Food Hypersensitivity Reactions to Seafish in Atopic Dermatitis Patients Older than 14 Year of Age - The Evaluation of Association with Other Allergic Diseases and Parameters

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Abstract

Background: Seafood allergy is among one of the common food allergies. Decrease in consumption of omega-3 polyunsaturated fatty acids (PUFAs), prevalent especially in oily fish, has been proposed to contribute to the increased prevalence of allergic diseases. Aim: The aim of this study was to evaluate, in atopic dermatitis (AD) patients, the relation between the occurrence of food hypersensitivity reaction (FHR) to seafish and the occurrence of other atopic diseases and parameters. Methods: Complete dermatological and allergological examination was performed in patients included in the study; 332 patients were examined, with the average age 26.8 years (SD 9.2 years). Results: The FHR to seafish was confirmed in 11% of patients. Patients suffering from FHR to seafish suffered significantly more from sensitization to fungi (in 46%), from reactions to celery (in 34%), and from persistent eczematous lesions (in 82%). Conclusion: FHRS to seafish in AD patients are associated with persistent eczematous lesions and with the higher occurrence of sensitization to fungi and reactions to celery. The occurrence of bronchial asthma, rhinitis, positive family history, and onset of AD under 5 years of age is higher in patients with reactions to seafish, but the difference is not statistically significant.

Key Words: Atopic dermatitis, bronchial asthma, food hypersensitivity reaction to seafish, rhinitis

Introduction

Seafood allergy is among one of the common food allergies, with fish and shellfish being two of the “big eight” categories of food allergens. The prevalence of fish and shellfish allergies is 0.3% and 0.6%, respectively, in the world population. Parvalbumin and tropomyosin have been identified as the major allergens in fish and shellfish, respectively. The main clinical manifestations of allergic reactions to fish include vomiting and diarrhea, whereas the extreme form of reaction is life-threatening anaphylactic shock. Patients with fish allergy can however also react to aerosolized proteins generated by cooking or processing of fish resulting in dyspnea, wheezing, urticaria, edema, and light headedness. An adverse reaction to fish may be of nonallergic origin, due to food contamination or newly formed toxic products, but the most frequent type of adverse reactions to fish are immunologic-mediated reactions; such allergic reactions may be both IgE-mediated and non-IgE-mediated. On the other hand, fish is also a major source of long-chain omega-3 fatty acids. In recent decades, a decrease in consumption of omega-3 PUFAs, prevalent especially in oily fish, has been proposed to contribute to the increased prevalence of allergic diseases, such as atopic dermatitis (AD), asthma bronchiale, and allergic rhinitis. AD starts in infancy and affects 2 of 10 children; it is also highly prevalent among adults. It is the leading nonfatal health burden attributable to skin diseases, inflicts a substantial psychosocial burden on patients,
and increases the risk of food allergy, asthma, allergic rhinitis, other immune-mediated inflammatory diseases, and mental health disorders, originally regarded as a childhood disorder mediated by an imbalance towards a T-helper-2 response and exaggerated IgE responses to allergens; it is now recognized as a lifelong disposition with variable clinical manifestations and expressivity, in which defects of the epidermal barrier are central.[6] The progression of atopic disorders from AD in infants to allergic rhinitis and asthma in children is usually described as atopic march. Studies investigating the coprevalence of AD and food hypersensitivity reactions (FHRs) are still scarce and exact data are not available.[12-14] Many studies demonstrate the prevalence of allergic diseases; however, most studies analyzed a limited period from infancy to later childhood and/or to early adolescence. Limited data are available on the frequency of IgE-mediated food sensitization and food allergy in adults with AD. [15-17] Adult AD patients show much higher rates of sensitization to foods than healthy individuals, in particular to food proteins cross-reactive with airborne allergens, rather than the food allergens that typically predominate amongst children with AD. [17] In our previous studies, we recorded the occurrence of FHRs (food allergy, food intolerance) in AD patients older 14 years of age and their relation to the occurrence of other atopic diseases and parameters also.[18-22] The term food hypersensitivity reaction represents the umbrella term for food allergy and for nonallergic food hypersensitivity (=food intolerance). The term food allergy is used to describe the clinical symptoms that are mediated by the immune system; number of IgE-, cellular-, mixed IgE-, and cell-mediated food hypersensitivity disorders have been described.[23,24] Food intolerance is a nonallergic hypersensitivity to food that does not include the immune system even though the symptoms are similar to those of IgE-mediated allergic reactions. An impaired histamine degradation based on reduced diamine oxidase activity and the resulting histamine excess may cause numerous symptoms mimicking an allergic reaction.[23,24]

