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Controversies in allergy: food testing and dietary avoidance in atopic dermatitis

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Atopic dermatitis (AD) is the most common inflammatory skin disease in children, with an incidence of 15–30% in childhood. It is most common in industrialized countries, and its incidence continues to increase.^{1, 2} Over one half of children with AD develop eczematous lesions in first year of life and 90% of children with AD develop lesions by age 5.³ The pathogenesis of AD is multifactorial; a combination of genetic predisposition, impaired skin barrier function, and exposure to environmental triggers, such as allergens, irritants, and microorganisms. The defective skin barrier allows penetration of allergens and microorganisms, leading to contact (of allergens and microorganisms) with the immune system. This contact can then lead to immune activation and inflammation. There is often accompanying elevated total immunoglobulin E (IgE), and allergic sensitization to foods and aeroallergens. Additionally, AD can lead to the development of the “atopic march”, where there is a progression of allergic disorders from early AD to food allergy (FA), allergic rhinitis and finally asthma.⁴ This review focuses on the intricacies, reasons and controversies to consider when testing patients with AD for the contribution of FA.

Co-expression of atopic dermatitis and food allergy

Much like the incidence of AD, the incidence of food allergy is also increasing, with an estimated prevalence of 3–10%. FA and AD are often co-expressed, and a causal link of foods triggering skin lesions has been shown in some patients. One of the first studies to

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prove this link was published in 1983, where Sampson utilized double-blind placebo-controlled oral food challenges (DBPCFCs) in 26 children with elevated total IgE ranging in age from 16 month to 19 years.⁵ Possible trigger foods were avoided for 1–2 weeks prior to the DBPCFC. Importantly, no foods were tested that had a convincing history of anaphylaxis. Fifteen of 26 children (58%) demonstrated FA: 9 children to 1 food, 4 children reacted to 2 foods, and 2 reacted to three foods.⁵ Furthering this work, Sampson and McCaskill then found that 57% of a highly selected group of pediatric patients with AD had a positive reaction to food.⁶ These findings were supported by Burks et al who examined 46 patients with eczema referred to an allergist, 61% of whom demonstrated sensitization by skin prick testing (SPT) and 33% of whom reacted to foods.⁷ However, given the concern of bias related to allergy referral, Eigenmann et al examined 63 children referred to a dermatologist. Forty-one of 63 children demonstrated sensitization to foods, and 23/63 were felt to have clinically significant FA diagnosed by oral food challenge (OFC) (n=11/19), convincing history with elevated IgE (n=11) or elevated IgE alone (n=1).⁸ Together, these early challenge studies provide the evidence of AD-FA link. It is important to note that these children had refractory, moderate- severe AD that had failed topical steroid management.

The prevalence of FA in patients with AD varies with age and severity of AD. A birth cohort of 620 infants demonstrated that as atopic dermatitis severity increased, adverse reactions to foods increased.⁹ More recently, a population based cohort study of over 4000 infants (HealthNuts) demonstrated that children with AD were 6 times more likely to have FA to cow milk, egg or peanut at age 12 months compared to infants without AD. Additionally, children diagnosed at a younger age and requiring more medical therapy were more likely to have a FA.¹⁰

It is important to note that studies of FA and AD in older children and adults have been less convincing, with fewer existing studies. In one DBPCFC study, 33 adults with severe AD demonstrated little benefit to elimination diets.¹¹ To evaluate the possibility of wheat allergy, a study of 179 adults with reported wheat allergy demonstrated that approximately 4% of patients reacted during DBPCFC, and allergy did not correlate with testing.¹² Milk allergy was even less common, where approximately 1% of adult patients demonstrated allergy to milk.¹³ A review of the association of AD and FA in adults found that challenge proven FA in adults with AD is uncommon, and interestingly, only half of patients with challenge proven sensitivity had improvement of AD with dietary elimination.¹⁴ Thus, food-triggered atopic dermatitis is unlikely in adults.

