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Food Allergy and Atopic Dermatitis: How Are They Connected?

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Abstract Food allergy predominantly affects children rather than adults with atopic dermatitis (AD). Early food sensitization has been found to be significantly associated with AD. Three different patterns of clinical reactions to food allergens in AD patients have been identified: 1) immediate-type symptoms, 2) isolated eczematous late-type reactions, and 3) combined reactions. Whereas in children, allergens from cow's milk, hen's egg, soy, wheat, fish, peanut, or tree nuts are primarily responsible for allergic reactions, birch pollen–related food allergens seem to play a major role in adolescent and adults with AD in Central and Northern Europe. Defects in the epidermal barrier function seem to facilitate the development of sensitization to allergens following epicutaneous exposure. The relevance of defects in the gut barrier as well as genetic characteristics associated with an increased risk of food allergy remain to be further investigated. Many studies focus on sufficient strategies of prevention, which actually include breastfeeding or feeding with hydrolyzed formula during the first 4 months of life.

Keywords Allergens · Atopic dermatitis · Food allergy · Sensitization · Pathogenesis · Prevention · Prevalence

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by a course of exacerbations and remissions. Several exogenous and endogenous triggers, such as seasonal and perennial allergens, have been identified. A subgroup of AD patients additionally suffer from food allergy. Many studies have addressed the frequency of sensitizations to food allergens rather than investigating the prevalence of clinically relevant food allergy. To date, most of the prevalence data available refer to children rather than adult AD patients. Although the clinical reaction pattern to food allergens could be well-defined, the pathogenesis of food allergy in AD patients is still not fully understood. Preliminary results—mainly from animal models—indicate that defects in the epidermal and the gut barrier function may facilitate sensitization to allergens through epicutaneous and gastrointestinal exposure. However, the relevance of barrier defects in AD patients to the development of food allergy remains to be elucidated in more detail. Further knowledge on the pathogenesis of food allergy in AD patients also would be essential for the identification of sufficient strategies of prevention and would help us to understand how food allergy and AD are connected.

Prevalence and Course of Disease

A subset of children and a minority of adult patients suffer from a combination of AD and food allergy. The diagnostic procedures indicated to confirm the diagnosis of food allergy, in particular late-type reactions, remain time-consuming because double-blind, placebo-controlled food challenges need to be performed. This may explain why studies addressing the prevalence of food allergy in AD show a broad methodologic variety. Studies frequently focus on the assessment of sensitization via IgE to food allergens rather than on the results of oral food challenges, which are still recommended as the diagnostic "gold standard."

Data from previous studies based on the outcome of oral food challenges indicate that approximately one third of children with severe AD suffer from IgE-mediated food allergy [1, 2]. Many studies address the identification of possible predictors of the development of food allergy in children. In a large cohort study of 2,184 children from 12 countries, early-onset eczema was found to be associated with high-risk IgE levels of food sensitization [3•]. In children whose eczema developed before age 3 months, the frequency of high-risk IgE levels to milk, hen's egg, and/or peanut was the greatest. The lowest frequency of high-risk IgE levels was observed for manifestation of eczema after 12 months. Interestingly, children with high-risk IgE levels had the most severe eczema and the youngest age at onset. Because oral food challenges were not performed, the clinical relevance of the IgE levels and prevalence of food allergy in this study population remains unclear.

Regarding the course of food allergy, it is well-known that about 50% to 80% of children with allergy to milk or hen's egg develop tolerance until school age. In a prospective, population-based cohort study, the natural history of allergic sensitization in children was examined (age 0–6 years) [4]. In 53% of children with eczema and sensitization at 6 years, sensitization to food allergens already had been observed at 6 months of age. Moreover, early food sensitization assessed by specific IgE between 3 and 18 months of age was found to be significantly associated with AD and asthma. Further longitudinal analyses in this cohort by the same research group also included 120 food challenges in 66 children over a 6-year period [5]. Food allergy was diagnosed in 15% of the children with AD. It should be emphasized that in this study, (isolated) late-type reactions occurring 1 day following food exposure may have been missed because late-type reactions were not assessed by physical examination, but rather by telephone call. In addition, most of the food challenges were performed with an open protocol. The highest prevalence of food allergy was observed at 18 months of age (3.6%). In accordance with the studies cited above, children suffering from food allergy were more frequently sensitized and showed higher IgE levels.

