O, Uysal G. The effect of Buzzy application on pain level during vaccine injection in infants. J Nurs Care Qual. 2023;38(1):E9-E15. doi: 10.1097/NCQ.0000000000000656.
17. Yilmaz G, Alemdar DK. Using Buzzy, Shotblocker, and bubble blowing in a pediatric emergency department to reduce the pain and fear caused by intramuscular injection: a randomized controlled trial. J Emerg Nurs. 2019;45(5):502-11. doi: 10.1016/j.jen.2019.04.003.
18. Jenkins N, Orsini F, Elia S, Perrett K. Minimising immunisation pain of childhood vaccines: the MIP pilot study. J Paediatr Child Health. 2021;57(3):376-82. doi: 10.1111/jpc.15229.

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Dupilumab to induce tolerance to SLIT-Melocotón®

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Key words

Dupilumab; LTP-syndrome; food allergy; Pru p3; SLIT-melocotón®.

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Impact statement

Monoclonal antibodies switch is used as a tool to induce tolerance in SLIT. In case of multiple food allergy syndrome, off-label indication must be considered.

Summary

Food allergy is an increasing problem for population, and treatments inducing tolerance using sublingual immunotherapy is currently under study. Our aim as allergists is to achieve tolerance to sublingual allergen specific immunotherapy with sublingual immunotherapy (SLIT-peach). We present a case report consisting of a 40-year-old woman with anaphylactic reactions after eating fruit and other plant-foods due to sensitization to nonspecific lipid transfer proteins (nsLTP). Her diagnose was LTP-syndrome. This protein is the main pannallergen in our area and causes crossed reaction to multiple plant foods. The principal allergen in this syndrome is rPru p3, present in peach and most vegetables, fruits, nuts and grains. Serum specific IgE levels were performed using microarrays and positive for seven nsLTPs: rAra h9, rCor a8, nJug r3, rPru p3, rTri a 14, nArt v3 and rPla a3. Immediate reaction to SLIT in the fourth month of maintenance-dose led us to interrupt pru p3 immunotherapy. Immediate reaction to omalizumab in the fourth dose in hospital consisting in anaphylaxis prompted us to switch to dupilumab. After four months with this monoclonal antibody, we reintroduced sublingual immunotherapy with pru p3 SLIT-peach® achieving maintenance dose of four drops a day with no clinical reactions. SLIT-peach® in our patient is crucial for her due to her restricted diet, the severity of reactions and lack of quality of life measured by Europevall questionary. There are no cases reported for dupilumab in this use.

Introduction

Food allergy is an abnormal immune response as a result of genetic and epigenetic factors. Over the last years, prevalence has significantly increased (1). There are multiple causes of this rise of food allergy. The use of genetically-modified foods including hybrids resulting from the crossing of species, the strong rise of global trade, the cooking method (for example roasted in peanuts increase allergens (2) to the gastrointestinal mucosal immune system) and expansion of international cuisine in our modern society has led to a more complex diagnosis of food allergic reactions. Indeed, there are large geographical differences in the prevalence of food allergy and food sensitization in Europe (3).

Prevention and defining risk factors are the cornerstone of clinical trials. According to clinical presentations, there is a wide range of forms for food allergy. In our area – southern Europe – the peach nsLTP allergen Pru p 3 is a dominant sensitizing allergen and peaches are a common food trigger, although multiple foods can be involved (4). Symptoms can range from mild to severe, from oral pruritus (oral allergy syndrome) to anaphylactic shock, which is a severe and potentially life-threatening al-

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lergic response. Current management of food allergy consists of removing the allergen from the diet. This still remains the gold standard approved in treatment by the US Food and drug administration (FDA), but an exclusion diet can become a nightmare. Food allergy patients must always carry rescue medication including epinephrine and use it in case of accidental exposure (5). This condition can cause a significant impact on quality of life for patients and their families, which may lead to social changes and nutritional deficiencies caused by the extensive dietary restrictions (6).