Regarding other allergic diseases, children with early onset, severe and persistent AD, and elevated total and specific IgE (sIgE) antibodies are most at risk for the development of asthma and allergic rhinitis, further illustrating the role of atopic dermatitis in the development of atopic diseases. Additionally, there is also evidence that in some infants, food sensitization precedes the development of AD, and in others, AD precedes the development of food sensitization.¹⁵ Food sensitization alone is a noted risk factor for the atopic march.^{16, 17} These studies highlight how early AD promotes FA and the development of other atopic diseases, such as asthma and allergic rhinitis.

Types of clinical reactions to foods in atopic dermatitis

Children with reactions at OFC typically have one of three types of reactions: Immediate (IgE) reactivity, delayed eczematous reactions (thought to be non-IgE mediated) or combined immediate-type and late eczematous reactions. Immediate reactions are IgE-mediated, occur within 2 hours, with signs and symptoms typical of IgE-mediated FA (including skin symptoms such as urticaria, angioedema, flushing; gastrointestinal symptoms, respiratory symptoms or anaphylaxis.) Cutaneous reactions occur in the majority of patients with FA and AD. In contrast, delayed eczematous reactions typically occur 6–48 hours after OFC with flares of eczema. Finally, some patients can present with combined reactions, with immediate symptoms upon ingestion followed by an exacerbation of eczema. These combined reactions may be cutaneous only, or have other symptoms, particularly of the gastrointestinal tract. The reported frequency of types of reactions vary. A study of 106 DBPCFCs to foods in 64 children with AD demonstrated that 45% had mixed reactions and 12% had late reactions alone.¹⁸

Diagnosis of food allergy in atopic dermatitis

The diagnosis of FA in AD should be made in accordance with published guidelines^{19–21} which suggest testing should occur in children with an immediate response after ingestion of a potentially causal food, and should be considered in children with moderate to severe AD after optimal skin care is attempted. Diagnosis requires a detailed clinical history, evidence of allergic sensitization via skin prick testing (SPT) and/or sIgE testing, and trial of an elimination diet. If necessary, an OFC may be needed to confirm diagnosis.^{21, 22} Specific to patients with AD, diagnosis can be complicated the fact that AD has a waxing and waning course, exposure to other triggers such as irritants, aeroallergens, microbes, and patients with atopic dermatitis can have high levels of total and sIgE that may not be clinically relevant.

If sensitization exists, does it predict food allergy?

When diagnosing FA, SPT to foods have a negative predictive value (NPV) of 90–95%, and thus negative testing may be helpful to rule out FA in patients with AD. However, the positive predictive value (PPV) of SPT is <50%. Similarly, negative serum sIgE levels may help rule out a FA, but the PPV is also low.^{23, 24} Thus, commercially available testing with SPT and *in vitro* food sIgE assays are well known to have a general poor PPV and high false positive rate.^{21, 25–27} Additionally, although predictive values for sIgE levels have been established, these studies focused on immediate reactivity, and specific cutoffs in food-triggered AD are not known. As these children often make high levels of total IgE and sIgE, published cut-offs may not be accurate in these patients. However, testing may help in deciding which foods one should attempt a targeted elimination diet to confirm diagnosis. If eczema control significantly improves with elimination, a food trigger can be considered, followed by OFC if necessary. Thus, although testing has known limitations, it may be helpful in identifying potential trigger foods that can be subsequently confirmed through careful, selective elimination diets, followed by OFC if necessary.²²

Atopy patch testing (APT) has also been evaluated for use in food triggered AD with some reported success, although its use remains controversial due to lack of standardization and reproducibility.^{28, 29}

Several studies have aimed to determine the frequency of positive food allergen testing in children with AD. Keck et al. evaluated baseline serum sIgE to 6 foods in infants ages 3–18 months with mild to severe AD with no history of FA at baseline and again after 3 years.³⁰ At follow-up, 90% of children had ingested the allergens tested and 20% had experienced immediate reactions to 1 or more foods including egg, peanut and cow milk.³⁰ Remarkably 80% of children had neither serologic evidence of allergy nor clinical evidence of FA. A similar study of over 2000 Canadian children with AD from age 1 to age 3 found 4% of children to be “transiently sensitized” at age 1, the majority of which had mono-sensitization to one food resolving by age 3.³¹ Only 3% of children were considered persistently “sensitized”.³¹ Interestingly, children who were only “transiently sensitized” were still at an increased risk of FA when compared to healthy controls despite resolution of their sensitization by 3. The authors attributed the FA risk in the transient sensitization cohort due to the fact that they were noted to be more likely to avoid common food allergens.³¹

