

The Role of Food Allergy in Atopic Dermatitis

Pia J. Hauk, MD

Corresponding author

Pia J. Hauk, MD

Department of Pediatrics, National Jewish Medical and Research Center, J320, 1400 Jackson Street, Denver, CO 80206, USA.

E-mail: haukp@njc.org

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Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease affecting more than 10% of all children. Sensitization to foods triggers isolated skin symptoms in about 30% of children. These symptoms include immediate reactions within minutes after ingesting food without exacerbation of AD and early and late exacerbations of AD. It is important to identify clinically relevant sensitizations to foods using skin prick tests, a specific IgE blood test (ImmunoCAP; Phadia, Portage, MI, USA), and double-blind, placebo-controlled food challenges to initiate appropriate dietary interventions and avoid unnecessary dietary restrictions. Children with AD triggered by food allergens demonstrate a distinct immune response upon stimulation of their peripheral blood mononuclear cells with food allergen. A defective skin barrier and increased intestinal permeability appear to facilitate allergen sensitization. Appropriate skin care to maintain skin barrier function and dietary avoidance of highly allergenic foods during infancy may help to prevent allergen sensitization, thereby reducing the severity of AD and food allergies.

Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease [1] that affects more than 10% of all children at some time during childhood [2]. During infancy, the face, scalp, and extensor surfaces of the extremities are most affected. In older children, acute eczema lesions with dry, erythematous, and excoriated skin occur more commonly in the flexural areas of the body. Associated pruritus frequently leads to scratching and breakdown of the skin barrier, allowing the entry of environmental allergens and pathogens and perpetuating chronic skin inflammation. Intense itching contributes to

sleep disturbance and an overall decrease in quality of life for affected patients and their families [3].

AD is frequently associated with allergic sensitization, elevated serum IgE levels, and a family history of atopic diseases [1]. Despite ongoing controversy about the role of food allergens in AD [4], numerous studies have established that food allergies play a pathogenic role [5,6], and food allergy and atopic dermatitis often occur together [7]. Based on oral challenges, three patterns of cutaneous reactions to food have been described in patients with AD [8,9]: immediate reactions, within minutes after ingesting food, without exacerbation of AD; early exacerbations of AD related to pruritus and scratching; and late exacerbations of AD. Immediate skin reactions present as an erythematous rash, urticaria, and angioedema; they can be complicated by gastrointestinal, respiratory, and cardiovascular symptoms of anaphylaxis. Late exacerbations of AD develop after 6 to 48 hours and may occur after immediate-type reactions.

Prevalence of Food Allergy in Atopic Dermatitis

The prevalence of food allergy in patients with AD depends on the age of the patient and the severity of the AD. Based on double-blind, placebo-controlled food challenges (DBPCFCs), the prevalence of food allergy in infants and young children with AD can be estimated at 40% [6,7,10]. Seven foods—cow's milk, egg, soy, wheat, peanut, fish, and cashew—accounted for 89% of the positive challenges in patients with AD who were between the ages of 4 months and 21.9 years [10]; 99% could be correctly identified using screening skin prick tests (SPTs). In younger children with AD, cow's milk, egg, soy, and wheat have been identified as causing about 90% of reactions [5]. Oral food challenges performed to identify food proteins that trigger AD caused cutaneous reactions (pruritic, macular, or morbilliform eruptions in sites with a predilection for AD) in 75% of all positive challenges [11,12]. Isolated skin symptoms were present in only 30%. Most reactions occurred within 1 hour of starting the food challenge, but some patients developed increasingly severe AD during repeated daily challenges. Because more than half the children with AD triggered by certain foods react with worsening eczema after oral challenges,

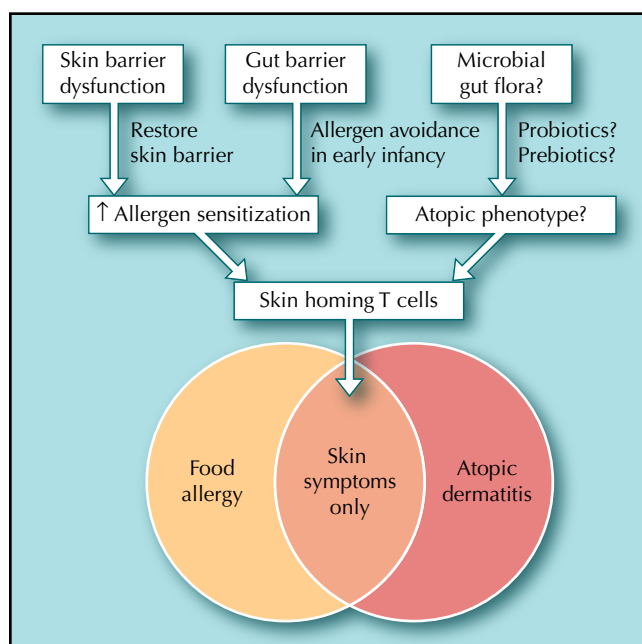


Figure 1. Pathogenic factors contributing to the development of food allergies and atopic dermatitis, with recommended interventions.

