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Food Allergy and Atopic Dermatitis: Separating Fact from Fiction

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The relationship between food and atopic dermatitis (AD) is complex. A common misunderstanding is that food allergies have a significant impact on the course of AD, resulting in uncontrolled attempts at elimination diets and undertreatment of the skin itself. Studies have shown that only a small portion of cutaneous reactions to food in the form of late, eczematous eruptions will directly exacerbate AD in young infants who have moderate-to-severe AD. Given the low frequency of food allergies actually inducing flares of AD, the focus should return to appropriate skin therapy, and identification of true food allergies should be reserved for recalcitrant AD in children in whom the suspicion for food allergy is high. A different relationship between food and AD involves delaying or preventing AD in high-risk infants by exclusive breastfeeding during the first 4 months of life. Finally, the skin barrier defect in AD may allow for easier and earlier sensitization of food and airborne allergens; therefore, exposure of food proteins on AD skin may act as a risk factor for development of food allergies.

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Atopic dermatitis (AD) is a common disease affecting 15% to 30% of children[1] and is characterized by skin barrier defect and chronic inflammation. It runs a course of flares and remissions with triggers that many times remain obscure, but some that have been implicated are inhalant allergens, bacterial colonization of the skin, irritating substances, changes in climate, and psychological stress.[2] Food is thought of as one of the more common causes or trigger for AD, but this association is overly emphasized. Although sensitization and allergy to food occur in infancy and are more prevalent in children with AD, they oftentimes do not play as significant a role in the course of AD as is believed.[3]

To better understand the cutaneous reactions induced by food allergies, it is important to recognize that just as AD can be associated with or without elevated immunoglobulin E (IgE) levels, food allergies can also be IgE or non-IgE mediated.[4,5] The overestimation of food allergy's effect on AD likely stems from the observation of more common, immediate-type, IgE-mediated cutaneous reactions, such as urticaria and erythema. These reactions are more visible and readily attributable to food exposure because of their rapid development, but they do not represent flares of AD. By contrast, eczematous flares that occur as delayed-type hypersensitivity reactions are generally non-IgE mediated. These reactions may be overlooked because they develop 2 or more hours after food challenges, and this delay may render correlation between the food exposure and reaction more difficult (Fig. 1).[6]

Nevertheless, parents often consider their child's AD as an "allergic" manifestation of a presumed food allergy. The influence of the media and/or popular culture may play a role, but parents are also receiving differing opinions from primary care providers and dermatologists.[7] Greater than 90% of parents and 60% of primary care providers may point to food allergy as the cause for AD and result in referrals to allergists and extensive testing.[7] The allergy literature frequently implicates food allergy as an exacerbating factor for AD, whereas the dermatology literature views food-induced AD as an uncommon event. To illustrate, the following is a statement from the dermatology literature (a) and one from the allergy literature (b)

a. "True food-induced atopic dermatitis is rare . . ."[3]
b. "it is clear that foods, such as cow's milk and hen's eggs may directly provoke flares of atopic dermatitis in sensitized infants . . ."[6]

These conflicting viewpoints likely lead parents to experience frustration and consequently resort to elimination diets without proper guidance from nutritionists. The result may be incomplete avoidance of the suspected food, thereby render-

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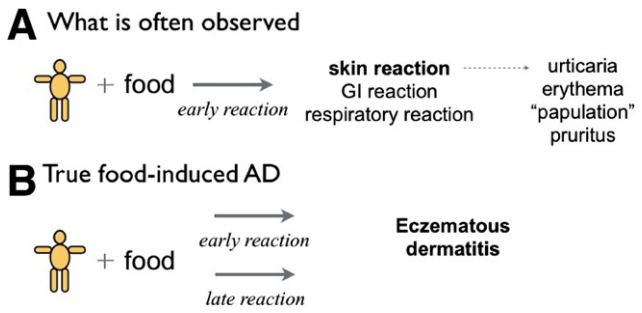

Figure 1 (A) shows the types of reactions that are often observed when a child develops food allergies. They occur early and can be easily correlated to food exposure. The skin reactions commonly include urticaria, erythema, and pruritus; on occasion "papulation" was reported. These reactions are mistakenly overinterpreted as flares of atopic dermatitis. (B) illustrates that a true food allergy-related flare of AD occurs when food exposure results in an eczematous reaction. This usually occurs late after a food challenge, but can infrequently occur early.

ing the attempt unsuccessful, or even malnutrition.[8] Even more importantly, focus on elimination diets takes away from the emphasis on good skin care.