In a retrospective study, oral food challenges of 125 children (median age, 4 years), 96% of whom suffered from AD, were evaluated [6•]. The aim of the study was to assess in how many cases an elimination diet that had been recommended previously had been necessarily indicated. The children who were included were on an elimination diet excluding foods that they had never eaten or had once tolerated without a known reaction based on in vitro diagnostic results. Patients excluded from oral food challenges were those with a history of a life-threatening reaction; a convincing reaction within the past 6 to 12 months, but also with high food-specific serum IgE levels (ie, ImmunoCAP assay [Phadia AB, Uppsala, Sweden] levels exceeding previously published 95% predictive values for milk, hen's egg, peanut, or fish); or a clearly positive skin prick test reaction. The authors stated that 1) in the majority of cases (89%), elimination diet was unnecessary, and 2) food allergy was overdiagnosed due to reliance on IgE test results.

Food allergy predominantly affects children (rather than adults) with AD and commonly represents a transitory phenomenon due to the development of tolerance. This may contribute to the fact that in adult patients with AD, studies investigating the co-prevalence of AD and food allergy are still scarce. In a subgroup of adult AD patients (17 of 37) sensitized to birch pollen, birch pollen–associated food allergens could be identified as a specific trigger of AD [7].

The results of a population-based study in Germany involving 1,739 unselected patients who had completed questionnaires confirmed that food allergy in adult AD patients is rare [8]. While 23.5% individuals initially reported suffering from AD, further examinations revealed that only in 28 patients (1.6%) could the diagnosis of current AD be confirmed. Nine of 27 patients who had undergone further diagnostic procedures such as skin prick testing and determination of IgE were presented with oral food challenges with suspected food allergens. Although five of nine were negative, oral allergy syndrome was observed in three individuals, and a significant worsening of AD following oral food challenge occurred in one individual.

In summary, children with high-risk IgE levels demonstrate the most severe eczema and have the youngest age at onset. Early food sensitization (at between 3 and 18 months of age) has been found to be significantly associated with AD. Food allergy in children with AD may be overdiagnosed; however, late-type reactions may be underdiagnosed because of the study designs of food challenges. In adults suffering from AD, further prospective studies, including placebo-controlled oral food challenges, in large cohorts are still needed to assess the frequency of clinically relevant food allergy.

Clinical Features of Food Allergy in Atopic Dermatitis

A subgroup of patients with AD may additionally suffer from food allergy. In these cases, food allergy may act as a trigger of eczema. Therefore, three different clinical patterns are described after ingesting food [10]:

1. Immediate-type symptoms such as erythema, angioedema, urticaria, but no eczema, bronchial, gastrointestinal, or cardiovascular symptoms of anaphylaxis, which appear within minutes after ingesting the relevant food.
2. Isolated, eczematous, late-type reactions, which normally appear as flare-ups of typical eczematous lesions occurring within hours to 2 days after ingestion.
3. Combined reaction pattern of non-eczematous, immediate-type reactions and eczematous, late-type reactions.

Breuer et al. [10] performed 106 oral provocation tests in children suffering from AD with suspected food allergy, noting a positive reaction in 46%, 12% of which showed isolated late eczematous reactions and 45% combined reactions; the rest suffered from isolated immediate-type reactions. It must be noted that considering the time-consuming procedure of evaluating a possible late-type reaction, this clinical feature may be underdiagnosed in the literature.

Allergens

The gold standard procedure for diagnosing food allergy is the oral provocation test, which, particularly in AD, should be performed in a double-blind, placebo-controlled manner. Only a few studies are available investigating the prevalence and thereby the relevant food allergens in AD via oral food challenges. Data from these studies demonstrate that in children with AD, food allergy often occurs in early childhood and is caused by cow's milk, hen's egg, soy, wheat, fish, peanuts, or tree nuts in about 90% of the cases [11•]. Allergies to seafood, peanuts, and nuts are more likely to persist, whereas allergies to milk, eggs, wheat, and soy generally resolve by late-childhood [12].

