

ORIGINAL ARTICLE

Sensitisation to outdoor and indoor fungi in atopic dermatitis patients and the relation to the occurrence of food allergy to peanuts and walnuts

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Summary

The aim of this study is the evaluation of the relation between the sensitisation to outdoor and indoor fungi and allergy to peanuts and walnuts in atopic dermatitis patients aged 14 years and older. The complete dermatological and allergological examinations were performed in all included patients; the occurrence of food allergy to peanuts and walnuts was recorded (specific IgE, skin prick test, history of allergic reaction) and the sensitisation to mixture of outdoor fungi and indoor fungi was also examined (skin prick test, specific IgE). The statistical evaluation of the relation between the sensitisation to outdoor and indoor fungi and the occurrence of food allergy to peanuts and walnuts was performed; 329 patients were included in the study, 110 men and 219 women, the average age 26.8 years. The sensitisation to outdoor fungi was recorded in 91 patients (28%), the sensitisation to indoor fungi was recorded in 61 patients (18.5%), the occurrence of food allergy to peanuts was confirmed in 90 (27%) patients and to walnuts in 121 (36.7%) patients. We confirmed, that patients suffering from sensitisation to outdoor fungi suffer significantly more from food allergy to peanuts and walnuts. The significant relation between the sensitisation to indoor fungi and food allergy to peanuts and walnuts was not confirmed.

KEYWORDS

atopic dermatitis, food allergy to peanuts and walnuts, indoor fungi, outdoor fungi

1 | INTRODUCTION

Nuts (tree nuts and peanuts) are nutrient dense foods with complex matrices rich in unsaturated fatty and other bioactive compounds: high-quality vegetable protein, fibre, minerals, tocopherols, phytosterols and phenolic compounds. By virtue of their unique composition, nuts are likely to beneficially impact health outcomes. Epidemiologic studies have associated nut consumption with a reduced incidence of coronary heart disease and gallstones in both genders and diabetes in women. Limited evidence also suggests beneficial effects on hypertension, cancer, and inflammation. Interventional studies

consistently show that nut intake has a cholesterol-lowering effect, even in the context of healthy diets, and there is emerging evidence of beneficial effects on oxidative stress, inflammation, and vascular reactivity. Blood pressure, visceral adiposity and the metabolic syndrome also appear to be positively influenced by nut consumption.¹ On the other hand, nuts are a well-known cause of food allergy, with estimated prevalence rates of approximately 1% in the general population.² The at-risk subject is an atopic individual, with heightened risk for those with atopic dermatitis and/or other food allergies. Allergic reactions to nuts are due to allergenic seed storage proteins that elicit specific IgE antibodies. They affect principally young

children and may be particularly severe and even life-threatening. Severity of coexisting atopic diseases (asthma, rhinitis, and atopic dermatitis) predicts which patients are most likely to develop life-threatening allergic reactions to tree nuts and peanuts.^{3,4} A minority of children with peanut allergy developed tolerance with time. The English or common walnut (*Juglans regia*) is a frequently consumed tree nut with high nutritional value and claimed health benefits.¹ In walnut allergic individuals, however, symptoms of ingestion of walnut can vary from oral allergy symptoms to anaphylaxis.^{5,6} A recent systematic review of population-based studies points to a prevalence of 4.3% when diagnosis is based on food challenge tests and <1% when sensitization is assessed by skin prick test.³ Walnut allergy is the most reported tree nut allergy in the United States.⁴ In Europe, walnut sensitisation was demonstrated in 2%-3% of the population, a number very similar to peanut sensitisation.^{7,8} Peanuts (*Arachis hypogea*), which botanically are groundnuts or legumes, are widely identified as part of the nuts food group. In addition, peanuts have a similar nutrient profile to tree nuts.^{9,10} Another additional concern regarding the tree nuts and peanuts is potential toxicity through contamination of nuts with mycotoxins, particularly aflatoxins, which is a problem that affects agricultural economies.^{11,12} Fungi are very common in the environment, they have a far greater impact on the patients' immune system than pollen or other allergenic sources and some foods (cereals, vegetables, and fruit crops) can be affected both before and during storage with fungi.¹³ *Alternaria* and *Cladosporium* species are considered to be important outdoor allergens, in contrast, xerophilic species of *Penicillium* and *Aspergillus*, excluding *Aspergillus fumigatus*, are implicated in allergic diseases as indoor allergens. Tree nuts are among the commodities with moderate-to-high risk of Aflatoxins contamination, since they are generally produced under environmental conditions, which also favour growth of aflatoxigenic fungi and toxin production.¹³ The evaluation of sensitisation to fungi in atopic dermatitis patients has been the subject of only limited studies with respect to the relation to the occurrence of food allergy to nuts. A clear growth inhibition of the fungal species *Alternaria* and *Cladosporium* caused by 2 novel peanuts allergens was demonstrated.^{14,15} In our last study, we confirmed, that patients suffering from sensitisation to mixture of fungi suffer significantly more from food reactions to nuts and fish. We found no relation between the sensitisation to fungi and the occurrence of food hypersensitivity reactions to other foods (tomatoes, kiwi, apples, spices, oranges, capsicum, celery, carrots and strawberries).¹⁶ Among the over 100 000 fungal species reported, only a few hundred have been described as opportunistic pathogens causing human illness through 3 specific mechanisms: direct infection of the host, elicitation of deregulated immune responses and toxic effects due to secondary metabolites.¹⁷⁻²⁰