As allergists, immunotherapy is our *modus vivendi* to improve quality of life (7). There are currently no treatments approved by the FDA for food allergy. New advances in food immunotherapy have been developed, including allergen-specific treatments which can be administered in specialized centers (8) through various routes (oral, sublingual and subcutaneous). The lack of protocols and the time spent in active treatment, including human resources are well known in the allergy office. The new biologic therapies have been recently proposed either as monotherapy or as adjuvant therapy in food allergy-immunotherapy (9).

Dupilumab is a human monoclonal IgG4 antibody that specifically targets the alpha subunit of interleukin 4 receptor (IL-4R), thereby inhibits IL-4 and IL-13 signaling (cytokines produced by intestinal mast cells) and reduces type 2 inflammation involved in this type of IgE mediated reactions. It was firstly approved by the FDA (U.S. Food and Drug Administration) and later by the EMA (European Medicines Agency) for moderate to severe atopic dermatitis, severe asthma with type-2 inflammation and more recently for chronic rhinosinusitis with nasal polyposis (10). It is currently being investigated in clinical trials for food allergy and eosinophilic esophagitis (Phase 2 and 3, respectively) (11).

Case presentation

We report a case of a 40-year-old woman that first consulted for recurrent episodes of food-induced anaphylaxis (consisting in generalized urticaria, angioedema, dyspnea and hypotension). At least she experienced sympthoms of anaphylaxis seven times in one year. The first episode reported in our allergy office was in 2007. She recognized the ingestion of vegetable food as the cause (fruit: peaches, pineapple, kiwi, hazelnuts; veggies: tomato, lettuce; and legumes: lentils). She is also asked about cofactors due to a careful anamnesis taking; physical exercise, NSAIDs and emotional stress was present in most cases.

We performed an extensive allergy study in our patient in March 2019. We first carried out a Skin Prick Test (SPT) for common aeroallergens in our area and tropho-allergens. Our method to read skin prick test is to characterize the wheal size by its average diameter. The mean wheal diameter is considered positive for a measure of > 3 mm. The results obtained were positive for *Chenopodium, Salsola,* olive and mugwort pollen with no clinical expression at the current time; she referred neither asthma nor rhinitis. Food allergy tests were also performed. The commercial skin prick test used is from Roxall® Industry 0.1 mg/ml. The results were positive for hazelnut, peanut, walnut, sunflower seed, pistachio, tomato, corn, pepper, pear, strawberry, kiwi, banana, celery, cayenne, grains (wheat, rice, rye) and peach LTP. Also, Prick-by-prick tests were positive for soybean, lentils, carrot, sesame and grapes.

Allergen-specific IgE were determined using *in vitro* quantitative assay (microarray analysis-ISAC-112). Crossed reactivity markers showed the results for seven nonspecific lipid transfer protein (nsLTP). Results are measured in standard ISAC units (ISU): rAra h9 (peanut): 0.9 ISU, rCor a8 (hazelnut): 0.7 ISU, nJug r3 (walnut): 1.6 ISU, rPru p3 (peach): 1.9 ISU, rTri a 14 (wheat): 0.3 ISU, nArt v3 (*Artemisa*): 2.6 ISU and rPla a3 (*Platanus*): 1.8 ISU. There is no specie-specific sensitization for food allergens. Neither primary sensitization for aeroallergens is found.

Based on these findings, our patient was diagnosed with "LTP Syndrome" that manifested as recurrent anaphylactic reactions and recurrent urticarial due to multiple food ingestion (oFASS-5: Grade 5 severe reaction) according to the oFASS-5 Score (Food Allergy Severity Score). NSAIDs and exercise were tolerated without eating plant foods. She turned out to avoid those foods that she recognized as a trigger. She avoided nuts, kiwi, pear, peach, corn, soybean, wheat and corn. After the years, she started to avoid other foods that she recognized as triggers (her diet was restricted to egg, meat, chicken, eggplant and zucchini, she avoided all fruits because of recurrent generalized urticaria and also avoided grains such as wheat, corn, rice and soya).

