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Is Kiwifruit Allergy a Matter in Kiwifruit-Cultivating Regions? A Population-based Study

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Abstract:

Background: Although kiwifruit is known as a common cause of food allergy, population based studies concerning the prevalence of kiwifruit allergy does not exist. We aimed to determine the prevalence and clinical characteristics of IgE-mediated kiwifruit allergy in 6-18 year old urban schoolchildren in a region where kiwifruit is widely cultivated

Methods: This cross-sectional study recruited 20,800 of the randomly selected 6-18-year-old urban schoolchildren from the Rize city in the eastern Black Sea region of Turkey during 2013. Following a self-administered questionnaire completed by the parents and the child, consenting children were invited for skin prick tests (SPTs) and oral food challenges (OFCs). Children with suspected IgE-mediated kiwifruit were skin prick tested with kiwifruit (commercial allergen and prick-to-prick test with fresh kiwifruit) and a predefined panel of allergens (banana, avocado, latex, sesame seed, birch, timothy, hazel, cat, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*). All children with a positive SPT to kiwifruit were invited for an open OFC. The prevalence of IgE-mediated kiwifruit allergy was established using open OFCs.

Results: The response rate to the questionnaire was 75.9% (15783/20800). The estimated prevalence of parental-perceived IgE-mediated kiwifruit allergy was 0.5% (72/15783) (95% CI, 0.39-0.61%). Of the 72 children, 52 (72.2%) were skin tested, and 17 (32.7%) were found to be positive to kiwifruit with both commercial extract and kiwifruit. The most frequently reported symptoms in kiwi SPT-positive children were cutaneous (n = 10, 58.8%) followed by gastrointestinal (n = 6, 35.3%) and bronchial (n = 4, 23.5%). Oral symptoms were reported in six (35.3%) children. All children with kiwifruit positive SPTs were found positive during the oral challenge. The confirmed prevalence of IgE-mediated kiwifruit allergy by means of open OFC in 6–18-year-old urban schoolchildren living in Rize city was 0.10 % (95% CI: 0.06-0.16).

Conclusion: Prevalence of parental-perceived and clinically confirmed kiwifruit allergy is not consistent. In contrast to expectations, kiwifruit allergy prevalence was low in a city where it is cultivated and highly consumed.

Key words: kiwifruit, kiwifruit allergy, kiwifruit allergy prevalence

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Introduction

Since the first report of kiwifruit allergy in 1981, several studies conducted in schoolchildren and university students have shown that kiwifruit is among the common causes of self-reported food allergy. (1-3) In a recent report from the eastern Black Sea region of Turkey,

kiwifruit allergy was found to be the third most common food allergy among 6-9 year old urban schoolchildren. (4) Allergic reactions to kiwifruit may manifest as a spectrum from mild local symptoms in the oral cavity to severe systemic reactions.(5-8) Patients with associated pollen allergy are more likely to have the oral allergy syndrome, whereas those without pollen allergy are more likely to have anaphylaxis or wheeze.(9) Although kiwifruit allergy may be the result of cross-reactivity with pollen and latex (10, 11) and is most frequently associated with birch and grass pollinosis (12, 13), monosensitization to kiwifruit has also been reported. (6, 8, 14) However, little information exists about rates of kiwifruit allergy in regions that regularly cultivate kiwifruit for agricultural purposes.

We aimed to determine the prevalence and clinical characteristics of kiwifruit allergy in Rize, a city in the Eastern Black Sea region of Turkey where kiwifruit is widely cultivated for the last 15 years.

Methods

Study population

We conducted a cross-sectional study and recruited 20,800 6 to 18-year-old urban schoolchildren from the center and four districts of the Rize city in the eastern Black Sea region of Turkey during January and February 2013. Children were recruited using random sampling of public primary and secondary schools in each age group; there were comparable numbers of boys and girls in all age groups.