To further examine the predictive value of food-antigen sIgE, Spergel et al. investigated over 1,000 infants ages 3–18 months with mild-severe AD and no history of FA receiving pimecrolimus therapy.³² Approximately 16% of the infants developed 1 or more IgE-mediated food allergies during the 3 year course of the study.³² sIgE cut points were assigned for 6 foods based on published literature and analyzed with a logistic regression model. The authors found that screening sIgE had little utility in determining the probability of developing an IgE-mediated FA for most foods tested.³² It is notable that the overwhelming majority of children studied had mild-moderate AD, thus confirming the understanding that food allergens are a less likely contributor in this population. Together, these studies illustrate that sensitization may not correlate with symptoms.

In contrast to the early studies demonstrating the AD-FA link, the above studies did not perform confirmatory oral food challenges (OFCs) and there are significant concerns with using SPT and serum sIgE alone for diagnosis of FA in AD as mentioned. However, to investigate immediate and delayed reactions in sensitized subjects with AD, Hanifin’s group completed a novel study undertaking serial OFCs in 17 children with severe AD.³³ The children were admitted and placed on an elimination diet. OFCs were started 24–28hr after skin inflammation subsided unless the child had a historical IgE-mediated FA.³³ Impressively, only 1 of the 17 subjects developed eczematous changes within 1 hour of cow milk ingestion that recurred on re-challenge.³³ More striking was the fact that no other children had reproducible reactions, including 15 challenges to egg and 16 to wheat.³³ Although these patients underwent rigorous testing with repeated OFCs in an inpatient setting, they did not have standardized testing prior to challenge and no food sIgE or SPT wheal sizes were reported.

Additionally, a retrospective review of OFCs performed in patients with AD found a similar low likelihood of reactivity. In a total of 364 oral challenges undertaken in patients with mild, moderate and severe AD all avoiding foods due to positive SPT or sIgE, 325 (89%)

had no immediate reaction and no negative challenge subjects had delayed eczematous flares the day following the OFC.²⁵ APTs have similar limitations showing no better PPV over SPT with one study noting a PPV of dermatitis development upon challenge after positive APT anywhere between 40 and 90% depending on the allergen being tested.³⁴ It is important to note that this study enrolled some patients with mild disease and was retrospective which may account for differences between the DBPCFC studies of children with more severe disease described above.

Dietary Elimination

Given the limitations and controversies in testing patients with AD for potential food triggers, the question remains of what is the likelihood that patients will experience significant improvement in their skin after foods are eliminated from the diet? Parent and patient perception of the importance of one's diet in triggering AD is clearly high. A large proportion of parents of children with AD perceive their child to have FA (55%) when compared to parents of children without AD (12%),³⁵ and many families attempt food exclusion diets even without direction from medical providers.^{36, 37} Perceived improvement in severity of skin disease appears to be no different, with one adult population reporting that 50% trialed a dairy elimination diet, and the majority of these patients felt there was improvement or even a full resolution of skin disease.³⁸ However, elimination diets may not be the only measure to improve parental worry as good AD control may provide a similar benefit. One interventional study found a significant decrease in level of parental concern of eczema secondary to foods following 3 months of therapy with tacrolimus. Initially, 95% of these parents reported worsening their child's AD secondary to foods, but adequate therapy for their child's AD alleviated many of these concerns.³⁹

Looking with a more objective lens at the success of dietary elimination, several studies have demonstrated the benefits of dietary elimination in food-triggered AD. In a study of 17 children with positive OFCs and AD, children had significant improvement in AD symptoms compared to children with AD (and no FA) and as compared to children who did not adhere to elimination diet.⁴⁰ Interestingly, total IgE and SPT did not predict responsiveness to dietary elimination. In a study of egg elimination in children with confirmed egg reactivity, there was a significant decrease in affected skin area and improvement in symptom score in children who received dietary advice to eliminate egg when compared to children not given this dietary advice.⁴¹ Older studies also demonstrated benefits in AD control with milk and egg exclusion in some patients that may not have been correlated with SPT.^{42, 43} A Cochrane review of dietary elimination in eczema concluded that although there was little evidence in milk or egg avoidance in general, it was beneficial in children with suspected egg allergy and present sIgE to egg.⁴⁴