Sublingual immunotherapy can prevent severe allergic reactions to LTP-containing foods. In October 2019, we prescribed sublingual immunotherapy with a Pru p 3-enriched peach extract (SLIT-peach 100% ALK) due to the patient's impaired quality of life (FAQLQ-AF of 161 points from a total of 174), the restricted diet and the severity of the anaphylactic reactions. Previous laboratory tests were carried out, obtaining the following results: total IgE 18.40 kUA/l, specific IgE for Pru p 3: 8.87 kUA/l, specific IgG4 for Pru p 3: 0.04 kUA/l, baseline serum tryptase 3 µg/l.

In spite of the good initial tolerance to the standard immunotherapy regimen, one week after achieving a maintenance dose of 4 drops daily at home, our patient experienced a generalized urticaria with outbreaks of gastroenteritis ten minutes after her daily dose, requiring urgent hospital treatment. No triggers such as food, exercise or non-steroidal anti-inflammatory drugs were involved.

In November 2019, we introduced omalizumab 150 mg every 4 weeks as compassionate treatment (adjusted by weight and

total IgE) to induce SLIT tolerance. We started subcutaneous inoculation of omalizumab each 4 weeks without SLIT in the hospital. One hour after her fourth dose of omalizumab she experienced generalized urticaria, bronchospasm and hypotension, requiring urgent treatment and hospital admission. Serum tryptase was performed one hour after the reaction, with the following result: 18 µg/l. Four weeks after this episode we proceeded in the Allergy office to skin prick test with omalizumab excipients with negative results.

In summary, we were facing a patient with recurrent anaphylaxis to multiple plant-based foods, with LTP-Syndrome and in the beginning cofactors were present. Due to the wide restricted diet, poor quality of life and failed tolerance to SLIT-peach® treatment (including systemic reaction to omalizumab) in December 2020 we started with subcutaneous dupilumab as compassionate use according to the established treatment regimen: an initial subcutaneous dose of 600 mg, following a maintenance dose of 300 mg every two weeks. Three months later (March 2021) and during treatment with dupilumab, we reintroduced oral immunotherapy (IOT) with SLIT-peach® showing good tolerability and achieving a maintenance dosing of four drops a day.

In September 2021, we once again measured total IgE 8.30 kUA/l, specific IgE for Pru p 3: 4.68 kUA/l and specific IgG4 for Pru p 3: 0.90 kUA/l. At that time, we decided to discontinue treatment with dupilumab since the patient did not present any further allergic reactions, and she has maintained a good tolerance to oral immunotherapy up until now. After one year with SLIT she can eat small amounts of tomato and lettuce that she previously didn't tolerate.

Conclusions

We report the case of a young woman patient with severe anaphylaxis due to the ingestion of multiple plant foods with failure treatment to oral immunotherapy (IOT) with SLIT-peach 100%. The use of biologics to induce tolerance to oral immunotherapy has been a tool strategy since anti-IgE is with us (12). There are multiple case reports of patients with food allergy (egg, milk, peanuts) and adjuvant treatment with omalizumab to induce tolerance to IOT. Results of reviews suggest that the use of omalizumab could potentially lead to safer and more efficient IOT protocols (13). Our patient had an immediate reaction with significant serum tryptase elevation compared to baseline-tryptase, after the fourth injection with omalizumab. Anaphylactic reactions to this and other biological treatments are described in several case reports (14). Indeed, within patients that have a history of anaphylactic reactions, women and young patients face a higher risk to have an anaphylactic reaction to omalizumab. These adverse effects are described in the omalizumab data sheet. In a recent review, dupilumab has the lowest rate of anaphylactic reactions (15). Our strategy was to switch to dupilumab, to induce tolerance to IOT.