Among adults, allergies to cow's milk, wheat, and hen's egg are rare, although exact data are not available. Aside from allergies persisting since childhood, in Northern and Central Europe, allergies to birch pollen–related foods (hazelnut, carrot, celery, apple) are more common. However, birch pollen–associated food allergy also may be clinically relevant in younger children, especially children with severe AD and a high sensitization level to birch pollen [10]. Recent studies focused on the sensitization pattern by means of recombinant allergens (hazelnut, peanut, apple, carrot) to obtain more detailed information about a potential risk of severe anaphylactic reactions and possible mechanisms of sensitization. In cases in which food allergy is based on cross-reactivity to birch pollen, the sensitization to the major allergen of apple, Mal d 1, is usually associated with mild allergic symptoms such as the oral allergy syndrome, while sensitization to Mal d 3 is associated with a greater risk of systemic reactions [13]. Celery [14] and carrot [15] more frequently induce systemic reactions than apple [16], hazelnut [17], or cherry [18]. As a further relevant allergen in patients with cross-reactivity to birch pollen, Gly m 4 has been identified and can be associated with severe systemic reactions [19, 20]. Due to very low concentrations of Gly m 4 in soy, clinically relevant reactions mostly occur after ingestion of high amounts of soy (eg, in protein shakes). Additional soy allergens—without homology to pollen allergens—associated with a higher risk of severe systemic reactions are Gly m 5 and Gly m 6 [21]. Regarding the allergens of peanut, sensitization to the allergens Ara h 1, Ara h 2, Ara h 3, and Ara h 9 seems to be associated with more severe reactions than sensitization to Ara h 5 and Ara h 8. Only for Ara h 8 and Ara h 5 could homologies to the birch pollen allergens Bet v 1 and Bet v 2 be identified [22, 23].

All studies based on assessment of the sensitization pattern by means of recombinant allergens included patients suffering from food allergy or showing sensitization to food allergens. Future studies need to investigate whether patients with AD show a different sensitization pattern to recombinant food allergens compared with patients with suspected food allergy but without AD.

Pathogenesis of Food Allergy in Atopic Dermatitis

Epidermal Barrier Dysfunction

Sensitization to food allergens may occur even though the food in question has not yet been integrated into the diet. This phenomenon may be a result of epidermal skin barrier defects. These defects can be based on genetic factors such as filaggrin (*FLG*) mutations, other mutations in the epidermal differentiation complex located on chromosome 1q21 [24•], or variations in the expression due to the cytokine milieu [25]. A skin barrier defect such as mutations in the *FLG* gene strengthens the "outside–inside" theory of AD, which proposes skin barrier defects as one initiating pathogenetic factor in AD resulting from alleviated penetration of an allergen through the skin—especially inhalant allergens—and leading to allergic skin inflammation. In animal models, it has been shown that sensitization to food proteins through epicutaneous exposure, especially after removal of the stratum corneum or genetically impaired skin barrier, is stronger than it is via other routes

[26–28] and favors a T-helper type 2 immune response typical of acute AD lesions with production of interleukin-4 and IgE [29, 30]. Once epicutaneous sensitization has occurred, normal oral tolerance to the allergens cannot be achieved. The best known genetic factor is the *FLG* null or loss-of-function mutation, which can be found in up to 50% of patients with severe AD. *FLG* belongs to the epidermal differentiation complex and is important for skin barrier function and skin hydration. It has been shown that *FLG* mutations are associated with a higher risk of allergic sensitizations and allergic disorders (eg, allergic rhinitis and allergic bronchial asthma), which leads to the question of whether percutaneous exposure leads to early sensitization. Clinical data support the findings from animal models.

In a cohort study of 13,971 preschool children, Lack et al. [31] observed that application of peanut oil containing creams increased the risk of developing an allergy to peanut (OR, 6.8). However, for the development of clinically manifest food allergies, no association with *FLG* mutations could be demonstrated [32].

Gut Barrier Dysfunction

Food allergy may be the result of a failure to develop tolerance or the loss of preexisting tolerance. This may be caused by defects in immune or nonimmune barriers (eg, defective digestive process; abnormalities in the development of regulatory T cells, soluble IgA, Peyer's plaques, and associated dendritic cells, which are critical for induction tolerance) [33]. Tight junctions among the epithelial cells represent a further barrier controlling the uptake of allergenic material from the gut lumen. For a disruption of this physical barrier (eg, due to physiologic stress or bacterial infections), a higher risk of the development of sensitization has been shown [34].

Whether other factors, such as the bacterial colonization of the gut, have an impact on the risk of developing sensitization to foods is in need of further investigation. Actual data show no differences in the bacterial pattern of patients with or without sensitization to food [35].

Immune Response

The gastrointestinal tract contains a major part of the immune system, with several immunologic cellular and humoral components that build the immunologic homeostasis between the host immune system and the gut environment. In particular, interactions among immunocompetent cells of the host's immune system (eg, T cells, dendritic cells, endothelial cells, and basophils) as well as immunologic modification induced by dietary material [34, 36] and bacterial products (eg, CpG and adenosine triphosphate) are important factors for the development and maintenance of immunologic tolerance, and their dysregulation may have an impact in leading to the development of food allergies.

There is evidence that certain individuals have a genetic background to favor a T-helper type 2 cytokine profile and abnormal IgE response following development of allergy. There may be genetic factors increasing the risk of allergy to particular foods. In studies on *HLA* in relation to different food allergens, genetic differences were found for peanut-allergic patients, but not in those allergic to cow's milk [37].

