In the past decade, prodigious leaps in the understanding of atopic dermatitis (AD) have begun to flesh out the picture of a complex and multifactorial disease. While skin barrier dysfunction may well be the primary or “root cause” in some or perhaps even most patients, it has also been conclusively demonstrated that barrier damage can occur as a secondary phenomenon in the presence of inflammation. This underscores the fact that barrier impairment is always an important aspect of AD, regardless of its primacy. Thus, the stage is set for a deeper exploration of the complex relationship between AD and diet. In this brief review we will explore some of the key studies that have shaped the thinking about this contentious relationship, culminating in a very current viewpoint that suggests that the skin barrier dysfunction of AD may actually drive the development of food allergy, and not the other way around.

CONNECTIONS

Diet has long been implicated in the pathogenesis of AD, and this relationship has been fraught. A paper in the British Medical Journal from 1830 summarized it by saying: “There is probably no subject in which more deeply rooted convictions have been held...as regards the causation and treatment of the latter...” In a more contemporary take, the National Institute of Allergy and Infectious Diseases (NIAID) stated that it, “does not mean to imply that atopic dermatitis results from food allergy,” and that “…the role of food allergy in the pathogenesis and severity of this condition remains controversial.”

It continues to be a contentious area, with many families and health care practitioners promoting the idea that food is an important driver of eczema. In a recent study of 211 patients with AD, more than half (57 percent) reported discussing diet with a health care provider, but over one third (38 percent) felt the discussion was unhelpful. In the same report, 68 percent of children were reported to have excluded foods from the diet. Another study found that the perceived prevalence of food intolerance is more than 10 times higher than the true prevalence, and others confirm the fairly widespread practice of untested and unsupervised dietary modification in an attempt to control AD, with up to 71 percent of patients having made a dietary change. It is abundantly clear that there are clinical gaps in this area that require addressing. Food driving AD is not an unreasonable notion, as about one third of moderate to severe AD patients have verifiable food allergies: type I hypersensitivity reactions with hives, angioedema, or anaphylaxis. Such a reaction constitutes bona fide food allergy and remains a critically important consideration for patients. Although correlation most certainly does not equal causation, it can be hard to ignore the power of their allergenicity: a single bite is often enough to trigger an impressive immediate reaction. While this reaction could secondarily trigger an AD flare, it is fundamentally different from a primary eczematous response, and assuredly not what people are talking about when searching for causative foods.

Several studies have sought to separate these concepts of food allergy and what might be called “food-induced atopic dermatitis.” In a carefully controlled environment, 19 children with severe, unremitting atopic dermatitis were challenged with test foods and observed for a worsening of AD rather than an urticarial response. Remarkably, only one patient had worsening AD after food challenge. Another study by Hill, et al. sought delayed eczematous reactions several days after a cow’s milk challenge, and
found evidence of such in only 28 out of 135 children, or about 20 percent of these highly-selected patients with a history strongly suggestive of cow’s milk allergy. Importantly, 12 of the 28 positive cases (43 percent) had negative skin prick tests to cow’s milk allergen, suggesting an alternative pathogenesis than type I allergy. Finally, all of the patients with eczematous exacerbations, save one, showed associated gastrointestinal and/or respiratory manifestations, making an isolated eczema flare an extremely rare occurrence.

A striking study by Thompson and Hanifin demonstrated another potential facet of this relationship. They found that in 80 percent of cases in which patients were convinced that food was a significant factor contributing to their AD, such concerns became negligible once better control of the eczema was achieved. Importantly, such a finding helps to dismiss the idea that non-allergic mechanisms could be at play—regardless of the mechanism or any test results, the patients simply seemed to be able to tolerate foods that they previously had suspected as being triggers.

This draws two possibilities into the light: the first is the idea that much of the concern about foods is emotional and/or psychological. There is significant literature that highlights the power of placebo in dietary change across several disease states, and it would not be surprising if this at least partially explained some of these cases. This is magnified in the context of a waxing and waning disease like AD, in which it has been convincingly argued that misattribution is common and presumably works in both directions: that food can cause AD as well as that excluding foods can improve it.

The second possibility, admittedly very speculative, is that there may be something of a threshold effect at play. That is to say, when eczema is more severe and undertreated, certain factors may be more likely to trigger a flare than when things are better controlled. This is particularly relevant when invoking non-allergic mechanisms for potential food-related exacerbations. This area remains somewhat murky, but is important to consider, as some foods may simply be pro-inflammatory, working to exacerbate the disease outside of a specific allergic mechanism.

While these studies certainly do not disprove true food-induced AD, and in fact validate its existence to some degree, they underscore how rare it is, even in carefully selected high-risk patients. Moreover, they confirm that such an eczematous reaction does not correlate with skin prick or serologic testing in a reliable way, calling their use into question for this specific clinical scenario. The Hill, et al. study underscores the rarity of an isolated eczematous response, with nearly all of the patients having associated

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gastrointestinal or respiratory symptoms as well. Finally, the Thompson and Hanifin study raises the specter of non-specific inflammatory effects playing a small role, possibly modulated by background disease severity.