it is important to evaluate the status of the skin at 24 hours and at later time points after the challenge [13••]. Otherwise, late eczematous reactions may be missed. Based on subsequent open challenges to cow's milk and various cereals, concurrent cereal allergy was detected in 73% of 90 young children with cow's milk allergy and residual eczema or gastrointestinal symptoms on a milk-elimination diet [14]. Therefore, cereal allergy should be considered in children allergic to cow's milk who do not respond satisfactorily to a strict milk-elimination diet.

Because DBPCFCs are time-consuming procedures performed on preselected patients and include the risk of inducing an anaphylactic reaction, epidemiologic studies have been conducted to estimate the prevalence of food allergies in patients with AD. An Australian birth cohort study examined the relationship between AD and IgE-mediated allergy to cow's milk, egg, and peanut in 487 high-risk infants [15]. These children were grouped as having no AD or in quartiles of increasing severity of AD, based on topical steroid use. At age 12 months, the cumulative prevalence of AD was 28.9%. The prevalence of IgE-mediated food allergy (based on positive SPTs) and reported adverse allergic reactions to food increased with increasing AD severity. The infants most severely affected by AD had a relative risk of 5.9 for having IgE-mediated food allergy relative to those with no AD. The same authors reported evidence of IgE-mediated food sensitization to the three major food allergens (cow's milk, egg, and peanut) in more than 80% of infants with moderate to severe AD who were referred to their allergy department [16] or to a university-affiliated dermatology department [17], using 95%

positive predictive values for food-allergy reactions of SPT wheal diameters [18] and food allergen-specific IgE values in children less than 2 years of age [7].

A multicenter, international study of 2184 children with active eczema who were between 11.8 and 25.4 months of age showed the highest frequency of significantly elevated specific IgE to milk, egg, and/or peanut in infants whose eczema developed during the first 3 months of life and the least in those whose eczema occurred after 12 months [7,19•]. Of infants with severe eczema that developed before 3 months of age, 64% had high levels of food-specific IgE, indicating an association between early-onset severe AD and significant sensitization to these food allergens. In particular, the degree of sensitization to cow's milk and egg expressed in the results of radioallergosorbent tests (RAST classes) in 397 children with AD (ages 12–24 months) was found to be significantly related to severity of AD and a higher risk of persistent disease [20].

Data from the Melbourne Atopy Cohort Study, a prospective birth cohort study of 552 infants with a family history of atopic disease, showed an association between sensitization to food extracts at age 6 months and increased risk of developing eczema up to age 7 years in children not affected by AD before age 6 months [21]. However, eczema before age 6 months was also associated with an increased risk of acquiring new sensitization at 1 and 2 years of age, suggesting that allergen sensitization precedes and predicts the development of AD in some patients, whereas in others, eczema occurs prior to sensitization and predicts its development.

Pathogenesis of Food Hypersensitivity Reactions Epidermal barrier dysfunction

In many cases, sensitization to food allergens occurs in children without prior ingestion of that food. Epidermal barrier dysfunction in genetically predisposed patients with AD has been implicated in facilitating the penetration of environmental allergens and promoting allergic skin inflammation [22••]; primary systemic sensitization may follow (Fig. 1). Recently, sensitization to peanut protein has been attributed independently to the application of skin preparations containing peanut oil to inflamed skin in a large cohort of preschool children who had no prenatal sensitization from the maternal diet and negative tests for peanut-specific IgE in the cord blood [23].

Gut barrier dysfunction

Similar to a disturbed skin barrier, gut barrier dysfunction has food-allergy implications, which have been studied using intestinal permeability tests. A current review of the literature on gut barrier dysfunction concluded that constitutive defects of the intestinal barrier are not the primary cause of allergic diseases, but alterations of the mucosal immune system by infection, stress, or other

factors may contribute to food allergy in susceptible individuals by increasing intestinal permeability [24••]. A recent study reported a significant association between the severity of food allergy and food hypersensitivity reactions and an increase in the intestinal permeability index [25]. Even though the intestinal permeability test results were not strictly dependent on IgE-mediated processes, the authors suggested that increased intestinal permeability may be related to mechanisms involved in early food sensitization and development of oral tolerance in early infancy, including allergen transfer via breast-feeding and the microbial environment of the gut. Using the Ussing chamber method to quantify protein transfer across the intestinal mucosa, researchers demonstrated increased antigen transfer across the gut barrier in biopsy specimens from the upper small intestine of children with AD [26]. This transfer may initiate and perpetuate immune responses to environmental allergens, including food allergens.