1.1 | Aim of the study

The aim of this study is to evaluate the sensitisation to outdoor and indoor fungi allergens and the relation to the occurrence of food allergy to walnuts and peanuts.

2 | METHOD

In the period 2008-2017, 329 patients suffering from atopic dermatitis at the age of 14 years and older were examined. All these patients were examined in the Department of Dermatology, Faculty Hospital Hradec Králové, Charles University of Prague, Czech Republic. The diagnosis of atopic dermatitis was made with the Hanifin-Rajka criteria.²¹ Exclusion criteria were long term therapy with cyclosporin or systemic corticoids, pregnancy, breastfeeding. Patients with atopic dermatitis having other systemic diseases were excluded from the study as well. Complete dermatological and allergological examination was performed in patients included in the study. This study was approved by Ethics committee of Faculty Hospital Hradec Králové, Charles University of Prague, Czech Republic.

We examined the sensitisation to mixture of outdoor and indoor fungi and the occurrence of food allergy to peanuts and walnuts. The statistical evaluation of the relation between the sensitisation to mixture of outdoor and indoor fungi and the occurrence of food allergy to peanuts and walnuts was performed.

2.1 | Evaluation of parameters monitored

2.1.1 | Sensitisation to outdoor fungi (mixture) and indoor fungi (mixture)

It was determined according to the specific IgE (sIgE) level and the skin prick results (SPT) results. Commercial extracts Alyostal (Stallergens, France) was used for SPT. The serum level of the sIgE has been measured with the method of CAP (system FEIA—Pharmacia Diagnostics, Uppsala, Sweden). The level of specific IgE higher than 0.35 U/mL was assessed as positive. The sensitisation was confirmed in positive results in sIgE and/or SPT examination.

2.1.2 | The diagnosis of food allergy to peanuts and walnuts

It was made according to the patient's history and according to the results in sIgE and in skin prick tests. The patients answered whether they had suffered from immediate or late food reactions (oral allergy syndrome [OAS], gastrointestinal problems, the occurrence of skin problems, respiratory problems). Peanuts and walnuts were not examined in the challenge test because of anaphylactic reaction danger.

2.2 | Statistical analysis

We analysed the data to determine whether the occurrence of sensitisation to mixture of outdoor and indoor fungi is associated with the occurrence of food allergy to peanuts and walnuts. Pairs of these categories were entered in the contingency tables and the chi-square test for relationship of these classifications was performed with the level of significance set to 5%. When we study a contingency table, our null hypothesis is the independence of the 2 classifications. We

use the chi-square test on the 5% significance level. It means that we reject the null hypothesis (independence) when the *P*-value is <5%. If so, to see in which direction the dependence works, we use the coefficient of concordance (CC). If the CC is positive, the dependence is direct. If the CC is negative, the dependence is indirect.