Aim of this study was to evaluate in AD patients the relation between the occurrence of FHRs to seafish and the occurrence of other atopic diseases and parameters, such as the occurrence of FHRs to other foods, the sensitization to mites, animal dander, dust, bird feather, mixture of grass, mixture of trees, mixture of fungi, the occurrence of asthma bronchiale, allergic rhinitis, duration of AD, the onset of AD, and family history about atopy.

Materials and Methods
During the period 2007–2016, 332 patients suffering from AD older than 14 year of age 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 AD was made with the Hanifin–Rajka criteria.[25] Complete dermatological and allergological examinations were done in the patients included in the study. The severity of AD was evaluated according to the SCORAD index.[26] Exclusion criteria were long-term therapy with cyclosporin or systemic corticoids, pregnancy, and breastfeeding. Patients with AD having other systemic diseases were excluded from the study as well. This study was approved by Ethics Committee of Faculty Hospital Hradec Králové, Charles University of Prague, Czech Republic. The statistical evaluation of the relation between the FHRs to seafish and the occurrence of FHRs to other foods (such as tomatoes, kiwi, apple, spices, peanuts, oranges, capsicum, tangerines, celery, and carrot), and inhalant allergens (such as trees, grass, mites, animal dander, fungi, dust, and bird feather), and to other parameters (such as the occurrence of asthma bronchiale, family history about atopy, allergic rhinitis, onset of AD, and duration of eczematic lesions) was performed.

The diagnosis of FHRs to seafish and other foods: It was made according to the patient’s history. The patients answered whether they had suffered from immediate or late food reactions (oral allergy syndrome [OAS], gastrointestinal problems, the occurrence of skin problems, and respiratory problems). The answers concerning the possible food reactions reflect the patient’s history (repeatedly observed food reactions in patient’s history) and were not based on the results of examinations, such as specific IgE and skin prick tests (SPTs). The occurrence of FHRs in AD patients was evaluated in our previous studies also, and it was described in more details previously.[18-22]

Sensitization to mites, animal dander, dust, bird feather, mixture of grass, mixture of trees, and mixture of fungi: It was confirmed according to the specific IgE level (sIgE) and the SPT results. Commercial extracts Alyostal (Stallergens, France) was used for SPT. The serum level of the sIgE had 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 diagnosis of asthma bronchiale: It was made according to the results in spirometry at allergological outpatients department and according to the data about wheezing. Asthma was diagnosed as at least three separate episodes of wheezing, each at least 3 days in duration during the past year.

The diagnosis of allergic rhinitis (seasonal or perennial): It was made according to the anamnestical data such as recurrent nasal symptoms/rhinitis (recurrent nasal discharge or blockage with attacks of sneezing and itchy eyes).
The evaluation of duration of AD: The AD lesions were evaluated as persistent or occasional according to the dermatologist’s examination during one previous year and according to the patient information. Persistent lesions were defined as eczematous lesions on the different parts of the body appearing in the period shorter than 1 month. It was evaluated according to the visit to the dermatologist every 2 month, and according to the patients’ information. Occasional lesions were defined as episodes of eczematous lesions; the patient had been without lesions of AD at least 1 month during 1 year. It was evaluated according to the SCORAD index\textsuperscript{[26]} with the evaluation of affected skin area and intensity.