This study was carried out in three phases. In phase 1, questionnaires were distributed to the children and collected after approximately one week. In phase 2, children who consented to participate were skin prick tested (SPT) with kiwifruit (commercial allergen and prick-to-prick test with fresh kiwifruit). In phase 3, all children with a positive SPT to kiwifruit were invited for an open oral food challenge (Fig. 1). The type of kiwifruit cultivated in Rize city is fuzzy kiwifruit (*Actinidia deliciosa*), and the 'Hayward' is the most common cultivar. This cultivar was used for testing during the study. Verbal and written informed consent was obtained for SPT and oral food challenge from all parents and children.

The study was approved by the Recep Tayyip Erdogan University Ethics Committee.

Questionnaire Development and Content

We took great care to ask, to the fullest extent possible, simple and brief questions in order to increase participation, ensure comprehensibility and enable parents to provide accurate answers. The questionnaires were validated on a sample of 20 subjects (10 with known food

allergy and 10 without any food allergy) through 20 in-depth interviews conducted by three of the investigators at different times (MHA, SD, SH).

Fig. 2 summarizes the questionnaire. Information on personal and familial atopic diseases such as asthma, allergic rhinitis, and atopic dermatitis were also obtained.

Questionnaire Administration

Each child took home a standard questionnaire to be completed together by the parents/caregivers and child.

Skin prick tests

Among the children who reported an adverse reaction to kiwifruit on the completed questionnaire, the following were invited for formal SPTs: 1) those that experienced any reaction following re-consumption of kiwifruit and 2) those who avoided kiwifruit after the reaction. All the children with suspected IgE-mediated kiwifruit allergy who consented to participate were invited for SPTs to kiwifruit (commercial allergen solutions and prick-to-prick test with fresh kiwifruit) and a predefined panel of allergen solutions (banana, avocado, latex, sesame seed, birch, timothy, hazel, cat, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*) (Allergopharma, Reinbek, Germany). The SPTs were performed on the forearm.

Oral food challenges

All the children with suspected IgE-mediated kiwifruit allergy who consented to participate were invited for an open oral food challenge. All food for challenges were freshly prepared for each child. Challenge protocols were developed on the basis of current available literature. (6, 15) The titrated doses used for peeled kiwifruit puree were 0.1, 0.5, 1, 1.5, 2.5, 5, 15, 25 and 50 mg, in total 100 mg (~ 2 kiwifruit), given in 15-minute intervals. Oral challenges were considered positive if a single or a combination of the clinical reactions, including cutaneous, nasal, ocular, bronchial, gastrointestinal, laryngeal, cardiovascular and other (sweating, pallor, fainting, loss of consciousness) symptoms were noted. The dose interval was 15 minutes. Children were observed at least two hours following the last dose of the challenge.

Oral challenge was not performed when a patient failed to provide informed consent or when a patient had a convincing history within the last year of severe anaphylaxis to kiwifruit, which was defined as objective findings (marked laryngeal edema, significant wheezing, or hypotension) that developed immediately after the isolated ingestion of kiwifruit and required emergency management.

Challenges were stopped at the discretion of the evaluating physician when objective signs and symptoms indicated a positive response, and medications were administered as needed. A previously described scoring system was used to determine the severity of the challenge reactions (16), which were scored as minimal, mild, moderate, or severe.

Statistics

All analyses were performed using SPSS statistical software version 10.0 (SPSS Inc. Chicago, IL). A descriptive analysis was used for the characterization of the study population. Results were expressed as means $\pm$ SEM for continuous variables or percentages with 95% confidence intervals for binary responses on the questionnaire. Comparisons of binary responses were performed with Pearson χ^2 test (with the Yates correction when applied) or Fisher exact test when needed, and odds ratios (OR) and 95% confidence intervals (CI) were calculated. To compare age between two or more groups, Wilcoxon-Mann-Whitney test, and Kruskal-Wallis one-way ANOVA were used. $P < 0.05$ was considered statistically significant.