Therefore, clarifying the relationship between food and AD with the existing evidence is a first step in offering sound advice to help manage this chronic disease. The following is a review of 3 different perspectives on the relationship between food and AD: (1) food allergies and their true effect on AD, (2) the timing of introduction of solid foods in infancy and prevention of AD, and (3) skin barrier defect in AD as a risk factor for developing food sensitization.

Food Allergies

The prevalence of food allergies in children in general is estimated to be approximately 4% to 10%, with greatest prevalence in the first few years of life and gradual decrease during the first decade as tolerance develops.[5,9,10] Approximately 90% of allergenic foods in children are accounted for by hen's egg, cow's milk, soy, fish, wheat, peanuts, and tree nuts.[10-12] The natural course of food allergy is different for each allergen. Allergies to peanuts, nuts, and seafood are more likely to persist, with a small fraction of patients developing tolerance, whereas allergies to milk, eggs, wheat, and soy generally resolve by late childhood.[10]

Strong Association Between Food Sensitization and AD

Food allergy is much more common in children with AD, with an association that ranges from 20% to 80%, but is more accepted to be around 30%.[4,13,14] Although not all patients with AD have elevated IgE, as many as 40% to 80%[4,15] have been found to have high food-specific IgE levels. Sensitization to food occurs early, peaking at approximately 6 to 9 months of age,[16] and generally does not increase during later childhood.[17,18] The presence of IgE to food and aeroallergens is associated with earlier-onset and more severe AD,[13,18-20] and in fact, the greater the level of IgE and the earlier it is elevated, the more severe and persistent the AD is likely to be.[20] The relationship also holds true in the reverse direction because patients with early AD that develops before 3 months of age are at significantly greater risk of acquiring food allergies compared with those who develop AD after 12 months of age.[14,21] These data suggest that the presence of food sensitization and allergy earlier in life predicts a prognosis of severe AD, but conclusions about its role in the pathogenesis of AD cannot be made. Of note, the strong association between AD and food allergies does not exist in adults with moderate-to-severe AD.[11]

What Kinds of Reactions Occur from Food Allergies?

Food allergies have clinical manifestations on the skin and gastrointestinal and respiratory systems. For the purpose of this review, signs of allergic reactions on the skin will be the focus. Cutaneous reactions have been categorized as noneczematous versus eczematous, and in addition, early versus late.[22] Noneczematous reactions tend to occur immediately after the exposure to the food, usually in less than 1 hour. The typical reactions include pruritus, urticaria, angioedema, and diffuse morbilliform erythema. These reactions do not cause immediate exacerbations of AD, and they are commonly associated with gastrointestinal or respiratory symptoms. Acute urticaria and angioedema are among the most common symptoms, and acute contact urticaria or allergy can also occur.[5]

Eczematous reactions occur less frequently. They usually manifest as a late event, which is generally defined as 2 to 6 hours or more after exposure to the food.[22-26] Infrequently, eczematous reactions can develop as an early event or in combination with noneczematous reactions.[24,27]

How to Diagnose Food Allergies

Before one orders tests to evaluate for food allergies, the distinction between sensitization and allergy needs to be recognized. The presence of food-specific IgEs supports sensitization, but it does not necessarily translate to food allergy, which is a clinical response upon exposure to a specific food. Children who are sensitized may not necessarily develop a clinical reaction. For example, a child who has developed tolerance to cow's milk may have persistent milk-specific IgE but may be able to ingest cow's milk without any clinical symptoms.