The onset of AD: It was evaluated according to the patient history (the onset of AD under 5 years of age or later).

The family history: The atopy history was evaluated according to the patient information (the occurrence of allergy, AD, asthma bronchiale, rhinoconjunctivitis in parents, brothers, sisters, and children).

**Results**

Three hundred thirty two patients were examined, 112 men and 220 women with the average age of 26.8 ± 9.2 years and with the average SCORAD 33.1 ± 13.1 points.\textsuperscript{[26]} The FHRs to seafish were confirmed in 35 (11%) patients. The reactions to fish were recorded as mild OAS, vomiting, pruritus, and worsening of AD. The results are summarized in four tables and in complements to these tables. The characteristics of the patients with the occurrence of the followed parameters are recorded in Table 1. The relation between the occurrence of reactions to seafish and the occurrence of FHRs to tomatoes, kiwi, apple, spices, peanuts, oranges, capsicum, tangerines, celery, and carrot in 332 patients is recorded in Table 2. The significant direct relation between the occurrence of FHRs to celery and the occurrence of FHR to fish was confirmed; the coefficient of concordance was calculated to see in which direction the dependence worked. In Complement to Table 2, the significantly rising occurrence of sensitization to fungi in patients suffering from reactions to seafish is shown. In patients with reactions to seafish, the sensitzation to fungi was in 46%; in patients without reactions to seafish, the sensitzation to fungi was in 28%. The difference was statistically significant.

The relation between the occurrence of reactions to seafish and the occurrence of positive family history about atopy, asthma bronchiale, rhinitis, onset of AD under 5 years of age, and persistent lesions in 332 patients is shown in Table 3. The significant direct relation between the occurrence of reactions to seafish and persistent lesions of AD was confirmed; the coefficient of concordance was calculated to see in which direction the dependence worked. In Complement to Table 3, the significantly rising occurrence of persistent eczematous lesions in patients suffering from reactions to seafish is shown. In patients with reactions to seafish, the occurrence of persistent eczematous lesions was recorded in 82%; in patients without reactions to seafish, the occurrence of persistent eczematous lesions was recorded in 59%. The difference was statistically significant. In Complement to Table 3, the occurrence of asthma bronchiale, rhinitis, positive family history, and onset of AD under 5 years of age is shown in patients with and without reactions to seafish also. The occurrence of asthma bronchiale, rhinitis, positive family history, and onset of AD under 5 years of age was higher in patients with reactions to seafish, but the difference was not statistically significant.

The relation between the occurrence of reactions to seafish and the occurrence of inhalant allergy (trees, grass, mites, animal dander, fungi, dust, and bird feather) in 332 patients is shown in Table 4. The significant direct relation between the occurrence of reactions to seafish and the sensitization to mixture of fungi was confirmed; the coefficient of concordance was calculated to see in which direction the dependence worked. In Complement to Table 4, the significantly rising occurrence of sensitization to fungi in patients suffering from reactions to seafish is shown. In patients with reactions to seafish, the sensitization to fungi was in 46%; in patients without reactions to seafish, the sensitization to fungi was in 28%. The difference was statistically significant.

**Discussion**

The goal of this study was to show the occurrence of FHRs to seafish in AD patients and to evaluate the relation between these reactions and other parameters in atopic march, such as the occurrence of FHRs to other foods, the sensitization to mites, animal dander, dust, bird feather, mixture of grass, mixture of trees, mixture of fungi, the occurrence of asthma bronchiale, allergic rhinitis, duration of AD, the onset of AD, and family history about atopy. There are no studies dealing with this questions in adolescents and adults. The recorded early allergic reactions to food (oral allergy syndrome, asthma bronchiale, some gastrointestinal disorders, such as spasm and diarrhea) have a high diagnostic importance, because the early symptoms after ingestion of food have a clear diagnostic connection with the ingested food. These patients eliminate fishes usually from childhood and they had recorded that these reactions are reproducible after a casual ingestion. The reactions to fish were recorded as mild OAS, vomiting, pruritus, and worsening of AD altogether in 35 patients (11%). Regarding the evaluation of the relation between the
occurrence of FHRs to seafish and followed parameters, we confirmed that patients suffering from FHRs to seafish suffered significantly more from sensitization to fungi (in 46%), from reactions to celery (in 34%), and from persistent eczematous lesion (in 82%). In patients without the reaction to seafish, the sensitization to fungi was recorded in 28%, to celery in 8%, and persistent eczematous lesions were recorded in 59%. On the other hand, the occurrence of asthma bronchiale, rhinitis, positive family history, and onset of AD under 5 years of age was higher in patients with reactions to seafish, but the difference was not statistically significant.