Results

Of the 20800 children, 15783 (75.9%) returned a completed questionnaire and were included in the study. Overall, 72 [0.5%, (95% CI, 0.39–0.61%)] children with parental-perceived IgE-mediated kiwifruit allergy were recruited for the second-phase [48 (66.6%) girls, OR, 0.25; 95% CI, 0.12-0.49; $p < 0.00006$].

The most frequently reported clinical manifestations were cutaneous ($n = 28$, 38.8%), followed by gastrointestinal and respiratory (14 each, 19.4%), nasal ($n = 10$, 13.8%), and ocular ($n = 4$, 5.5%). Oral symptoms (labial or oropharyngeal pruritus, angioedema of the oral mucosa, tongue, lips, palate or oropharynx) were reported in 19 (26.4%) children. In nine (12.5%) children, the reaction was reported to involve more than one organ system. Collapse was reported in one (1.4%) child.

Of the 72 children, 52 (72.2%) (16 boys, OR, 0.23; 95% CI, 0.10-0.54, $p < 0.0008$) were skin tested; 16 children refused skin testing and we could not contact the remaining 4. In total, 17 (32.7%) of tested children were found to be positive to kiwifruit with both commercial extract and fresh kiwifruit (i.e., prick to prick test). The most frequently reported symptoms in these kiwifruit SPT-positive children were cutaneous ($n = 10$, 58.8%), gastrointestinal ($n = 6$, 35.3%), bronchial ($n = 4$, 23.5%), and nasal and ocular (three each 17.6%). Oral symptoms were reported in six (35.3%) children. In seven (41.2%) children; the reaction was reported to involve more than one organ system.

Of the 17 children with positive kiwifruit SPT, 10 children had positive SPT to Dp/Df (58.8%), six to hazel (35.3%), five to timothy (29.4%), four to birch (23.5%) and two to both banana and latex (11.8% each). Isolated kiwifruit sensitization was documented in five children. Nine children (52.9%) were sensitized to any pollens (birch, hazel or timothy) together with kiwifruit.

A total of 36 (36/52, 69.2%) children in the parental-perceived group were also sensitized to one or more of the allergens tested. SPTs to *Dermatophagoides pteronyssinus* (Dp), *Dermatophagoides farina* (Df) were found to be positive in 22 (22/36, 61.1%) children, to hazel in 10 (27.7%), to birch in eight (22.2%), to timothy in six (16.6%), to cat in three (13.8%), to latex and banana in two each (5.5%), and to sesame seed in one (2.7%).

Of the 52 children who were skin tested, 49 also had open oral challenges. The remaining three children (one child in kiwifruit SPT-negative group and two in the kiwifruit SPT-positive group) refused to be involved in challenges. All 34 children who were kiwifruit-negative by SPT also tested negative by oral challenge.

Of the 17 children (3 boys) with kiwifruit positive SPTs, oral challenges were performed in 15 (3 boys, OR, 16.0; 95% CI, 2.67-95.75, $p < 0.0024$) and all were positive. The remaining two children (both girls) refused to undergo oral challenge because of a recent major reaction. The clinical reactions to oral challenges in kiwifruit SPT-positive group were urticaria ($n = 7$, 47%), urticaria-angioedema ($n = 3$, 20%) and oral symptoms ($n = 4$, 27%). A systemic reaction with urticaria, cough, nasal discharge and conjunctival hyperemia was observed in one challenge (6.6%). Of the nine children sensitized to both kiwifruit and any pollens (birch, hazel or timothy), four (44.4%) had oral allergy syndrome, four (44.4%) had urticaria and one (11.1%) had urticaria-angioedema.

The severity of challenge reactions was mild in 14 (93%) children and moderate in one child (7%). None of the children reacted severely to any oral challenges. Children with a positive reaction in terms of urticaria-angioedema and oral symptoms were given an antihistamine. Adrenaline with a dose of 0.01 mg/kg was administered intramuscularly to the child for systemic reaction. Analysis of the reactivity to oral challenges by gender revealed that 20.0% of boys and 80.0% of girls reacted to oral challenges.