The clinical implications of these findings were supported by a study of breast-fed infants with atopy, in whom breast-feeding was replaced by hypoallergenic formula. Concomitant decreases in intestinal permeability and concentrations of fecal α -1 antitrypsin and urinary eosinophil protein X were demonstrated, and Scoring Atopic Dermatitis (SCORAD) scores, a marker of AD severity, diminished [27]. Because clinically relevant sensitizations to foods frequently occur in children with AD without prior ingestion, entry of allergens through a defective skin barrier, increased intestinal permeability, or allergens in breast milk should be considered as triggers of an immune response that may lead to either systemic allergic reactions or skin inflammation.

Immune response leading to skin inflammation

Cutaneous inflammatory changes have been attributed to homing of allergen-specific T cells to the skin and to T cell–derived cytokines. In children with milk-induced AD, in vitro stimulation of their peripheral blood mononuclear cells with casein resulted in expansion of T cells positive for cutaneous lymphocyte antigen (CLA), suggesting the recruitment of casein-specific T cells to the skin [28].

When the immune response to casein of peripheral blood mononuclear cells was evaluated in 25 children with AD who were matched for age, SCORAD index, and percentage of CLA-positive T cells, children sensitized to milk showed significantly higher numbers of cultures producing tumor necrosis factor (TNF)- α or interleukin (IL)-10 than milk-tolerant children, who instead had a significant increase in cells producing interferon (IFN)- γ [29]. In this study, total IgE levels and numbers of CLA-positive T cells increased with age in patients with AD, but the different cytokine patterns produced by casein-stimulated lymphocytes, which could help distinguish immunologic features of eczema triggered by food or

other allergens or independent of them, were age-independent. However, when the cellular immune response in young children with moderate to severe AD was compared with the response in nonallergic children without eczema, children with AD showed an early impairment of production of IL-10 in response to a variety of environmental stimuli, including food allergens [30]. This response was associated with an attenuated helper T-cell (T_H1) IFN- γ response to food allergens and supports a more T_H2 -skewed cytokine pattern, as in acute AD [31]. Children with AD also had a significantly lower spontaneous production of IL-10, IFN- γ , and TNF- α compared with unaffected children [30].

In addition to CD4⁺ T cells, eosinophils have been implicated in the pathogenesis of AD [31]. Using a murine model of food allergy independent of adjuvant, researchers demonstrated that food allergens can indeed trigger cutaneous early-phase and late-phase allergic reactions [32•]. Oral ingestion of peas expressing a gene for α -amylase inhibitor-1 (α -AI) promoted an α -AI-specific IgG1 and IgE response. Subsequent food allergen challenge with α -AI in the skin elicited an early response with mast cell degranulation and the presence of immunoglobulins. The late-phase response was characterized by a lymphoid and eosinophilic infiltrate that was regulated by CD4⁺ T cells, IL-13, and eotaxin-1, consistent with clinical findings in humans.

Effects of Single Nucleotide Polymorphisms

A recent attempt was made to assess the effect of single nucleotide polymorphisms (SNPs) in cytokine-related genes on the severity of food allergy and AD in 220 Japanese children [33]. SNPs in the *IL4* (C-590T), *IL-4 receptor* (A1652G), *FCER1B* (G6842A) and *STAT6* (G2964A) genes were assessed in relation to IgE production and the role of the *IL-10* (C-627A) gene as a regulatory cytokine. Environmental confounders and clinical severity scores were correlated with SNPs. Although no single SNP detected severity of food allergy or AD, the combination of the SNP with laboratory data and environmental factors appeared to determine disease severity. In particular, the *IL-10* AA SNP, which resulted in lower IL-10 production, was significantly associated with higher serum IgE levels. More extensive studies are required to study the significance of SNPs related to food allergy and AD in populations at risk.

Diagnostic Approach to Atopic Dermatitis Related to Food Allergens

Before being referred to an allergist, children with AD suspected to be triggered by food allergens are frequently tried on elimination diets for foods that have been associated with eczema exacerbations and food allergic reactions, such as milk, egg, soy, and wheat [5].