The first suspicion for food allergies usually arises from parents. Unless major immediate anaphylactic reactions have occurred, however, history has proven to be an unreliable way to diagnose food allergy.[28] Studies have reported poor correlation, with only 25% to 48% sensitivity and 72% to 97% specificity.[5,24,26,29]

Many of the symptoms of food allergies are IgE-mediated, and therefore initial testing in an outpatient setting is deter-

mined on the basis of presence of food-specific IgEs. The skin prick test has a high negative predictive value (>95%) and is most informative when it is negative. However the positive predictive value ranges between 30% and 50%.[11] Therefore, the skin prick test is useful for excluding immediate food hypersensitivity, but a positive result may only suggest hypersensitivity.[5,28,30]

Laboratory testing for food-specific IgE also has a high negative predictive value, estimated to be 75%, but the positive predictive value can be low, ranging from 20% to 60%.[6,24] Recently, diagnostic levels of food-specific IgEs have been determined, and specific IgEs above these levels may offer a positive predictive value of >95% for food allergy. These levels are available for certain foods, most reliably for hen's egg, cow's milk, fish, and peanut, and they are applicable to young children younger than 2 years of age.[5,31] However, decision points are not reliable for wheat and soy.[32] Furthermore, the clinician must pay attention to the type of assay used because the actual diagnostic levels differ as the result of technical discrepancies and differences in allergen sources among the different assays. Finally, these decision points are for immediate-type reactions and not meant to predict risk for late eczematous reactions to foods.[33]

Although skin prick tests and serum IgE measurements can confirm sensitization, neither can on its own prove clinical allergy to a specific food with reliability or consistency. The diagnostic levels for specific IgE can help to avoid oral food challenges (OFCs), but the utility of this test is limited for certain foods in young children, as long as the assay used is the same as that in the published studies.

The "gold standard" test to confirm or disprove food allergy is the OFC, particularly in the form of double-blinded, placebo-controlled OFCs.[5,34] OFCs are time-consuming with potential for severe reactions, and they should be performed by experienced health-care professionals who have access to emergency equipment. Despite the mentioned caveats, OFCs are especially useful because observation after food exposure for 24 hours or more can allow for assessment of both early and late reactions to the food, thereby picking up both IgE and non-IgE-mediated processes.[22]

Eczematous allergic reactions to food have similarities to allergic contact dermatitis in that both are T-lymphocyte mediated, with the former being associated with food-specific T-lymphocytes.[35] In addition, their clinical morphologies resemble each other. These shared features have led to atopic patch testing (APT) as a way to investigate food-induced eczema. APT is carried out similarly to patch tests that are performed in dermatology clinics, with the application of small amounts of food allergens to a clear area on a patient's back. The application sites are checked for contact urticaria at 20 minutes and again at 48 and 72 hours.[36] Smaller reports have supported the use of APT in combination with IgE testing to increase the positive predictive value for diagnosing food allergy, thereby bypassing the need for OFCs.[25,26] However, the authors of some prospective studies[36,37] have reported that APT offers only a small added benefit, if any, to standard SPT and serum IgE measurements. In addition, the methodology appears to require more standardization and therefore is not yet generally recommended for routine diagnosis of food-induced AD.[38]

Evidence from Studies—What Do We See from Oral Food Challenges?

As reviewed previously, food allergies can result in a variety of cutaneous reactions, only some of which will exacerbate AD. Observations from OFCs are very useful in determining the pattern of the reactions and their effect on AD. OFC studies generally included children with moderate-to-severe AD who were suspected of having food allergies. In many of the studies, before OFC, the patients were given low-allergenic diets composed of hydrolyzed formula or rare-foods diet. After the OFC, some studies observed patients for immediate reactions only,[28-30,39] whereas others observed for 24 hours or longer to detect delayed reactions.[23-27] Many of the studies defined reactions occurring within 2 hours of the food challenge as immediate and after 2 hours as delayed, although this varied somewhat among the different studies.[23-27]

In children with AD, positive reactions occurred approximately 30% to 80% of the time, of which 70% to 94% were cutaneous.[24,26,29,31,40,41] Most of the reactions occurred early after food exposure, usually in the form of urticaria,[24,28,31] and approximately 10% to 25% of clinical reactions occurred late and were observed 2 hours or more after the food challenge.[24,26,31]