This may be a good point to outline at least provisional definitions for some of the terminology discussed:

- Sensitization or Sensitivity can be defined as having positive IgE blood testing or skin prick testing to a food regardless of clinical applicability.
- IgE-mediated food allergy refers to a clinical response to a food, including urticaria, angioedema, or anaphylaxis in someone who is sensitized.
- Food intolerance is a broader category including non-immunologic issues such as inability to digest lactose ("lactose intolerance"), but may also include irritable bowel syndrome, reactions to sulfites, and even the immune-mediated disease celiac sprue in some taxonomies.
- Less-specific “inflammatory” foods and “anti-inflammatory” foods that may indirectly contribute to or modulate against some degree of inflammation in the body either directly or indirectly through better overall health, weight loss, and even through the powerful placebo effect of feeling better about one’s health and diet.

**IS THE PROOF IN ELIMINATING THE PUDDING?**

We have thus far looked at scenarios that utilize food challenge, but do exclusionary diets improve AD? While the notion of simply removing troublesome foods remains appealing, a recent comprehensive review of the literature has concluded that, “current evidence suggests that strict diet management is not effective in the treatment of AD in the vast majority of patients.”22 It is worth examining a few studies more closely to gain insight into the subtleties therein.

In 1978, Atherton, et al. performed a 12-week double-blind, controlled, crossover trial of an egg and cow’s milk exclusion diet in 36 children with AD. They found that 14 patients responded better to the exclusion diet than to the control diet, whereas only one responded better to the control diet.23 Notably, there was no correlation between a positive skin prick test and response to the exclusion diet, suggesting that this was not type-I allergy mediated.

Businco, et al. placed 59 children on a four-week elimination diet of cow’s milk, eggs, or both (depending on their diet), and reported an almost unbelievable 80 percent clinical improvement.24 Critically, the mean age of those who responded was significantly younger than those who did not respond (3.5 vs 4.7 yrs) (p < 0.01). The authors attempted to justify this by positing that the foods were more likely to be part of the younger children’s diet. Here again, they concluded that skin prick tests and serum IgE tests would not be helpful for predicting benefit.

Other studies have been less convincing. What do we make of the double-blind randomized controlled trial of egg and cow’s milk exclusion diet completed in 40 patients over six weeks by Neild, et al.?25 They found no statistically significant differences in skin area affected, itching, or topical steroid use between the groups. And what about the study of 29 children with AD on a two-week elimination diet? It showed significant improvement in itch and body surface area affected by eczema, challenging the conclusions of the Neild, et al. study. Notably, the elimination diet did not improve sleep disturbance or clinical severity scores.26 Concerningly, only 13 of the 29 children completed the trial, and only two of the children were ultimately able to identify relevant foods. Worse, they reported similar clinical improvement in three of eight children who had stopped the elimination diet during the study, yet again raising the possibility that other factors may be at work.

Thus far, these studies have employed general or unselective elimination diets that focus on presumably high-risk foods, specifically cow’s milk and egg. A tailored elimination diet is one in which foods are chosen based on testing. Eliminating only specific foods with cause may be a more strategic approach.

A study of 100 children with AD demonstrated encouraging results with an elimination diet based on positive double-blind placebo-controlled food challenges (DBPCFCs). This tailored diet not only improved disease severity, but also decreased topical corticosteroid use by 85 percent compared to control.27 The food allergy breakdown in this study was notable for being similar to the most common IgE-mediated allergens: egg (67 percent), peanut (54 percent), and milk (30 percent), to name a few. Another study placed...
DID YOU KNOW?

There have been multiple reports of children with AD on elimination diets worsening into more severe IgE-mediated reactions (including fatal anaphylaxis) to the excluded foods. A recent paper found that 19 percent of patients with a history of food-triggered AD and no prior immediate reactions developed new immediate food reactions after starting an elimination diet.

44 children with AD on a tailored elimination diet. This study was less rigorous than the previous one, unfortunately, and was based on an open oral provocation test. Here the elimination diet found moderate to marked improvement in an impressive 40 of 44 patients. The lack of a placebo control group and a blinding method are significant limitations of this study, despite the high success rate. Unlike those in the prior study, the most common offending foods here were chocolate, cheese, and yogurt, which were found to be generally negative on serum IgE testing.

Our wariness toward elimination diets as a method of controlling AD makes sense, as elimination diets are being challenged in the allergy world, as well. The concept of strict allergen avoidance as a method of food allergy control has been undermined by the recent success of oral immunotherapy (OIT), in which patients are systematically given the allergen in an attempt to build up their tolerance. Numerous studies of OIT to foods commonly associated with AD flares (cow’s milk, egg, and wheat) shed light on the complex relationship between food allergies and AD. A review by Eigenmann, et al. comparing such studies concluded that “skin rashes and AD flares were reported [during OIT trials], but worsening of AD seemed to be mostly marginal.”