A systematic review of available studies found 9 randomized controlled trials involving a total of 421 participants. This review found no overall benefit for unselected egg and cow milk elimination in participants.⁴⁴ As mentioned previously, one study did note an egg free diet to be beneficial in children with a positive sIgE to egg with improvement to affected body surface area and severity as compared to those not on an avoidance diet.⁴¹ Nonetheless, half of the children with positive testing to egg did not improve, and this study

was performed only in infants ages 11 to 17 months of age which may help explain the benefit. An earlier cross-over study in a wider age range (1 to 23 years) showed only a 25% response rate in AD improvement when following a 6 week cow milk and egg exclusion diet versus a diet containing a cow milk and egg control preparation.⁴⁵ The best response was noted in young children with severe eczema and SPT and sIgE was not helpful in predicting response.

Together, these findings demonstrating clinical reactivity on OFC with clinical improvement of AD upon dietary elimination have led to current practice guidelines that recommend children with moderate- severe AD less than 5 years of age undergo SPT or sIgE testing for common food allergens or foods that are positive on testing, food challenge or trial of elimination is recommended, followed by strict avoidance of any food identified to be contributing to AD.^{20, 21}

Potential risks of elimination diets

While it may seem benign to simply eliminate foods of potential concern from one's diet with confirmed reactivity, a growing body of literature disputes that elimination diets are without adverse effects, particularly in young children. Potential nutritional hazards of elimination diets have been a primary concern with dietary elimination for many years. Focus has been placed in studying broad avoidance of multiple foods and avoidance of dairy/cow milk. Cow milk elimination diets in particular have been associated with slower growth, decreased expected length/height, and decreased nutritional intake including calcium.⁴⁶⁻⁴⁸ The younger the child at the time of avoidance, the more risk there is of an effect on growth.⁴⁸ Looking specifically at avoidance in AD, an early study of cow milk elimination found over half of patients with severe recalcitrant AD to have intake < 75% the RDA for calcium intake and compared to none of the controls.⁴⁹ Children with comorbid AD and FA are at significant risk for growth deficiency, particularly when avoiding cow milk, noted by low weight and height z scores while body mass index may remain normal.⁵⁰ It is important to note, however, that adequate dietary supplementation during elimination diets can overcome potential growth deficits.⁵¹ Yet, this requires close monitoring by the child's medical team and consideration for referral to a dietician.

While nutritional concerns previously dominated the risks of eliminating foods, recent studies have brought to attention the concern of inciting development of IgE-mediated allergy by practicing food avoidance. Our published retrospective experience discovered 19% of patients with food-triggered AD and no previous history of an immediate IgE-mediated reaction developed a new immediate reaction following the onset of an elimination diet of that allergen. The percentage of patients with new immediate reactions was over 50% when all patients with possible food-triggered AD were considered.⁵² Up to one third of these new reactions were anaphylaxis.⁵² Additionally, Nachson et al. recently published their cohort of new onset FA where 83% of patients developing a new FA confirmed by OFC developed their allergy after an avoidance period of a median of 45 weeks.⁵³ It is important to note that FA can develop in some fairly quickly with dietary avoidance as 3 of their subjects had merely avoided the new allergen for a period of 7-14 days.⁵³ Thus, a detailed discussion of risks and benefits of dietary elimination is required.