2.3 | Results patients

Three hundred and twenty-nine patients were examined, 110 men and 219 women with the average age 26.8 years (SD 9.2 years) and with the average SCORAD 33.1, SD 13.1 points. The sensitisation to outdoor fungi was recorded in 91 (28%) patients, to indoor fungi in 61 (18.5%) patients, no sensitisation to fungi was recorded in 231 patients (70%). The occurrence of food allergy to peanuts

TABLE 1 The characteristic of patients with the occurrence of the followed parameters

- Three hundred and twenty-nine patients examined—110 men, 219 women, the average age 26.8 y (SD 9.2 y)
- The average SCORAD 33.1, SD 13.1 points
 - The sensitisation to outdoor fungi was recorded in 91 (28%) patients
 - The sensitisation to indoor fungi was recorded in 61 (18.5%) patients
 - No sensitisation to fungi was recorded in 231 patients (70%).
 - The occurrence of food allergy to peanuts was recorded in 90 (27%) patients
 - The occurrence of food allergy to walnuts was recorded in 121 (36.7%) patients
 - The occurrence of food allergy to walnuts and peanuts in 105 patients (31%)

TABLE 2 The recorded symptoms of food allergy to peanuts and walnuts in 329 patients (=100%)

Symptoms	Allergy to peanuts (%)	Allergy to walnuts (%)
Oral allergy syndrome	85 (26)	110 (33)
Pruritus	18 (5.5)	28 (8.5)
Gastrointestinal problems	17 (5)	25 (7.5)
Worsening of atopic dermatitis	6 (2)	10 (3)

Parameters	Allergy to peanuts yes (%)	No allergy to peanuts (%)	Total number of patients (%)
Sensitisation to outdoor fungi yes	34 (10)	57 (17)	91 (28)
No sensitisation to outdoor fungi	56 (17)	182 (55)	238 (72)
Total number of patients	90 (27)	239 (72)	329 (100)
<i>P</i> value	.012, CC = .319 403		

The significant direct relation between the occurrence of sensitisation to outdoor fungi and the occurrence of food allergy to peanuts was confirmed, the coefficient of concordance (CC) was calculated to see in which direction the dependence works.

was recorded in 90 (27%) patients, to walnuts in 121 (36.7%) patients. The characteristic of patients with the occurrence of the followed parameters is recorded in Table 1. These symptoms of food allergy to peanuts were recorded: oral allergy syndrome in 85 patients (26%), pruritus in 18 patients (5.5%), gastrointestinal problems in 7 patients (5%) and worsening of atopic dermatitis in 6 patients (2%). These symptoms of food allergy to walnuts were recorded: oral allergy syndrome in 110 patients (33%), pruritus in 28 patients (8.5%), gastrointestinal problems in 25 patients (7.5%) and worsening of atopic dermatitis in 10 patients (3%), Table 2. The relation between the occurrence of sensitisation to outdoor and indoor fungi and allergy to peanuts and walnuts was recorded in Tables 3-6.

The significant relation was confirmed between the patients suffering from sensitisation to outdoor fungi and the occurrence of food allergy to peanuts (*P*-value = .012, CC = .319 403) and the occurrence of food allergy to walnuts (*P*-value = .0000, CC = .57 671). No significant relation was found between the sensitisation to indoor fungi and allergy to peanuts (*P*-value = .170) and allergy to walnuts (*P*-value = .102).