Our clinical objective was to achieve IOT without adverse reactions. The use of dupilumab as an off-label therapy (16) is in our case a successful achieving IOT tolerance. So far, there are few reported cases in literature supporting evidence for the use of dupilumab as a potential treatment in food allergy (17). Thus, it would be necessary to continue developing lines of research on the use of biologics in food allergy, analyzing its efficacy and safety in this condition.

Fundings

None.

Contributions

MSZP: writing - original draft, writing - review & editing. YPP: data curation, formal analysis. SSRS: investigation, conceptualization. CNG: methodology, project administration. AIEP: resources, software. JCML: validation. ACM: supervision, visualization.

Conflict of interests

The authors declare that they have no conflict of interests.

References

1. Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol. 2014;133(2):291-307; quiz 308. doi: 10.1016/j.jaci.2013.11.020.
2. Vissers YM, Blanc F, Skov PS, Johnson PE, Rigby NM, Przybylski-Nicaise L, et al. Effect of heating and glycation on the allergenicity of 2S albumins (Ara h 2/6) from peanut. PLoS One. 2011;6(8):e23998. doi: 10.1371/journal.pone.0023998.
3. Lyons SA, Clausen M, Knulst AC, Ballmer-Weber BK, Fernandez-Rivas M, Barreales L, et al. Prevalence of Food Sensitization and Food Allergy in Children Across Europe. J Allergy Clin Immunol Pract. 2020;8(8):2736-46.e9. doi: 10.1016/j.jaip.2020.04.020.
4. Skypala IJ, Bartra J, Ebo DG, Antje Faber M, Fernández-Rivas M, Gomez F, et al. The diagnosis and management of allergic reactions in patients sensitized to non-specific lipid transfer proteins. Allergy. 2021;76(8):2433-46. doi: 10.1111/all.14797.
5. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020;13(10):100472. doi: 10.1016/j.waojou.2020.100472.
6. Sicherer SH, Noone SA, Muñoz-Furlong A. The impact of childhood food allergy on quality of life. Ann Allergy Asthma Immunol. 2001;87(6):461-4. doi: 10.1016/S1081-1206(10)62258-2.
7. González Pérez A, Carbonell Martínez A, Escudero Pastor AI, Navarro Garrido C, Miralles López JC. Pru p 3 oral immunotherapy efficacy, induced immunological changes and quality of life improvement in patients with LTP syndrome. Clin Transl Allergy. 2020;10:20. doi: 10.1186/s13601-020-00325-y.

8. Wasserman RL, Hague AR, Pence DM, Sugerman RW, Silvers SK, Rolen JG, et al. Real-World Experience with Peanut Oral Immunotherapy: Lessons Learned From 270 Patients. J Allergy Clin Immunol Pract. 2019;7(2):418-26.e4. doi: 10.1016/j.jaip.2018.05.023.
9. Fiocchi A, Vickery BP, Wood RA. The use of biologics in food allergy. Clin Exp Allergy. 2021;51(8):1006-1018. doi: 10.1111/cea.13897.
10. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet. 2019;394(10209):1638-50. doi: 10.1016/S0140-6736(19)31881-1.
11. Hirano I, Dellon ES, Hamilton JD, Collins MH, Peterson K, Chehade M, et al. Efficacy of Dupilumab in a Phase 2 Randomized Trial of Adults With Active Eosinophilic Esophagitis. Gastroenterology. 2020;158(1):111-22.e10. doi: 10.1053/j.gastro.2019.09.042.
12. Albuhairi S, Rachid R. Biologics and Novel Therapies for Food Allergy. Immunol Allergy Clin North Am. 2021;41(2):271-83. doi: 10.1016/j.iac.2021.01.002.
13. Sicherer SH, Sampson HA. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol. 2018;141(1):41-58. doi: 10.1016/j.jaci.2017.11.003.
14. Li L, Wang Z, Cui L, Xu Y, Guan K, Zhao B. Anaphylactic risk related to omalizumab, benralizumab, reslizumab, mepolizumab, and dupilumab. Clin Transl Allergy. 2021;11(4):e12038. doi: 10.1002/clt2.12038.
15. Sastre J, Dávila I. Dupilumab: A New Paradigm for the Treatment of Allergic Diseases. J Investig Allergol Clin Immunol. 2018;28(3):139-50. doi: 10.18176/jiaci.0254.
16. Muñoz-Bellido FJ, Moreno E, Dávila I. Dupilumab: A Review of Present Indications and Off-Label Uses. J Investig Allergol Clin Immunol. 2022;32(2):97-115. doi: 10.18176/jiaci.0682.
17. Rial MJ, Barroso B, Sastre J. Dupilumab for treatment of food allergy. J Allergy Clin Immunol Pract. 2019;7(2):673-4. doi: 10.1016/j.jaip.2018.07.027.