Exacerbation of AD was observed in 2 forms. Indirect exacerbation was seen with early reactions in the form of generalized pruritus and/or morbilliform erythema within 2 hours of ingestion of the food. These immediate reactions led to increased scratching and eventually secondary exacerbation of eczematous lesions.[30] Hen's egg and cow's milk were significantly more likely to result in the aforementioned early reactions and were associated with elevated food-specific IgE.[24]

Direct exacerbation of AD with development of new eczematous outbreaks tended to occur as late reactions[23,24,26,31] and infrequently as early reactions.[27] Soy and wheat were more likely to cause late, eczematous flares, but reactions to cow's milk were also observed. Although some of these reactions were observed in the context of elevated food-specific IgE, a good portion also occurred in the absence of food-specific IgE.[23] See Table 1[23-27,31] for a summary of the reactions.

Delayed eczematous reactions that occurred in the absence of food-specific IgE comprise 5% to 25% of positive reactions (ie, 1.5%−20% of challenged patients overall) in OFCs. They were not predictable by skin-prick testing or IgE quantification.[24-26] The non-IgE-mediated reactions support the role of food-specific T cells, which have been found in patients who had food-induced exacerbation of their AD.[35,42-44]

Table 1 Summary of Patterns of Cutaneous Reactions to Food (on the Basis of Select Studies of OFCs[23-27,31])

	Early Reactions (defined as <2 hours after food challenge)	Late Reactions (defined as >2-24 hours after food challenge)
Type of cutaneous reaction	Frequently urticarial Infrequently eczematous	Frequently eczematous Infrequently urticarial
Association with food-specific IgE	Frequently increased food specific IgE	Frequently no increase in food specific IgE
Association with specific foods	Frequently with hen's egg and cow's milk; less with wheat	Frequently with soy and wheat; less with cow's milk

Do Elimination Diets Work?

Dietary elimination as an attempt to treat AD is not well supported. The cornerstone in treatment of food allergies is food avoidance, and this of course should be used when the suspected food is clearly proven to cause allergy. Establishing a diagnosis of food allergy when the reaction is immediate and severe may not be difficult, especially when exposure to a certain food results in obvious gastrointestinal or respiratory symptoms or cutaneous reactions in the form of urticaria, angioedema, pruritus, or generalized erythema within minutes. In these cases, parents are easily able to diagnose the allergy and exclude the specific food from the diet without necessarily seeking guidance from healthcare professionals.

In contrast, as reviewed previously, proving that food allergy results in a delayed, eczematous reaction that directly exacerbates AD is much more difficult and time-consuming, and only a small percentage of children actually appear to be affected. Furthermore, very little evidence exists to support dietary modification as a treatment for AD. A recent Cochrane review of randomized controlled trials of dietary exclusion for the treatment of AD concluded that the evidence available lends little support to the use of elimination diets, few foods diets, or elemental foods diets.[45] Only one study in the review showed a short-term benefit from egg-free diets in those who had elevated egg-specific IgE.[45] The conclusion from the Cochrane review does not absolutely refute dietary elimination as a potential treatment for AD in selected patients; rather, studies that can support dietary elimination in the appropriate setting of AD patients with proven exacerbation by food do not yet exist.

Despite the lack of support for elimination diets, parents frequently resort to them at the expense of good, standard skin care.[46] In fact, up to 75% of parents reported trials of elimination diets, many without professional guidance, and many with cases of AD involving only mild flexural dermatitis.[46,47] The trial of food elimination at home is not reliable and ultimately not recommended for several reasons. The elimination of food proteins is a difficult task, and incomplete elimination of a suspected food can lead to confusing results.[11] For example, parents need to be educated about hidden food proteins in prepared and packaged foods, such as egg protein in baked goods. In addition, when multiple foods are eliminated from the diet, unhealthy or dangerous outcomes may result, such as deficiency in calories, proteins, or minerals.[8,48]

Primary care physicians or pediatricians are much more likely than dermatologists to focus on food allergy as a contributor to AD, thereby influencing the parents to focus on food allergy as well.[7,49] This may take away from appropriate skin care, in addition to the "steroid phobia" often expressed by parents.[50] Redirecting the emphasis on correct skin care can alleviate concerns about the role of food allergy, as shown by a study that reported that focus on skin care resulted in a significant improvement of AD as well as a significant decrease in parental concerns and reports of food-related skin reactions.[51]