3 | DISCUSSION

The evaluation of sensitisation to outdoor and indoor fungi in atopic dermatitis patients has been the subject of only limited studies with respect to the relation to the occurrence of food allergy to walnuts and peanuts. We have not found any similar study dealing with this question; according to the literature, there are only few studies, that evaluated the sensitisation to fungi in atopic dermatitis patients and much remains to be studied with respect to prevalence patterns, exposure and disease relationships. The occurrence of food hypersensitivity reactions in atopic dermatitis patients was evaluated in our previous studies also and it was described in more detail earlier.²²⁻²⁵ This study confirmed that atopic dermatitis patients suffering from sensitisation to outdoor fungi suffer significantly more from food allergy to peanuts and tree nuts. On the other hand, no significant relation between the sensitisation to indoor fungi and allergy to peanuts and tree nuts was confirmed. The clinical history that represents one of the most important diagnostic criteria for an allergy is difficult to

TABLE 3 The relation between the occurrence of sensitisation to outdoor fungi and the occurrence of food allergy to peanuts

TABLE 4 The relation between the occurrence of sensitisation to outdoor fungi and the allergy to walnuts

Parameters	Allergy to walnuts yes (%)	No allergy to walnuts (%)	Total number of patients (%)
Sensitisation to outdoor fungi yes	54 (16.4)	37 (11.2)	91 (28)
No sensitisation to outdoor fungi	67 (20.3)	171 (51.9)	238 (72)
Total number of patients	121 (36.7)	208 (63.22)	329 (100)
P value	.0000, CC = .57 671		

The significant direct relation between the occurrence of sensitisation to outdoor fungi and the allergy to walnuts was confirmed, the coefficient of concordance (CC) was calculated to see in which direction the dependence works.

TABLE 5 The relation between the occurrence of sensitisation to indoor fungi and the occurrence of allergy to peanuts

Parameters	Allergy to peanuts yes (%)	No allergy to peanuts (%)	Total number of patients (%)
Sensitisation to indoor fungi yes	21 (6.4)	40 (12.1)	61 (18.5)
No sensitisation to indoor fungi	69 (21)	199 (60)	268 (81)
Total number of patients	90 (27)	239 (73)	329 (100)
P value	.170		

The significant direct relation between the occurrence of sensitisation to indoor fungi and the allergy to peanuts was not confirmed.

TABLE 6 The relation between the occurrence of sensitisation to indoor fungi and the occurrence of allergy to walnuts

Parameters	Allergy to walnuts yes (%)	No allergy to walnuts (%)	Total number of patients (%)
Sensitisation to indoor fungi yes	28 (8.5)	33 (10)	61 (18.5)
No sensitisation to indoor fungi	93 (28.2)	175 (53.2)	268 (81)
Total number of patients	121 (36.7)	208 (63.22)	329 (100)
P value	.102		

The significant direct relation between the occurrence of sensitisation to indoor fungi and the allergy to walnuts was not confirmed.

reconstruct for patients with a fungal allergy. In contrast to other allergies (seasonal pollen-derived allergies, food allergies), most patients sensitised to fungi are not aware of the source of exposure and can only report that the symptoms are more or less perennial. *Aspergillus fumigatus* has a high capacity to colonise the bronchial tract of asthmatic patients, causing severe persistent asthma and low lung function, and sometimes leading to allergic bronchopulmonary aspergillosis.¹⁷⁻²⁰

Alternaria spp. mycotoxins have been isolated from fruits (apple, pear, melon, apricot, grapes, raisins, strawberry, olive, citrus fruits and dried figs), vegetables (tomato, pepper and carrot) and potato, as well as from several processed foodstuffs manufactured with damaged raw materials (juices, preserves, sauces, etc.). Studies have also shown that aflatoxin contaminates some kinds of foods such as nuts, dried fruits and tea, since these groups are often exposed to fungal infestations.²⁶

We can speculate the reasons for the significant direct relation between the sensitisation to outdoor fungi and the allergy to tree nuts and peanuts in atopic dermatitis patients. The reason for this relation may be in the fact that tree nuts and peanuts have some protective antifungal effect; this effect cannot be applied in patients, who eliminate tree nuts and peanuts for a long time because of allergic reactions to these foods. Plants express a large number of antifungal proteins for protection against fungal disease such as pathogen-related (PR), thaumatin-like proteins, thionins, lipid transfer proteins (LTP), plant defensins, hevein- and knottin-type proteins, Ib-AMPs and snakins. Some members of these families have been classified into PR groups such as defensins (PR-12), thionins (PR-13) and LTPs (PR-14)²⁷⁻²⁹; variety of functions have been attributed to plant defensins. Petersson et al. discovered that the 2 novel peanut allergens were plant defensins with antifungal activity. A clear growth inhibition of the fungal species *Alternaria* and *Cladosporium* was demonstrated in this