Additionally, the practice surrounding introduction of allergenic complementary foods has changed significantly since many of the initial elimination diet studies were performed. In the era following the publication of “Learning Early About Peanut Allergy” or the LEAP study, the landscape of early allergenic food introduction has been transformed. LEAP demonstrated that early introduction of peanut with regular ongoing consumption in infants at high risk of FA development (as indicated by moderate-severe AD and/or a known egg allergy) led to a significant decrease in peanut allergy at age 5 when compared to children who were strictly avoiding peanut in their diet.⁵⁴ Only 3 subjects discontinued peanut consumption due to flares of their AD and subsequent conversion from a negative SPT at the study start to a positive SPT.⁵⁴ Of relevance to this discussion, over the long course of the trial, AD severity as measured by SCORAD assessment did not differ between the peanut consumption and the peanut avoidance groups and decreased in all subjects over all the study timepoints.⁵⁵ It can therefore be inferred that introduction of peanut in this population of children with severe AD did not affect their AD severity, nor did it prevent their AD from resolving or decreasing in severity over time. Disappointingly, little evidence exists at this time to direct introduction of other potentially allergenic foods. However, with primary prevention of FA within grasp, it becomes difficult to support sweeping recommendations for avoidance of allergenic foods in children with AD without confirmation of allergy by strongly positive tests (>95% positive predictive value) or confirmation of true clinical reactivity by a convincing historical reaction or by OFC.

Can improved atopic dermatitis control influence other atopy and quality of life?

The pathogenesis of AD is multifactorial, influenced by both environmental and genetic factors with induction of Th2 inflammation. Barrier dysfunction in AD contributes to both increased trans-epidermal water loss and increased penetration of allergens and microbes to the immune system. This increased penetration can further immune activation and inflammation. Increased water loss likely leads to xerosis, and skin changes may promote of colonization with an altered microbiota. For example, the skin of patients with eczema often is colonized with *S. aureus*^{56, 57} and likely contributes to disease pathogenesis. *S. aureus* has been shown to enhance Th2 inflammation.^{58–60} The inflammation provides an immunologic environment that further promotes allergic sensitization and symptoms. Additionally, it can result in downregulation of filaggrin gene expression (FLG), furthering epidermal barrier dysfunction.⁶¹

Lesional skin has been shown to have a Th2 cellular infiltrate and increased Langerhans cells that may increase antigen presentation.⁶² Additionally, it is becoming clear that epithelial cell cytokines, such as thymic stromal lymphopoietin (TSLP), IL-33 and IL-22 are important regulators of inflammation and the development of the allergic response.⁶³ These cytokines are released by skin epithelial cells (keratinocytes) when the skin barrier is disrupted, to promote the development of ILC2s, activate dendritic cells and trigger Th2 inflammation. Activated Th2 cells release IL4, IL5 and IL13 to promote B cell class switching and increased IgE. Thus, improved control of AD barrier not only decreases skin

inflammation and AD disease expression, but may improve overall immune dysregulation and decrease epithelial cytokine release, Th2 initiation and effector responses.

Current and future studies are investigating whether improved control of AD may improve quality of life or the atopic march. Therefore, appropriate food testing and elimination may be important to improve overall AD control in carefully considered patients, and may also help prevent further Th2 systemic inflammation.

Summary

Atopic Dermatitis is a chronic inflammatory skin disease with complex pathophysiology presenting challenges in management for both patients and providers. We have described the current evidence and controversies regarding FA testing and dietary elimination in AD. It is clear that exacerbations of skin disease do in fact occur in relation to food ingestions, but occurrence of these reactions is not as prevalent as is often perceived by the community. Food-triggered AD is most likely to occur in infants and young children with severe AD. Testing interpretation requires a nuanced clinical history and analysis, as allergic sensitization as determined by SPT and sIgE is frequently discovered in AD patients, however testing does not always aid in determination of disease triggers. In patients with true food- triggered AD, elimination of allergenic foods from the diet may improve AD control, but can also lead to subsequent development of IgE-mediated allergy, including anaphylaxis, in patients undergoing dietary elimination. As both clear risks and benefits exist from food avoidance in a proportion of AD patients, allergists/immunologists must play a vital role in actively determining the relevance of food sensitization in AD management in those at high risk.

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Abbreviations:

AD	atopic dermatitis
FA	food allergy
IgE	immunoglobulin E
sIgE	specific IgE
SPT	skin prick testing
Th2	T-helper type 2
DBPCFC	double-blind placebo-controlled food challenge
OFC	oral food challenge
IL	Interleukin

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