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Atopic status and thyroid autoimmunity do not predict omalizumab response in severe chronic spontaneous urticaria patients

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Key words

Urticaria; thyroid autoimmunity; atopic status; total IgE; omalizumab.

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To the Editor,

chronic spontaneous urticaria (CSU) is a rather frequent disease of variable severity characterized by recurrent wheals with or without angioedema for more than 6 weeks. Some patients show a continuous and very severe disease refractory to antihistamine treatment which worsens dramatically their quality of life. The anti-IgE mAb omalizumab is indicated as second line treatment in these cases. The clinical response largely depends on the endotype (either IgG-mediated autoimmune [type IIb] or IgE-mediated "autoallergic" [type I]) of the disease. Positive *in vitro* tests of basophil activation (either BAT or BHRA), antinuclear antibodies, autologous serum skin test (ASST) and low total IgE levels have been associated with a slow or absent response to the drug (1-5). Conversely, elevated total IgE are generally associated with a prompt response to omalizumab (5-12). Atopic diseases are a well-known cause of elevated IgE, but whether atopic status may be used as a marker of Type I CSU, thus predicting a rapid response to omalizumab, is still unclear (11). The association between CSU and thyroid autoimmunity has been known for almost 30 years (12), but, although typical type IIb CSU patients frequently show low IgE and autoimmune thyroiditis (14), whether thyroid autoimmunity may alone predict a poor or absent response to omalizumab is still undefined. In one study, the prevalence of thyroid autoimmunity was similar in CSU patients with different levels of total IgE (15). The present study investigated whether atopic status and thyroid autoimmunity may be practically useful to discriminate type I and type IIb CSU.

Total IgE levels and thyroid autoantibodies were measured, and atopic status was ascertained by SPT with airborne allergens before omalizumab treatment in 260 consecutive patients with severe CSU (M/F 88/172; mean age 49.5; mean disease duration 50.5 months (range 2-720 month), baseline UAS-7 level > 28). Based on the clinical response, patients were divided into early- (ER), late- (LR), and non- (NR) responders to omalizumab. An early response was defined as a reduction of at least 50% of the UAS-7 score within 4 weeks after the first administration. A late response was diagnosed if a reduction > 50% of UAS-7 score occurred 1-3 months after the start

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of the drug. Non-response was defined as the absence of any significant change in UAS-7 3 months after the start of the treatment. The chi-square test with Yates' correction, the two-tailed Student's t-test, or the Mann-Whitney non-parametric test were employed to compare the study groups where appropriate. Probability values < 5% were considered statistically significant. The internal review board of the clinic approved this retrospective, anonymous study.