| Table 1: The characteristics of patients with the occurrence of the followed parameters in 332 patients |
|---------------------------------------------------------------|
| **Followed parameter**                                      | **Number of patients from 332 (=100%)** |
| **Followed parameter present**                             | **Followed parameters absent** |
| Asthma bronchiale                                           | 146 (44%) | 186 (56%) |
| Rhinitis                                                    | 255 (77%) | 77 (23%)  |
| Persistent lesions                                         | 204 (61%) | 128 (39%) |
| Positive family history                                    | 190 (57%) | 142 (43%) |
| Onset under 5 year of age                                  | 251 (75%) | 81 (25%)  |
| Reaction to seafish                                        | 35 (11%)  | 297 (89%) |
| Reaction to tomatoes                                       | 65 (20%)  | 267 (80%) |
| Reaction to kiwi                                            | 62 (19%)  | 270 (38%) |
| Reaction to apple                                          | 55 (17%)  | 277 (83%) |
| Reaction to spices                                         | 64 (19%)  | 268 (81%) |
| Reaction to peanuts                                        | 92 (28%)  | 240 (72%) |
| Reaction to oranges                                        | 52 (16%)  | 280 (84%) |
| Reaction to capsicum                                        | 35 (11%)  | 297 (89%) |
| Reaction to tangerines                                     | 59 (18%)  | 273 (82%) |
| Reaction to celery                                         | 36 (11%)  | 296 (89%) |
| Reaction to carrot                                         | 20 (6%)   | 312 (94%) |
| Sensitization to trees                                     | 167 (50%) | 165 (50%) |
| Sensitization to grass                                     | 225 (68%) | 107 (32%) |
| Sensitization to mite                                      | 203 (61%) | 129 (39%) |
| Sensitization to animal dander                             | 158 (48%) | 174 (52%) |
| Sensitization to fungus                                    | 100 (30%) | 232 (70%) |
| Sensitization to bird feather                              | 47 (14%)  | 285 (86%) |
| Sensitization to dust                                      | 82 (25%)  | 250 (75%) |

| Table 2: The relation between the occurrence of food hypersensitivity reaction (FHS) to seafish and the occurrence of food hypersensitivity reaction to tomato, kiwi, apple, spices, peanut, orange, capsicum, tangerine, celery and carrot in 332 patients |
|---------------------------------------------------------------|
| **Followed parameters**                                      | **Tomato** | **Kiwi** | **Apple** | **Spices** | **Peanuts** |
| FHR to seafish yes                                           | 6 (2%)     | 9 (3%)   | 8 (2%)    | 9 (3%)     | 10 (3%)     |
| FHR to seafish no                                            | 65 (20%)   | 53 (16%) | 47 (14%)  | 55 (16%)   | 59 (18%)    |
| Total number of patients                                     | 65 (20%)   | 53 (16%) | 47 (14%)  | 55 (16%)   | 65 (20%)    |
| P                                                              | 0.701      | 0.290    | 0.290     | 0.307      | 0.701       |
| FHR to seafish yes                                           | 3 (1%)     | 3 (1%)   | 7 (2%)    | 12 (4%)    | 1 (0.3%)    |
| FHR to seafish no                                            | 49 (15%)   | 32 (9%)  | 52 (16%)  | 24 (7%)    | 19 (6%)     |
| Total number of patients                                     | 52 (15%)   | 35 (10%) | 59 (18%)  | 36 (11%)   | 52 (15%)    |
| P                                                              | 0.222      | 0.688    | 0.715     | 0.000*     | 0.405       |