Based on the data from the 15 children with reactions proven by oral food challenges, the prevalence of IgE-mediated kiwifruit allergy among 6–18-year-old urban school children living in the center and four districts of Rize city was 0.10 % (95% CI: 0.06-0.16; Table 1).

The prevalence of self-reported IgE-mediated kiwifruit allergy was significantly more than the prevalence of clinically confirmed kiwifruit allergy (odds ratio, 4.81; 95% CI, 2.76–8.40; $P<0.0001$).

Discussion

We found the prevalence of parental perceived kiwifruit allergy in 6-18 years-old urban school children as 0.5 % and the clinically confirmed kiwifruit allergy to be 0.1%. Similar to previous studies, we found large differences between the prevalence of perceived (self - or parent-reported) versus clinically confirmed kiwifruit allergy. (17, 18)

To the best of our knowledge, this is the first study investigating the prevalence of kiwifruit fruit allergy in a general pediatric population. Previous clinical studies on kiwifruit allergy have mostly been case reports or case series, and most have evaluated the cross-reactivity of kiwifruit with pollens or other fruits. A few population-based studies have considered the prevalence of food allergies and included kiwifruit as one of the food items. Strinholm et al. found a self-reported prevalence of kiwifruit allergy of 8.0% in 7-8 year-old Swedish school children. (19) This figure was found to be 7.8% in pollen allergic Danish young adults (18) and 39.0% in Finnish first-year university students. (2) The reported prevalence in our study was only 0.5%. However, one may expect a higher prevalence of kiwifruit allergy as it was widely cultivated and consumed in Rize. The wide variability among the results of the present study and aforementioned studies may be related to the methodological issues (i.e., differences in study populations, diagnostic methods used), and genetic factors. On the other hand, our results were in accordance with the results of a previous study conducted in 2009 in the same region by Orhan et al(4) An explanation may as well come from a recent study that showed the early introduction and frequent consumption of food allergens in the diet were associated with a lower rate of sensitization. (20)

Contrary to the findings of previous studies (21) reporting a higher prevalence of IgE-mediated food allergy among boys compared to girls, we found in our group that female sex was significantly associated with kiwifruit allergy. Girls comprised a rate of 66.6% and 80.0% in reported and confirmed groups, respectively. Strinholm et al. (19) also found a similar rate of reported kiwifruit allergy in girls (60.1%, 125 girls vs. 83 boys). Whether this was a characteristic of kiwifruit allergy should be observed in further studies.

Aleman et al. (6) studied the patients with allergy symptoms to kiwifruit (aged 5 to 54 years, median: 31.2 years) and found that SPT with kiwifruit were positive in 100% of their group, 81% of them were also allergic to pollen, 12% were exclusively allergic to kiwifruit, 7%

were sensitized to kiwifruit along with other fruits. In contrast to that study, only 32.7% of the children with perceived kiwifruit allergy in our study group had skin prick test positivity. Among them, 29.4% were solely positive for kiwifruit and 70.6% were also positive for other allergens, as 35.3% for hazel, 29.4% for timothy, 23.5% for birch and 11.8% for both banana and latex. As seen in our group, pollen sensitization rates are lower compared to the rates reported by Aleman et al. (6)

Also, symptoms reported, and confirmed in our study group were in contrast with those reported in previous studies in which the most common presentations of kiwifruit allergy were OAS followed by cutaneous manifestations, anaphylaxis, and gastrointestinal manifestations. (6, 14, 22, 23) The rate of reported oral symptoms in our study was one-third of the previous reports whereas cutaneous and gastrointestinal symptoms were more than three and eight times greater, respectively. The differences in sensitization rates and in clinical manifestations may be due to the differences in study populations as our survey comprised only children aged between 6-18 years-old in contrast to previous studies involved only adults or both children and adults. (6, 23) It is well known that; as age increases the rate of pollen sensitization increases (24) that may lead to a higher rate of pollen-fruit related symptoms (i.e., OAS).