Many clinical studies have demonstrated that eliminating relevant food allergens from the diet of the child or the nursing mother can lead to improvement in skin symptoms and that repeat challenges can lead to the return of symptoms [34]. However, unnecessarily extensive elimination diets expose the child or nursing mother to the risk of inadequate nutrition. They should be avoided by performing a thorough allergy evaluation, beginning with a detailed clinical history documenting the relationship between food exposure and symptoms of food allergy or between food-related eczema exacerbations and demonstration of sensitization to specific foods.

SPTs and measurement of specific IgE antibodies in the blood by ImmunoCAP testing (Phadia, Portage, MI, USA) detect sensitization to food allergens. Detection of sensitization by SPT is more sensitive for extracts from fresh fruits or vegetables or from baby food jars than for commercially available allergen extracts from fruits and vegetables; the fresh or baby-food extracts should therefore be preferred for SPTs when reactions to fruits and vegetables are suspected. Total IgE levels should always be measured in patients with AD who have been shown to have elevated concentrations of total IgE [35], in order to assess the ratio of total IgE to specific IgE antibodies; this ratio was reportedly inversely correlated with the severity of clinical reactions to DBPCFCs in peanut-allergic children [36].

In 97 children with food-related exacerbations of AD as confirmed by DBPCFCs, specific IgE and IgG4 antibodies to cow's milk, egg white, soybean, and wheat extracts were measured using allergy protein chips. The mean specific IgE levels to these allergens in patients with AD exacerbations after DBPCFCs were similar to those in patients with negative challenges. However, the allergen-specific IgG4 levels of patients with positive DBPCFCs were lower than in the group with negative challenges. Thus the mean specific IgE/IgG4 ratio was higher in the patients with AD who had eczema flares after DBPCFCs than in patients with negative challenges, suggesting that the function of IgG4 antibodies as blocking antibodies has to be reevaluated. IgE and IgG4 epitope mapping by microarray immunoassay, as recently reported for peanut allergen Ara h 2 [37], may provide further insight into the diversity of the immune response to complex food antigens and may help to predict the clinical response pattern in sensitized children. However, routine assessments of specific IgG values in response to foods (commercially available or offered as food allergen-specific IgG and IgE panels with results accompanied by instructions for specific elimination diets) are currently not recommended. Dietary recommendations based only on the results of such IgG food-allergen panels may put an IgE-sensitized patient at risk for a severe anaphylactic reaction if the clinical history and previous reactions to foods are not adequately considered. In addition, unnecessary dietary restrictions may be imposed when based on results of food-specific

IgG and IgE panels, leading to nutritional deficits. To avoid unnecessary dietary restrictions in patients with AD who are sensitized to many food allergens, the relevance of positive SPTs and ImmunoCAP tests to food allergens needs to be assessed by DBPCFCs or open food challenges [7,34,38].

Recently, the atopy patch test has been studied in patients with AD and food-related symptoms to see if the need for DBPCFCs can be reduced. A birth cohort of 495 unselected children was evaluated for food hypersensitivity at age 3 years, using a questionnaire, clinical examination, SPT, atopy patch test, histamine release, and specific IgE, followed by a food challenge in children with possible hypersensitivity to cow's milk or egg [39]. The atopy patch test could not predict food hypersensitivity not predicted by SPT, histamine release, or specific IgE [39]. Although the predictive capacity of the atopy patch test could be improved when combined with SPT and specific IgE measurements, oral food challenges could be avoided in only 0.5% to 14% of patients in a recent German study [40]. Therefore, atopy patch tests cannot be recommended for routine clinical practice in the diagnostic workup of food-related symptoms in children [39,40].

In summary, using an elimination diet as a diagnostic and therapeutic approach is reasonable in patients with sensitivity to a specific food confirmed by SPT, the presence of specific IgE antibodies, or both, along with a history of symptoms correlating with exposure to the food. When sensitization to multiple foods is confirmed by SPT or specific IgE antibodies—especially if the patient has a significantly elevated total IgE level and no significant history of an allergic reaction or worsening of eczema upon ingestion of the food—DBPCFCs should be performed to confirm clinically relevant sensitization and avoid unnecessary dietary restrictions.