Specific IgE and specific T cells play an important role in the pathogenesis of food allergy in AD. Predictive parameters for the outcome of oral food challenges can be serum levels of specific IgE, which are shown for immediate-type reactions to foods [38, 39]. Specific T cells must be shown to be involved in the development of late eczematous reactions. T-cell clones and cutaneous lymphocyte-associated antigen–positive lymphocytes generated from patients with food-induced eczema showed higher proliferative responses than those from nonresponders [9, 40–42] and released significantly greater amounts of tumor necrosis factor–α or interleukin-10 [43]. Murine data confirmed the important role of specific T cells in food-induced AD [44]. Patients sensitized to pollen allergens often develop an IgE response to cross-reactive food allergens. In AD patients, this reaction also may lead to exacerbation of AD, with a birch pollen–specific T-cell response in adults and children [7, 10]. More recently, Bohle et al. [45] showed that T-cell cross-reactivity between Bet v 1 and related food allergens is not restricted to IgE-reactivity, so that cooked food can also induce late eczematous reactions and a T-cell–, but not an IgE-mediated response in vitro.

Nutritional Aspects of Prevention

In the past, food allergy prevention strategies mainly focused on avoidance of allergens during infancy. However, in recent years, more and more studies have addressed the induction of oral tolerance; therefore, clinical recommendations regarding prevention have been revised [46].

Breastfeeding and Formula

The updated prevention strategies for the development of atopic diseases still highly recommend breastfeeding for all infants, irrespective of atopic heredity [47]. The expert group from the Section on Pediatrics of the European Academy of Allergology and Clinical Immunology (SP-EAACI) states that for high-risk infants, one of the most effective dietary regimens is exclusively breastfeeding for

at least 4 to 6 months, or exclusive feeding with formulas whose reduced allergenicity has been proven. High-risk infants are defined as those having at least one allergic parent or biological sibling.

Upon first view, the results of a recently published study by Kusunoki et al. [48] appear to be contradictory to the current recommendations with regard to breastfeeding. In this questionnaire-based survey study from Kyoto, Japan, parents of 13,100 schoolchildren 7 to 15 years of age were included [48]. The parents were asked to describe feeding patterns in infancy (complete, mixed/artificial, artificial) as well as confounding factors such as family history of allergic diseases, eczema within 6 months after birth, and food allergy in infancy (to hen's egg, milk, or wheat within the first year of life). In a univariate analysis, the prevalence of AD and food allergy was found to be significantly higher in those children who had been breastfed exclusively compared with those who had undergone mixed or complete artificial feeding. However, multivariate analysis taking into account the confounding factors revealed no significant difference. These results point to the relevance of reverse causation, which should be taken into account when statistical analyses are interpreted.

A recently published meta-analysis including 18 clinical trials and intervention studies confirmed the recent recommendations of prevention and, moreover, addressed the question of which formula should be recommended in cases in which breastfeeding is not (exclusively) performed [49]. Following the results of this meta-analysis, exclusive breastfeeding is recommended in the first months as well. In cases in which supplementation or exclusive use of a formula is indicated, a 100% whey protein, partially hydrolyzed formula reduced the risk of AD compared with feeding with intact cow's milk formula in infants, particularly those with a family history of allergy. These results are not contradictory to the guidelines provided by the SP-EAACI. However, the SP-EAACI emphasizes that in cases in which breast milk is not available, those "formulas with documented reduced allergenicity for at least 4 months" should be used [47].

Data from a follow-up study to the large German Infant Nutritional Intervention study confirm the long-term effect on prevention of AD (until the age of 6 years) conferred by hydrolyzed infant formulas in high-risk children during the first 4 months of life [50].

Introduction of Solid Food

Following the period of breastfeeding and/or administration of hydrolyzed formula, introduction of solid food is indicated. The SP-EAACI recommends the avoidance of solid food for at least 4 months [47]. From previous studies, no benefit from a delayed introduction of solid foods for the prevention of eczema can be concluded [51]. In children who already suffer from eczema, solid food should be introduced carefully in a "step-by-step" manner. Accompanying clinical symptoms such as immediate-type symptoms or worsening of eczema following ingestion should be documented in a diary, and the decision to proceed further should be discussed with the attending physician.