Previous studies have shown that people with kiwifruit and associated pollen allergy are more likely to present with oral allergy syndrome whereas kiwifruit allergic people with no pollen sensitization are most likely to present with systemic symptoms. (7, 9, 25). In accordance with these studies, the children in our study group with solely kiwifruit SPT-positive did not have any oral symptoms during the oral challenge.

Mastorilli et al. studied the endotypes of the pollen-food syndrome in children with seasonal allergic rhinoconjunctivitis (SAR). They defined a “non-panallergen” PFS endotype. Those children belonging to this group were sensitized to none of the examined panallergens (profilin, PR-10, nsLTP). The non-panallergen PFS endotype causes a very mild disease and highest frequency of mild SAR. Kiwifruit was the most common trigger of PFS and the only one offending food in “non-panallergen” PFS group. (26) In our study population, 69.2% of the children were also co-sensitized to other allergens; Dp/Df was the most common, followed by hazel, birch, and timothy. Contrast to Mastorilli et al., a child without any other co-sensitization, had anaphylaxis, and the other four children had urticaria-angioedema during OFC.

A limitation of our study might be the response rate to the questionnaires. In our study, 75.9% of the study population responded to the questionnaires. It is more likely that the ones

with kiwifruit associated complaints responded more, and this could result in the overestimation of the reported prevalence of kiwifruit allergy. In addition to this, only 72.2% of the children who report kiwifruit associated symptoms could be skin prick tested and further had an oral challenge with kiwifruit; this may lead to underestimation of the prevalence. However, our results were comparable with the previous study reporting the prevalence of general food allergy in the same region. (4)

Another limitation of our study is that we only performed open food challenges. Though DBPCFC is the gold standard to diagnose food allergy, it is time and labor consuming and not easy to perform. On the other hand, when screening the least suspected foods or when screening young children, open challenge testing might be acceptable. An open OFC is easy to perform, cost efficient, not a time-intensive procedure when compared with DBPCFC and when negative it definitely rules out food allergy. (27) If the diagnosis is still unclear after an open challenge (i.e., subjective symptoms such as nausea, headache, etc.), the physician should continue with a blind food challenge. The children in the present study reported strong and convincing clinical symptoms following kiwifruit ingestion. Skin tests were positive in all challenge-positive children and the symptoms occurred during food challenge were objective symptoms. Also, open OFCs were negative in all SPT-negative children. Therefore, we did not need to perform a DBPCFC in challenge-negative children.

It was not specified in the questionnaire that whether children not allergic to kiwifruit had consumed it on some occasions or whether the families used to consume it at home. Although one may suggest this as a limitation of the study, our aim was only to define the current prevalence of kiwifruit allergy.

In conclusion, this study shows that parental-perceived and confirmed kiwifruit allergy is not consistent. Although 0.5% of the children reported kiwifruit allergy, clinically confirmed prevalence of IgE-mediated kiwifruit allergy was 0.1% in 6–18-year-old children. In contrast to previous studies reporting higher prevalence, kiwifruit allergy prevalence was low in a city where it is cultivated and highly consumed in the diet. The results of our study also support at least in part the idea that early introduction of allergic foods in the diet may lead to low prevalence of allergy and higher tolerance to the food, questioning the idea of avoidance or late introduction to prevent food allergy.

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Table 1: Summary of positive oral food challenges

No	Age (years) / sex	Total dose given (mL)	Total time to reaction (min)	Symptoms
1	7 / F	10.6	85	Urticaria
2	7 / F	25.6	100	Urticaria
3	9 / M	5.6	65	Urticaria
4	11 / F	10.6	82	Urticaria
5	8 / F	3.1	48	Urticaria
6	8 / M	50.6	108	Urticaria
7	13 / M	3.1	50	Urticaria
8	6 / F	5.6	72	Urticaria-angioedema
9	10 / F	25.6	95	Urticaria-angioedema
10	13 / F	50.6	110	Urticaria-angioedema
11	12 / F	0.6	20	OAS
12	15 / F	1.6	30	OAS
13	11 / F	1.6	35	OAS
14	10 / F	5.6	70	OAS
15	13 / F	0.6	15	Anaphylaxis