Explanation: + = FHR reactions confirmed, − = no FHR. *The significant direct relation between the occurrence of FHR to celery and the occurrence of food hypersensitivity reaction to fish was confirmed; the coefficient of concordance (CC) was calculated to see in which direction the dependence worked.
The major fish allergens are the parvalbumins. Clinical studies have revealed that over 95% of fish allergy patients are sensitized to parvalbumin. They are members of the calcium-binding EF-hand protein family characterized by a conserved protein structure. They represent highly cross-reactive allergens for patients with specific IgE to conserved epitopes. In addition to the parvalbumins, several other fish proteins, enolases, aldolases, and fish gelatin, seem to be important allergens. Tropomyosin is a 34–38-kDa microfibrillar protein and its amino acid sequence is highly conserved among shellfish, as well as house dust mites and cockroaches. While tropomyosin is regarded as a major allergen in shellfish, recent studies reveal that patients with shellfish allergy can also develop hypersensitive reactions against other shellfish proteins such as arginine kinase and sarcoplasmic Ca-binding proteins. On the other hand, fish is a major source of long-chain omega-3 fatty acids. In recent decades, a decrease in consumption of omega-3 PUFAs, prevalent especially in oily fish, has been proposed to contribute to the increased prevalence of allergic diseases. A causal link between increased intake of omega-6 (n-6) PUFAs and increased incidence of allergic disease has been suggested. This is supported by biologically plausible mechanisms, related to the roles of eicosanoid mediators produced from the n-6 PUFA arachidonic acid. Epidemiological, ecological, and case-control studies have associated differences in the patterns of exposure to omega-6 (n-6) and omega-3 (n-3) PUFAs with differences in the incidence and prevalence of atopic sensitization or its clinical manifestations (allergies, atopic eczema, hay fever, and allergic asthma). Thus, n-3 PUFAs may protect against allergic sensitization and allergic manifestations. According to some studies, maternal fish intake during pregnancy has been reported to reduce risk of allergic outcome, including sensitization, in infants and children. Fish consumption in infancy has been studied as the time of introduction in some studies and as the frequency of intake in other studies. In most studies, fish in the child’s diet has been associated with reduced risk of eczema, rhinitis, wheeze, and asthma up to preschool age. However, there have also been reports of no association with allergic disease. Some studies also demonstrated that antifungal potency may be due to the abundance of linoleic and α-linolenic acids in the major fraction of fatty acids methyl esters. It may explain especially the significantly higher occurrence of allergy to fungi in patients, who eliminate fish from their diet. Regarding our previous studies, we confirmed that the occurrence of sensitization to fungi was significantly higher in patients, who suffered from FHRs to nuts and fish and who eliminated these foods.

According to Dhar, diagnosis of food allergy is not based on history or clinical examination. Parents giving a history of exacerbation of AD due to food should not be taken as a reliable indicator. There are many tests available but must be interpreted properly as there is a high rate of false-positive reaction with low predictive value. In India, Dhar assessed the severity of AD in infants and children after eliminations of certain dietary items. The study group comprised 100 children with AD. Their severity of itching, surface area of involvement, and SCORAD index were measured; 100 selected patients were advised to strictly adhere to a diet excluding milk and milk products, all kinds of nuts and nut-containing foods, egg and egg-containing foods, seafish and prawns, branjal and soybean for a

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**Complement to Table 2: The significantly rising occurrence of reactions to celery in patients suffering from reactions to seafish**

| Followed parameters | FHR to seafish yes | FHR to seafish no |
|---------------------|--------------------|------------------|
| Celery (+)          | 12 (34%)*          | 24 (8%)*         |
| Celery (−)          | 23 (66%)           | 273 (92%)        |
| Total number of patients | 35 (100%)       | 297 (100%)       |