79/260 (30%) of patients were atopic and 60/238 (25%) showed thyroid autoimmunity. On omalizumab treatment, 160 (61%) were ER, 55 (22%) LR, and 45 (17%) NR. In these 3 subgroups, 55 (34%), 15 (27%), and 9 (20%) patients, respectively, were atopic (p = NS), and 36/149 (24%), 14/49 (29%), and 10/40 (25%), respectively, showed signs of thyroid autoimmunity (p = NS). The median total IgE levels in the 3 subgroups were 154 IU/ml, 51 IU/ml, and 20 IU/ml, respectively (p < 0.05 for ER *vs* LR + NR; p < 0.05 for ER *vs* NR; p = NS for LR *vs* NR) (**figure 1**). Total IgE levels < 20 IU/ml were found in 11%, 19%, and 50% of patients, respectively (p < 0.001 for ER *vs* NR). Total IgE levels > 100 IU/ml were detected in 60%, 38%, and 21% of patients, respectively (p < 0.001 for ER *vs* NR; p < 0.005 for ER *vs* LR; p = NS for LR *vs* NR) (**figure 2**). 9/48 patients with thyroid autoimmunity showed total IgE levels < 20 IU/ml; such association was observed in 4/27 ER (15%), 1/13 LR (8%), and 4/8 NR (50%) (p < 0.05 for NR *vs* ER + LR).

This study confirmed the high prognostic value of baseline total IgE levels for omalizumab response (5-12). In contrast, it showed that atopic status cannot be adopted as a marker of Type I CSU or as a predictor of omalizumab response in CSU patients. Similarly, although confirming the well-known association between CSU and thyroid autoimmunity, the study shows that thyroid autoimmunity *per se* cannot be considered as a marker of Type IIb CSU or a predictive marker of poor response to omalizumab (15). Altogether, the detection of type IIb CSU patients requires the concordance of a series of different tests, including the autologous serum skin test, *in vitro* basophil activation tests, and positive IgG anti-FcεRI or anti-IgE (3). In conclusion, total IgE levels currently remain the only and most easily available prognostic marker for omalizumab response in patients with severe CSU.

Fundings

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Contributions

RA entirely contributed to this work.

Conflict of interests

The author declare that he has no conflict of interests.