In the case of strongly suspected food allergy causing flares of AD despite good skin therapy, evaluation by history and measuring specific IgE levels can be the first step as a guide for eventual OFC. The purpose is to answer the following question—does this patient have food allergy that results in direct exacerbation of AD? Therefore, the purpose is to evaluate for eczematous reactions, which are more likely to occur 2 to 6 hours or more after food exposure.[22] Sometimes the IgE levels will not be helpful in guiding OFCs because allergic reactions to foods may occur in the absence of measurable food-specific IgEs, as detailed previously. In these cases, parents may need to keep a diary of daily symptoms and food intake.

Once food is clearly implicated, therapeutic diets are recommended for a period of 12 to 24 months in early childhood. After this period the clinical relevance of food allergy should be reevaluated to avoid long-term, unnecessary or even harmful diets. Again, patients and their caregivers must be educated about the benefits and risks of food allergen avoidance.

Relationship Between the Timing of Solids Introduction and the Development of Allergy

A different question regarding food and AD is whether delaying introduction of solid foods to infants at high risk for AD can delay or prevent the development of AD. The most recent clinical report by the American Academy of Pediatrics states that exclusive breastfeeding for 4 to 6 months for infants who are at high risk for atopic disease (ie, positive family history) can help prevent or delay AD and cow's milk allergy until 2 years of age.[52] This recommendation is consistent with that of European groups.[53] Regarding the introduction of solid foods, the American Academy of Pediatrics states that no convincing evidence exists to delay any solid foods beyond 4 to 6 months of age, but this should not be interpreted as affirmation that introduction of highly allergic foods before 1

year of age is safe. In contrast, the American College of Allergy, Asthma and Immunology recommends that dairy products be introduced at 12 months; hen's egg at 24 months; and peanuts, tree nuts, fish, and seafood at 36 months.[54] The inconsistencies in recommendations arise from methodological differences among studies, and new reports state that introduction of solid foods before 4 months of age may actually protect against AD.[55] This particular relationship between food and AD deserves more clarification, and prudent introduction of foods on the basis of family history of atopy and food allergies should be guided by healthcare professionals.

Patients with AD and Filaggrin Mutation Are at Greater Risk for Sensitization to Food

Filaggrin (filament-aggregating protein) is a key protein required for barrier homeostasis of the skin, and mutations in the *FLG* gene have been shown to be a key risk factor for AD in European, Northern American, and some Asian populations.[56-58] *FLG* mutations are present in approximately 10% to 50% of patients with AD,[59] and even in AD patients who do not appear to have the mutation, filaggrin levels can be modified by the activity of AD, as acutely inflamed lesions express lower levels of filaggrin compared with uninvolved skin.[60]

FLG expresses the profilaggrin protein, which is cleaved to filaggrin, an important component in the terminal differentiation of the epidermis. It binds to keratinocyte intermediate filaments, serving as a scaffold for the formation of the cornified cell envelope, thereby providing barrier against moisture loss and protection from microbes and allergens. Filaggrin is relatively short-lived and is degraded into hydrophilic amino acids that make up the skin's natural moisturizing factor. Natural moisturizing factors are important in contributing to hydration of the stratum corneum. In addition, they influence the pH of the skin, and it is under acidic pH that proper regulation of protease activity, cutaneous antimicrobial defense, and barrier permeability occur.[61]

The barrier deficiency that results from *FLG* mutations lends support to the "outside-inside" theory of AD, which proposes the barrier defect as the initiating pathogenic factor that favors a T_h2 cytokine profile characteristic of acutely inflamed skin in AD.[62] In this setting, penetration of soluble allergens through the barrier-compromised skin could encourage T_h2-mediated responses, such as production of IL-4 and IgE.[56,63-65] The higher risk of asthma in patients with *FLG* mutations and AD has been established, although risk of asthma in those with *FLG* mutations without AD is not increased, which raises the question whether percutaneous exposure to aeroallergens leads to early sensitization and eventual development of asthma.[61] This mechanism has been observed in mice studies, in which the skin of mice was shaved to emulate a disrupted barrier. Epicutaneous sensitization to ovalbumin, a chicken egg albumin, was demonstrated, after which exposure to ovalbumin through the airways resulted in asthma-like symptoms.[66]