OAS, oral allergy syndrome;

FIGURE LEGENDS:

Figure 1: Flow chart of the study

Figure 2: Summary of the questionnaire

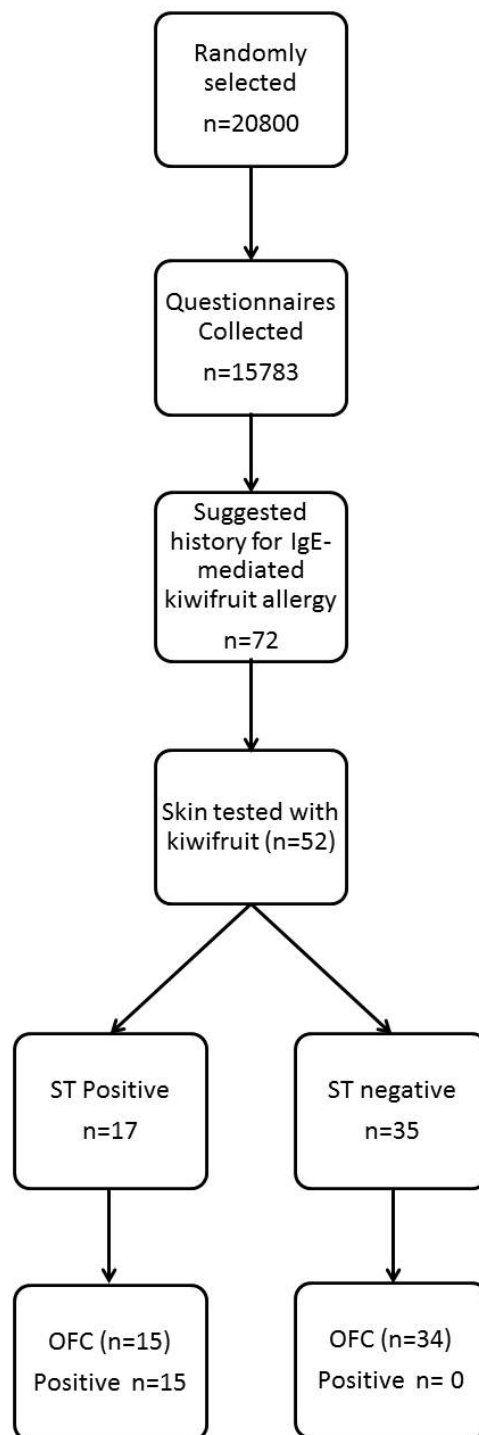


Figure 1: Flow chart of the study.

Figure 2: Summary of the questionnaire

Age /sex:

Has your child ever had an adverse reaction within two hours of eating kiwifruit? ☐ Yes ☐ No

If yes; please marked what happened. You can choose more than one option.

- ☐ cutaneous (eruption, itching, rash, swelling)
- ☐ oral (labial, oral pruritus, swelling of the oral mucosa, tongue or lips.)
- ☐ nasal (sneezing, itching, secretion, blockage)
- ☐ ocular (redness, itching, secretion)
- ☐ bronchial (cough, wheezing, shortness of breath)
- ☐ gastrointestinal (stomachache, nausea, vomiting, diarrhea)
- ☐ laryngeal (difficulty in swallowing, difficulty in speaking),
- ☐ cardiovascular (palpitations/tachycardia, hypotension)
- ☐ other (sweating, pallor, fainting, loss of consciousness)

Has your child consumed kiwifruit on another occasion following the adverse reaction? ☐ Yes ☐ No

If yes, did the similar reaction occur again? ☐ Yes ☐ No

If any of your answers is “yes” your child may have kiwifruit allergy. Do you give consent for further examination of your child for kiwifruit allergy? ☐ Yes ☐ No