Figure 1 *- Median IgE levels in the 3 subsets of omalizumab responders.*

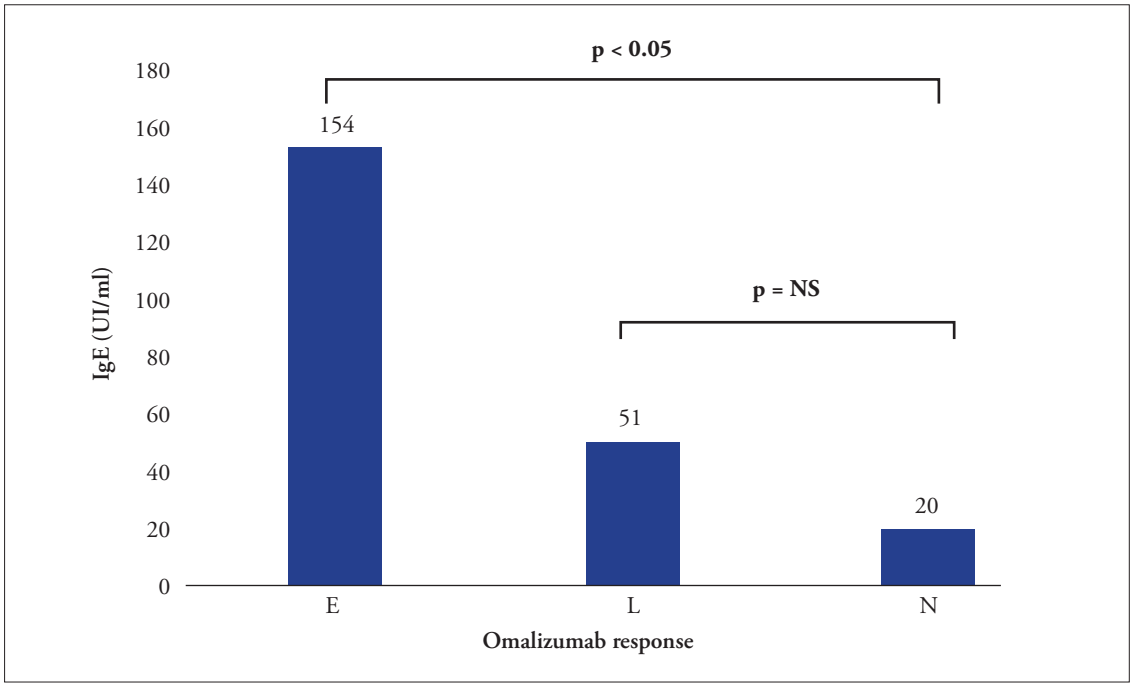
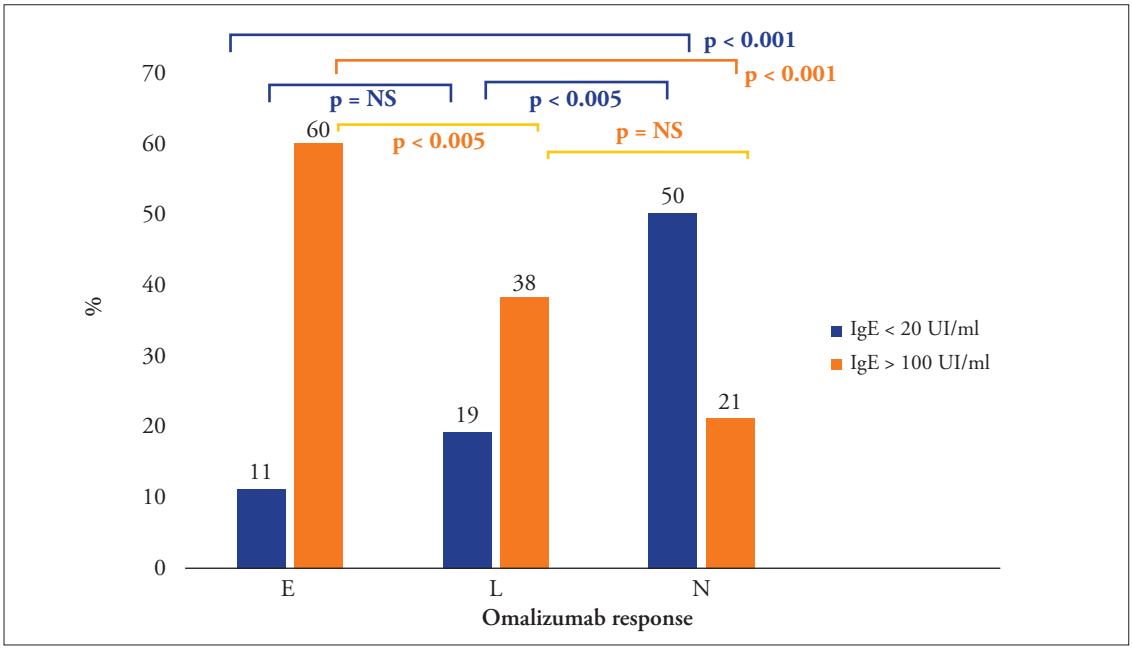


Figure 2 *- Prevalence of low (< 20 IU/ml) and high (>100 IU/ml) levels of total IgE in the 3 subsets of omalizumab responders.*