Risk Factors for the Development of Atopic Dermatitis and Food Hypersensitivity

As previously reported, dietary measures in high-risk infants during the first 4 to 6 months of life have been associated with a decreased risk of developing food allergy, especially cow's milk allergy and AD [41]. Recent data from the Isle of Wight prevention study on allergy prevention in high-risk infants revealed a reduction in allergic diseases for at least the first 8 years of life by strict avoidance during the first 12 months (and in the diet of lactating mothers) of cow's milk products, egg, wheat, nuts, fish, and soy, along with environmental control measures for house dust mites [42•]. The prevalence of AD in the prophylactic group was 50% of the prevalence in the control group without allergen avoidance, and the prevalence of food allergy was consistently lower in the prevention group. These data indicate that exposure during the first year of life to highly allergenic foods and environmental

allergens (eg, house dust mites) increases the risk of developing allergic diseases, including AD and food allergy, in infants with a familial predisposition for atopy.

The World Health Organization recommends exclusive breast-feeding for the first 6 months of life because of breast milk's many benefits for the infant, including protection against the development of allergic diseases. Interestingly, a prospective follow-up study of 200 unselected healthy newborns from birth to age 20 years found that exclusive breast-feeding, without dietary restrictions for the mothers, for at least 9 months was significantly associated with AD and food hypersensitivity at ages 5 and 11 years in children with a family history of allergies [43].

In addition to the duration of exclusive breast-feeding, the timing of solid-food introduction also appears relevant to the development of AD and atopic sensitization. The introduction of solid foods before age 4 months has been associated with a higher risk of AD up to age 10 years [44]. However, a prospective birth cohort study of 2612 German infants did not find evidence supporting a delayed introduction of solids beyond the first 6 months of life for the prevention of AD and atopic sensitization to the common food allergens (cow's milk, egg, wheat, peanut, soybean, and codfish) and common inhalant allergens, as determined by the presence of specific IgE antibodies at age 2 years [45]. In particular, delaying the introduction of grains beyond age 6 months has even been associated with the development of a food allergy to wheat [46]. Based on these data, prolonged exclusive breast-feeding and delaying the introduction of solid foods (including grains) past age 6 months suggests an increased risk for atopic sensitization and AD, and requires further investigation.

Selected studies have reported differences in the intestinal microflora between allergic and nonallergic children in early childhood [47], indicating that altered intestinal microflora may promote the development of atopic diseases, including AD and food allergies. Bacterial cultures from stool samples of allergic infants revealed a decreased percentage of bifidobacteria, bacteroides, and enterococci during the first year of life, but an increase in clostridia and *Staphylococcus aureus* [47]. It was thought that the use of probiotics (cultures of potentially beneficial bacteria) or prebiotic oligosaccharides, which can influence the constitution of the gastrointestinal bacterial flora, may help prevent or interfere with the progression of atopic diseases by restoring normal intestinal permeability and intestinal microflora.

The effect of probiotics has been studied in patients with AD or food allergies and in regard to the primary prevention of atopy [48]. One study reported improvement of AD in food-sensitized children only, using a mixture of *Lactobacillus rhamnosus* and *Bifidobacteria lactis* [49], but several studies failed to show a therapeutic effect on AD symptoms [50].

Current Therapeutic Approach

Skin care for infants with AD should include daily baths followed by application of a moisturizing cream to increase skin hydration and promote a healthy skin barrier that will help to decrease allergen sensitization through the skin. Prompt treatment of AD flares with topical corticosteroid preparations or calcineurin inhibitors, if indicated, is recommended to treat acute skin inflammation. Antihistamines are used to control pruritus and interrupt the itch-scratch cycle, which contributes to chronic skin inflammation. Dietary restrictions—avoiding highly allergenic foods during the first year of life—may help to prevent allergen sensitization in infants at risk for atopic diseases and may reduce AD severity in children with clinically relevant sensitization to specific foods.

Conclusions

Atopic dermatitis frequently occurs together with food allergies. Sensitization to foods leading to isolated cutaneous symptoms has been reported in one third of children with AD triggered by foods and needs to be considered as a significant trigger of AD flares. A defective skin barrier and increased intestinal permeability have been reported to facilitate allergen sensitization and contribute to systemic food allergic reactions or food-related AD flares, the latter reactions being attributed to the effect of food-specific T cells homing to the skin (Fig. 1). Promotion of a healthy skin barrier by appropriate skin care and attempts to prevent early sensitization to food allergens by avoiding highly allergenic foods during infancy may help to prevent AD and food allergies or interfere with disease progression (Fig. 1). It is important to identify clinically relevant sensitizations to food allergens in children with AD by a detailed history, SPTs, ImmunoCAP tests, and DBPCFCs, so that appropriate dietary interventions and therapy can be initiated.

Disclosure

No potential conflict of interest relevant to this article was reported.

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