This all culminates in a very complex place: general, unselected exclusion diets seem to be somewhat hit or miss and may have other non-immunologic mechanisms at work. Tailored exclusion diets appear more favorable, but they come with a cost: the more accessible serum or skin prick testing does not appear to be helpful in selecting these foods, making the much more onerous and expensive DBPCFC necessary to select the proper foods to exclude.

WHAT COULD GO WRONG?

If the bar is so high for testing, why not just pick a food and try an elimination diet? What could go wrong? Several things, actually. The first is that heavily restricted diets that are unsupervised can be harmful. Practices such as taking unpasteurized goat’s milk can expose children to dangerous infections, while feeding them exclusively rice milk can lead to severe malnutrition and hypoalbuminemia.

More insidiously, perhaps, is that there have been multiple reports of children with AD on elimination diets that worsened into more severe IgE-mediated reactions (including fatal anaphylaxis) to the excluded foods. A recent paper found that 19 percent of patients with a history of food-triggered AD and no prior immediate reactions developed new immediate food reactions after starting an elimination diet. Most were cutaneous reactions only, but a sobering 30 percent were anaphylaxis, with cow’s milk and egg being the most common offenders.

Dietary restrictions can be difficult for adults, perhaps even more so for children. They may thus add additional stress, a known triggering factor for AD itself. Lastly, dietary modifications can be a tremendous distraction to basic therapy, delaying treatment for someone who is suffering from itch, poor sleep, and sometimes even infections and pain while searching for a proverbial needle in a haystack—one that might not even be there.

LEAKY SKIN

Which brings us back to the beginning. We began with the notion that skin barrier dysfunction was a primary cause in at least some cases of AD. In 2015, the landmark Learning Early About Peanut Allergy (LEAP) study demonstrated that infants significantly reduced the risk of developing peanut allergy with early introduction of peanuts into the diet. Researchers concluded that, “...early environmental exposure (through the skin) to peanut may account for early sensitization, whereas early oral exposure may lead to immune tolerance.”

This idea that a deficient skin barrier could lead to developing food allergies represents a total reversal from where the discussion started: instead of looking for foods that cause the eczema, it appears that treating the eczema (and its associated leaky skin) could prevent food allergy. This model of transtuberculous sensitization has been nicely demonstrated in animals and likely bears out in people, as well. In the meantime, we have witnessed a significant shift in terms of clinical guidelines based on this new understanding: while previous guidance suggested delaying introduction of allergenic foods into the diet of high-risk children, current guidelines encourage those four to six months of age with AD to eat peanuts in order to reduce the risk of peanut allergy. It is crucial, however, to test those with severe AD and/or
known egg allergy prior to introduction, since they have the highest risk of already being peanut allergic.\textsuperscript{39}

Taking this a step further is the idea that skin barrier dysfunction is so central to AD that enhancing the barrier with moisturizers to “seal up the leaky skin” may actually prevent the very development of AD, and consequently, secondary diseases such as food allergy. Studies have already demonstrated cutting the development of AD in high-risk patients by up to 50 percent with moisturization alone, and larger studies are planned to confirm these findings.\textsuperscript{40-42}

There is a remarkable convergence with another developing line of thought: \textit{Staphylococcus aureus} colonization has increasingly been found to play an important pathogenic role in AD\textsuperscript{43} and, in turn, may also directly impact food sensitization. In a recent study, \textit{Staphylococcus aureus} colonization was found to be, independent of atopic dermatitis severity, associated with food sensitization and allergy.\textsuperscript{44} The authors hypothesize that this is via a sensitizing toxin secreted by \textit{staphylococcal} enterotoxin B (SEB).

### CONCLUSION

Tremendous advancements in understanding the pathogenesis of AD are leading to a new standard of care, with a higher bar set for disease education, treatment, and potentially even prevention. Patients will continue to ask about diet and eczema, and it is important to understand this tangled web. For those with allergies verified by skin prick testing, serology, or food challenge, avoidance may be absolutely necessary or at least helpful in some cases. For those without proven allergies, it may actually be detrimental to exclude foods as they may be more likely to develop a true food allergy. The gray area of potentially inflammatory foods or non-immunologic mechanisms of exacerbation leaves many unanswered questions.

Optimizing topical care takes on new importance, as an impaired barrier may be a gateway to transepidermal sensitization and actually developing allergies if left unchecked. At the same time, it is difficult to argue against recommending a healthy diet, as there is little doubt that eating well promotes health in every organ system, including the skin. But to do so while maintaining a focus on the skin, where we can rapidly and much more reliably make a difference, may represent the middle path. |

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