References

1. Gericke J, Metz M, Ohanyan T, Weller K, Altrichter S, Skov PS, et al. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. J Allergy Clin Immunol. 2017;139(3):1059-61.e1. doi: 10.1016/j.jaci.2016.07.047.
2. Endo T, Toyoshima S, Hayama K, Tagui M, Niwa Y, Ito M, et al. Relationship between changes in the 7-day urticaria activity score after treatment with omalizumab and the responsiveness of basophils to FcεRI stimulation in patients with chronic spontaneous urticaria. Asia Pac Allergy. 2020;10(2):e12. doi: 10.5415/apallergy.2020.10.e12.
3. Schoepke N, Asero R, Ellrich A, Ferrer M, Gimenez-Arnau A, E H Grattan C, et al. Biomarkers and clinical characteristics of autoimmune chronic spontaneous urticaria: Results of the PURIST Study. Allergy. 2019;74(12):2427-36. doi: 10.1111/all.13949.
4. Ertaş R, Hawro T, Altrichter S, Özyurt K, Erol K, Ketenci Ertaş Ş, et al. Antinuclear antibodies are common and linked to poor response to omalizumab treatment in patients with CSU. Allergy. 2020;75(2):468-70. doi: 10.1111/all.14033.
5. Marzano AV, Genovese G, Casazza G, Fierro MT, Dapavo P, Crimi N, et al. Predictors of response to omalizumab and relapse in chronic spontaneous urticaria: a study of 470 patients. J Eur Acad Dermatol Venereol. 2019;33(5):918-24. doi: 10.1111/jdv.15350.
6. Ertas R, Ozyurt K, Atasoy M, Hawro T, Maurer M. The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change. Allergy. 2018;73(3):705-12. doi: 10.1111/all.13345.
7. Weller K, Ohanyan T, Hawro T, Ellrich A, Sussman G, Koplowitz J, et al. Total IgE levels are linked to the response of chronic spontaneous urticaria patients to omalizumab. Allergy. 2018;73(12):2406-8. doi: 10.1111/all.13586.
8. Straesser MD, Oliver E, Palacios T, Kyin T, Patrie J, Borish L, et al. Serum IgE as an immunological marker to predict response to omalizumab treatment in symptomatic chronic urticaria. J Allergy Clin Immunol Pract. 2018;6(4):1386-8.e1. doi: 10.1016/j.jaip.2017.10.030.
9. Nettis E, Cegolon L, Di Leo E, Lodi Rizzini F, Detoraki A, Canonica GW, et al. Omalizumab in chronic spontaneous urticaria: Efficacy, safety, predictors of treatment outcome, and time to response. Ann Allergy Asthma Immunol. 2018;121(4):474-8. doi: 10.1016/j.anai.2018.06.014.
10. Asero R. Chronic spontaneous urticaria treated with omalizumab: what differentiates early from late responders? Eur Ann Allergy Clin Immunol. 2021;53(1):47-8. doi: 10.23822/EurAnnACI.1764-1489.147.
11. Asero R, Ferrucci S, Casazza G, Marzano AV, Cugno M. Total IgE and atopic status in patients with severe chronic spontaneous urticaria unresponsive to omalizumab treatment. Allergy. 2019;74(8):1561-3. doi: 10.1111/all.13754.
12. Cugno M, Genovese G, Ferrucci S, Casazza G, Asero R, Marzano AV. IgE and D-dimer baseline levels are higher in responders than nonresponders to omalizumab in chronic spontaneous urticaria. Br J Dermatol. 2018;179(3):776-7. doi: 10.1111/bjd.16593.
13. Leznoff A, Josse RG, Denburg J, Dolovich J. Association of chronic urticaria and angioedema with thyroid autoimmunity. Arch Dermatol. 1983;119(8):636-40.
14. Kolkhir P, Muñoz M, Asero R, Ferrer M, Kocatürk E, Metz M, et al. Autoimmune chronic spontaneous urticaria. J Allergy Clin Immunol. 2022;149(6):1819-31. doi: 10.1016/j.jaci.2022.04.010.
15. Asero R. Clinical variables of severe chronic spontaneous urticaria from total IgE standpoint: a retrospective study. Eur Ann Allergy Clin Immunol. 2022;54(1):30-3. doi: 10.23822/EurAnnACI.1764-1489.191.

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