study. The lipophilic extraction strategy was successful in identifying 2 novel allergens and 1 additional isoform in peanuts. They belong to pathogenesis-related protein family 12, the plant defensins. Pathogenesis-related proteins are characterised by the fact that they are synthesised particularly under stress conditions.³⁰ IgE reactivity to the peanut defensins was detected in particular in sera from patients with severe anaphylactic reactions to peanut. Defensins are widely distributed host defence peptides that mainly exhibit antimicrobial activity directed against bacteria, fungi, and viruses. Defensins in seeds of leguminous plants (Fabaceae; eg, peanuts and beans) are part of their innate immune response together with other antimicrobial peptides, such as lipid transfer proteins, chitinases, chitinase-like proteins, hemolysins and lectins, some of which are already known to be allergens as well.¹⁴ Most of the Fabaceae-derived defensins show antifungal activity. Plant defensins with antifungal activity have shown promise for use in both agricultural and therapeutic settings.^{31–36} The results of other research groups, described antifungal activity of plant defensins on *Alternaria* and *Cladosporium* species.^{37,38} Garcia-Olmedo et al. and Stotz et al. summarise that plant defensins show mostly antifungal activity, whereas lipid transfer proteins are directed against bacteria. Together, these 2 groups of defence proteins form a general barrier against pathogens.^{39,40}

Another reason may be in fact that decrease in consumption of omega-3 polyunsaturated fatty acids has been proposed to contribute to the increased prevalence of allergic diseases. Walnuts (plant n-3 fatty acid) and fatty fish (marine n-3 fatty acid) can have similar effects, because n-3 (omega-3) polyunsaturated fatty acids (PUFAs) can regulate inflammatory processes and response.⁴¹ Thus, it is considered that n-3 PUFAs will protect against atopic sensitisation and against the clinical manifestations of atopy. Decrease in consumption of omega-3 polyunsaturated fatty acids, prevalent especially in oily fish and walnuts, has been proposed to contribute to the increased prevalence of allergic diseases.⁴¹ Another reason for the significant direct relation between the sensitisation to outdoor fungi and food allergy to peanuts and walnuts may be the fact, that positive s IgE and SPT reactions to fungi are mostly observed in patients with multiple sensitivity to various allergens.^{42,43} Some previous studies have shown that *Alternaria alternata* is one of the most common indoor and outdoor airborne fungi, so it could permanently present some allergens to susceptible individuals. Therefore, control of *A. alternata* growth in indoor areas and avoidance with *A. alternata* could play an important role in reducing allergic reaction in susceptible individuals.⁴⁴

According to the latest results, the early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts.⁴⁵ Among infants with high-risk atopic disease, sustained peanut consumption beginning in the first 11 months of life, as compared with peanut avoidance, resulted in a significantly smaller proportion of children with peanut allergy at the age of 60 months. This intervention was safe, tolerated and highly efficacious. With the intention-to-treat analysis, peanut consumption was associated with an 86% reduction in peanut allergy at 60 months

of age among participants who had had negative results on a peanut-based skin-prick test at study entry and with a 70% reduction among those who had had positive test results at study entry.⁴⁵ The findings showed that early, sustained consumption of peanut products was associated with a substantial and significant decrease in the development of peanut allergy in high-risk infants. Conversely, peanut avoidance was associated with a greater frequency of clinical peanut allergy than was peanut consumption, which raises questions about the usefulness of deliberate avoidance of peanuts as a strategy to prevent allergy.⁴⁵ Furthermore research is required to clarify the role of peanuts and walnuts consumption with respect to the relation to the occurrence of sensitisation to outdoor fungi.

4 | CONCLUSION

We confirmed that patients suffering from sensitisation to outdoor fungi suffer significantly more from food allergy to peanuts and walnuts. The significant relation between the sensitisation to indoor fungi and food allergy to peanuts and walnuts was not confirmed.

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