In a similar fashion, epicutaneous sensitization to food allergens may also occur and result in allergies. Studies in mice again were performed in which the skin was tape-stripped. Two different protein antigens were applied to this disrupted skin, and a T_h2 response was elicited. Injection of these particular antigens into distant skin resulted in an eczematous, delayed-type hypersensitivity reaction. This was not the case with exposure to the same antigens to intact skin.[67] Furthermore, once epicutaneous sensitization occurred, normal oral tolerance to the antigens could not be achieved. In fact, subsequent exposure through the gastrointestinal mucosa resulted in further sensitization and stronger T_h2 response with increased IL-4 and antigen-specific IgE levels.[68]

Clinical support for epicutaneous sensitization in patients with AD is more circumstantial in a retrospective study of children with peanut allergy. These patients had a strong association with history of topical use of peanut oil, leading the authors to conclude that sensitization of peanut protein might have occurred through the application of peanut oil to inflamed skin.[69] In addition, data from a prospective birth cohort showed that infants with eczema at an early age are at higher risk for developing food sensitization.[21]

The data reviewed above should impact the clinician's choice of topicals for children with AD, as over-the-counter emollients formulated with potential allergens can act as sensitizers in barrier-disrupted skin. For example, oat is an ingredient found in popular emollients, and a French study suggests that prior exposure to oat-containing creams is associated with the 32.5% rate of sensitization and 4% rate of clinical allergy found in their group of AD children referred for allergy testing.[70] Peanut oil is another agent that warrants caution if *unrefined* peanut oil, such as that found in cooking oils is used for topical application. By contrast, hot-processed, *refined* peanut oil that is used as a base for a commercially available fluocinolone 0.01% oil has been shown to be safe to use even in children with peanut sensitization.[71]

The possibility of the skin as a site of sensitization then leads to the exciting potential to halt the so-called atopic march, which affects 40% to 50% of children with AD.[72-74] By aggressively protecting the barrier and treating inflamed skin of AD patients, the development of food allergies, asthma, and allergic rhinitis may be prevented or modified, thereby ultimately improving the quality of life and reducing the burden of healthcare costs of these patients. Future longitudinal studies are needed to lend support to this potential opportunity for intervention that holds promise for significant impact.

Conclusions

The relationship between AD and food is complex and can be viewed from several different perspectives. Food allergy as a cause of, or exacerbating factor for, AD is uncommon. If it truly plays a role in the course of a child's AD, then it likely does so in cases of severe AD in younger infants. Laboratory tests available cannot reliably predict which foods may be implicated. Diagnostic IgE values determined for specific

foods may be helpful in determining the foods that are highly likely to result in immediate-type clinical reactions, such as urticaria, erythema, or pruritus, which can lead to excessive scratching and indirect exacerbation of preexisting AD. However, tests based on IgE levels cannot predict the likelihood of all eczematous reactions, as some occur in the absence of detectable food-specific IgE levels. OFCs are the gold standard for food allergy testing and can allow for recognition of both early and late cutaneous reactions, including eczematous reactions. However, they are time-consuming, expensive, and not readily available to many patients. APT appears to be of questionable benefit in evaluating for non-IgE-mediated cutaneous reactions, as standardization of the methodology remains to be established. The most reliable way to treat AD is to focus on appropriate, consistent skin care, including control of inflammation and barrier restoration. If flares occur despite this, and food allergy is strongly suspected, then OFC should be pursued by health-care professionals experienced with the testing process. Once a food is clearly proven to be implicated, elimination diets should be undertaken only with careful supervision by physicians and nutritionists.

A second significant association between food and AD is that delaying the introduction of solids for 4 to 6 months to infants at high risk for atopic disease appears to reduce the incidence of AD. Finally, AD skin characterized by barrier deficiency appears to act as a site of early sensitization to food and aeroallergens. Therefore, aggressive protection of the skin and early avoidance of highly allergenic substances to the skin hold potential to be an important form of intervention to prevent the progression of the atopic march.

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