In patients with reactions to seafish, the reaction to celery is in 34%; in patients without reactions to seafish, the reaction to celery is in 8%. *The difference is statistically significant

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**Table 3: The relation between the occurrence of reactions to seafish and the occurrence of positive family history about atopy, asthma bronchiale, rhinitis, onset of AD under 5 years of age, and persistent lesions in 332 patients**

| Followed parameters | Family history | Asthma bronchiale | Onset of AD | Rhinitis | Lesions |
|---------------------|----------------|-------------------|-------------|----------|---------|
|                     | Positive | Negative | Yes | No | Under 5 y | Later | Yes | No | Persistent | Occasional |
| FHR to seafish yes | 23 (7%) | 12 (4%) | 19 (6%) | 16 (5%) | 30 (9%) | 5 (2%) | 31 (9%) | 4 (1%) | 29 (9%) | 6 (2%) |
| FHR to seafish no  | 167 (50%) | 130 (40%) | 127 (38%) | 170 (51%) | 221 (67%) | 76 (23%) | 224 (70%) | 73 (22%) | 175 (53%) | 122 (37%) |
| Total number of patients | 190 (57%) | 142 (43%) | 146 (44%) | 186 (56%) | 251 (76%) | 81 (25%) | 255 (77%) | 77 (23%) | 204 (61%) | 128 (39%) |
| P                  | 0.238    | 0.194    | 0.141    | 0.081    | 0.006*, CC=0.542 |

FHR: Food hypersensitivity reactions. *The significant direct relation between the occurrence of FHR to seafish and persistent lesions of AD was confirmed; the coefficient of concordance (CC) was calculated to see in which direction the dependence worked.
Complement to Table 3: The significantly rising occurrence of persistent eczematous lesions in patients suffering from reactions to seafish

| Followed parameters | FHR to seafish yes | FHR to seafish no |
|---------------------|--------------------|------------------|
| Persistent lesions (+) | 29 (82%)* | 175 (59%)* |
| Persistent lesions (−) | 6 (18%) | 122 (41%) |
| Total number of patients | 35 (100%) | 297 (100%) |

In patients with reactions to seafish, the occurrence of persistent eczematous lesions is in 82%; in patients without reactions to seafish, the occurrence of persistent eczematous lesions is in 59%. *The difference is statistically significant.

Complement to Table 3: The rising occurrence of asthma bronchiale in patients suffering from reactions to seafish

| Followed parameters | FHR to seafish yes | FHR to seafish no |
|---------------------|--------------------|------------------|
| Asthma bronchiale (+) | 19 (54%) | 127 (43%) |
| Asthma bronchiale (−) | 16 (46%) | 170 (57%) |
| Total number of patients | 35 (100%) | 297 (100%) |

In patients with reactions to seafish, the occurrence of asthma bronchiale is in 54%; in patients without reactions to seafish, the occurrence of asthma bronchiale is in 43%. The difference is not statistically significant.

Complement to Table 3: The rising occurrence of the onset of AD under 5 years of age in patients with reaction to seafish

| Followed parameters | FHR to seafish yes | FHR to seafish no |
|---------------------|--------------------|------------------|
| Onset of AD under 5 years of age (+) | 30 (85%) | 221 (74%) |
| Onset of AD later (−) | 5 (15%) | 76 (26%) |
| Total number of patients | 35 (100%) | 297 (100%) |

In patients with reaction to seafish, the onset of AD under 5 years of age is recorded in 85%; in patients without reactions to seafish, the onset of AD under 5 years of age is recorded in 74%. The difference is not statistically significant.

tolerance to restricted food when reintroduced to the diet after restriction for 6–12 months. Parents should be advised to give complementary food rich in nutrients if elimination diet is followed. According to another study, it has been well documented that avoidance of allergic foods is not preventive of food allergy. Emerging evidence from randomized controlled trials suggests that early introduction of allergenic foods, specifically peanut, is protective against the development of food allergy. Recent findings from interventional studies have prompted a shift in the mind set from avoidance to early introduction of potentially allergenic foods. Consensus statements from various global allergy, pediatric, and dermatology societies have been published encouraging the early introduction of peanut to infants at risk of developing food allergy. From this, Australasian guidelines have been updated to include the introduction of allergenic solid foods including peanut butter, cooked egg, dairy, and wheat products to all children in the first year of life, including those at high risk of allergy.