Essential Fatty Acids

In the evidence-based German guidelines for primary prevention of allergy (including eczema), a beneficial effect of fish consumption during the first year of life is noted [52]. The effect of maternal intake of fish oil during pregnancy and lactation (25th gestational week up to 3 to 4 months of breastfeeding) on the incidence of allergic disease in infancy was further investigated in a recent randomized, placebo-controlled trial [53]. Interestingly, from the first 6 to 12 months, the period prevalence of IgE-associated eczema in those consuming fish oil was significantly lower compared with those receiving placebo. Moreover, food allergy occurred less frequently during the first year of life.

Anandan et al. [54] addressed the usefulness of supplementation of omega-3 and omega-6 fatty acids for primary prevention of allergic disease. For this purpose, a systematic review and meta-analysis was performed in which at least 10 reports out of 3,129 articles were eligible. Based on the findings of four studies comparing omega-3 oils with placebo and on two studies comparing omega-6 oils with placebo, no consistent benefit for the prevention of AD or food allergy could be identified. Based on this meta-analysis, supplementation with omega-3 and omega-6 oils cannot be recommended for primary prevention of atopic allergic disease.

Blackcurrant seed oil (BCSO) represents an additional source that is rich in essential fatty acids. For this reason, Linnamaa et al. [55] focused on the preventive effects of BCSO administered to 151 pregnant or lactating mothers from the 8th to 16th week of gestation until cessation of breastfeeding, and their children until 2 years of age. Olive oil served as the control (n=162). A transiently reduced prevalence of AD at age 12 months could be observed. The authors concluded that BCSO may be useful for prevention in early life.

Taken together, maternal consumption of fish during pregnancy seems to have a preventive effect on the development of eczema and food allergy. In contrast, direct supplementation of essential fatty acids currently cannot be recommended for allergy prevention. Regarding the promising preliminary data cited above, the effect of essential fatty acids on the development of atopic manifestations should be investigated further, and data should be collected from prospective long-term studies.

Probiotics and Prebiotics

Based on the hypothesis that the pattern of intestinal colonization during infancy influences the risk of allergic diseases, many studies have focused on the effects of primary prevention by probiotics and prebiotics.

Lactobacillus and *Bifidobacterium* spp and *Saccharomyces boulardii* are the most commonly used probiotics [56]. In their study, Kalliomaki et al. [57] demonstrated promising results, with a significant reduction in the incidence of AD in the *Lactobacillus GG* group until age 7 years. This preventive effect could not be confirmed by further studies with a similar methodologic design [58, 59]. Kim et al. [60] recently published further data from a double-blind, randomized, placebo-controlled trial investigating a probiotic mixture of *Bifidobacterium bifidum* and *Lactobacillus acidophilus* used for prenatal and postnatal supplementation. The infants of those mothers who had received the probiotic mix during the last weeks of pregnancy up to 6 months after delivery suffered significantly less frequently from AD until age 1 year.

In two prospective, randomized, placebo-controlled trials, the beneficial effects of prebiotics on the development of AD could be observed in high-risk infants with use of a prebiotic mixture of galacto- and long-chain fructooligosaccharides administered during the first 6 months of life [61]. This effect could be confirmed as lasting for the first years of life [62]. In a recently published European multicenter study, infants with low atopy risk were recruited before age 8 weeks and randomly assigned to receive an immunoactive prebiotic formula (n=414) or a control formula (n=416) [63]. A total of 300 breastfed infants were observed as well. In the prebiotic group, a significantly lower rate of AD up to the first birthday could be observed compared with the control group fed with regular formula. The effect of probiotics/prebiotics on the prevention of food allergy has been investigated in a few studies without evidence of a beneficial effect.

Conclusions

Food allergens have been identified as a trigger of AD in a subgroup of pediatric and adult patients. The frequency of this phenomenon remains to be assessed more accurately by further studies, including double-blind, placebo-controlled food challenges. Moreover, physical examination also should be performed 1 day after the challenge to reliably assess late-type reactions.

Many studies have characterized relevant food allergens in different age groups. However, future studies should address the question of whether the sensitization pattern to food allergens in patients with AD differs from that of those patients with suspected food allergy but without AD.

Regarding the pathogenesis, interesting data have been published indicating that a dysfunction of the epidermal and gut barrier may contribute to the development of food allergy in AD. Further studies in humans are needed to elucidate the immunologic pathways in more detail.

Although data have been published supporting a preventive effect of probiotics/prebiotics on AD, clinical and immunologic effects remain to be confirmed in additional prospective studies. The immunoactive agents and the mode of action of a prebiotic/probiotic mix as well as the time frame of administration and the dosage need to be defined more exactly. Moreover, criteria for those infants who may benefit from prebiotic/probiotic formula remain to be identified in the future.

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