Conclusion

Seafood allergy is one of the most common food allergies; on the other hand, fish is also a major source of long-chain omega-3 fatty acids. In recent decades, a decrease in consumption of omega-3 PUFAs has been proposed to contribute to the increased prevalence of allergic diseases. In this study, we evaluated the relation between the occurrence of FHR to seafish and the occurrence of other atopic diseases and parameters in AD patients. The FHR to seafish was confirmed in 11% of
patients. These patients suffer significantly more often from persistent eczematous lesions of AD and from the higher occurrence of sensitization to fungi and reactions to celery. The occurrence of bronchial asthma, rhinitis, positive family history, and onset of AD under 5 years of age was higher in these patients also, but the difference is not statistically significant. According to our results, the FHRs to fish in AD patients might increase the risk of the occurrence of persistent eczematous lesion and increase the risk of bronchial asthma and rhinitis.

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Conflicts of interest
There is no conflict of interest.

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Table 4: The relation between the occurrence of reactions to seafish and the occurrence of inhalant allergy (trees, grass, mites, animal dander, fungi, dust, and bird feather) in 332 patients

| Followed parameters | Sensitization to aeroallergens | P | 0.392 | 0.210 | 0.826 | 0.402 | 0.034* CC=0.362 | 0.574 | 0.294 |
|---------------------|------------------------------|---|--------|--------|--------|--------|-----------------|--------|--------|
| FHR to seafish yes  | 20 (6%)                      | 15 (5%) | 27 (8%) | 8 (2%) | 22 (7%) | 13 (4%) | 16 (5%) | 16 (5%) | 19 (6%) | 10 (3%) | 25 (7%) | 7 (2%) | 28 (8%) |
| FHR to seafish no   | 147 (45%)                    | 150 (45%) | 198 (60%) | 99 (30%) | 181 (55%) | 116 (34%) | 139 (42%) | 158 (48%) | 84 (25%) | 213 (64%) | 72 (22%) | 225 (68%) | 40 (12%) | 257 (78%) |
| Total number of patients | 167 (50%) | 165 (50%) | 225 (68%) | 107 (32%) | 203 (62%) | 129 (38%) | 158 (48%) | 174 (53%) | 100 (30%) | 232 (70%) | 82 (25%) | 250 (75%) | 47 (14%) | 285 (86%) |

Pairs of these categories were entered in the contingency tables and the Chi-square test for relationship of these variables was performed with the level of significance set to 5%. The significant direct relation* between the occurrence of reactions to seafish and the sensitization to mixture of fungi was confirmed; the coefficient of concordance (CC) was calculated to see in which direction the dependence works.

Complement to Table 4: The significantly rising occurrence of reactions to seafish from food hypersensitivity reactions to seafish increased the risk of the occurrence of persistent eczematous lesion and increase the risk of bronchial asthma and rhinitis.

| FHR to seafish yes | Fungi (−) | 16 (5%) | 20 (6%) |
|-------------------|-----------|--------|--------|
| FHR to seafish no | 10 (2%)   | 100 (40%) |
| Total number of patients | 100 (30%) | 270 (80%) | 297 (100%) |

P = 0.034* CC = 0.362

The significant direct relation* between the occurrence of reactions to seafish and the sensitization to mixture of fungi was confirmed; the coefficient of concordance (CC) was calculated to see in which direction the dependence works.

In patients with reactions to seafish, the sensitization to fungi is in 46%; in patients without reactions to seafish, the sensitization to fungi is in 28%. *The difference is statistically significant.
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