[LITERATURE REVIEW]

Diet and Dermatitis: Food Triggers

RAJANI KATTA, MD; MEGAN SCHLICHTE, BSc
Baylor College of Medicine, Houston, Texas

ABSTRACT

Given increasing awareness of the link between diet and health, many patients are concerned that dietary factors may trigger dermatitis. Research has found that dietary factors can indeed exacerbate atopic dermatitis or cause dermatitis due to systemic contact dermatitis. In atopic dermatitis, dietary factors are more likely to cause an exacerbation among infants or children with moderate-to-severe atopic dermatitis relative to other populations. Foods may trigger rapid, immunoglobulin E-mediated hypersensitivity reactions or may lead to late eczematous reactions. While immediate reactions occur within minutes to hours of food exposure, late eczematous reactions may occur anywhere from hours to two days later. Screening methods, such as food allergen-specific serum immunoglobulin E tests or skin prick tests, can identify sensitization to specific foods, but a diagnosis of food allergy requires specific signs and symptoms that occur reproducibly upon food exposure. Many patients who are sensitized will not develop clinical findings upon food exposure; therefore, these tests may result in false-positive tests for food allergy. This is why the gold standard for diagnosis remains the double-blind, placebo-controlled food challenge. In another condition, systemic contact dermatitis, ingestion of a specific food can actually cause dermatitis. Systemic contact dermatitis is a distinct T-cell mediated immunological reaction in which dietary exposure to specific allergens results in dermatitis. Balsam of Peru and nickel are well-known causes of systemic contact dermatitis, and reports have implicated multiple other allergens. This review seeks to increase awareness of important food allergens, elucidate their relationship with atopic dermatitis and systemic contact dermatitis, and review available diagnostic and treatment strategies. (*J Clin Aesthet Dermatol.* 2014;7(3):30–36.)

The subject of diet and dermatitis has been studied for decades. Many patients with chronic dermatitis, and many parents of children with atopic dermatitis (AD), are concerned about whether diet can either cause or exacerbate dermatitis. This concern has intensified as the prevalence of food allergy has risen in recent decades, with increasing numbers of food-induced anaphylaxis.[1] In fact, the majority of parents of children with AD have attempted dietary changes.[2]

A number of studies have been performed to investigate the link between diet and dermatitis. Research has established that for some patients with AD, specific foods can indeed lead to an exacerbation of dermatitis. In the case of systemic contact dermatitis (SCD), specific foods can actually cause dermatitis. Establishing which patients may be helped by avoiding specific foods, however, requires a thorough medical evaluation.

ATOPIC DERMATITIS AND FOOD ALLERGY

Atopic dermatitis is a chronic, relapsing, inflammatory skin condition that causes erythematous, pruritic skin lesions. While estimates vary, particularly according to geographic region, it has an estimated lifetime prevalence in children of 10 to 20 percent, and a prevalence in adults of 1 to 3 percent.[3] A rising prevalence over the last several decades has been noted in particular in industrialized countries. Although clinical and family history are usually sufficient to make the diagnosis, the United Kingdom Working Party's minimum criteria for a diagnosis of AD (independent of age, sex, region, social class, or ethnicity) include a history of dermatitis involving the flexural surfaces, history of dry skin, onset prior to two years of age, personal history of asthma, history of cutaneous pruritus, and visible flexural dermatitis.[4] While the pathophysiology of AD is not fully understood, a genetic predisposition to skin barrier dysfunction in combination with environmental

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ADDRESS CORRESPONDENCE TO: Rajani Katta, MD, 1977 Butler Blvd., Suite E6.200, Houston, TX 77030

factors, such as irritants, microbes, extremes of temperature, psychological stress, and allergens, contribute to its multifactorial development.[5]

While the development of AD has clearly been shown to be multifactorial, one area of research has focused on food allergies as an exacerbating factor. It is well known that AD and food allergy are highly correlated. The overall estimated prevalence of food allergy in children with AD has ranged widely, from 20 to 80 percent,[6] due to different populations, AD severity, and defining criteria for food allergy. In general, food allergies are more likely with earlier onset and increasing severity of AD.[7] Werfel et al[8] summarized the results of eight studies and found a reported prevalence of food allergy in children with eczema, as proven by double-blind placebo-controlled food challenge (DBPCFC), ranging from 33 to 63 percent.[8] These studies included both unselected children with AD and those with moderate-to-severe AD.

While AD and food allergy are clearly correlated, the subject of food allergens serving as an exacerbating factor for AD has historically been a subject of controversy. Clinical studies over the last several decades, though, have confirmed that food allergy may play a role in exacerbating AD in some patients. Those most likely to be impacted are infants and children with moderate-to-severe AD. The proportion of AD patients whose skin symptoms are linked to food allergens has varied considerably in different studies. This is due to several variables: AD severity, age of subjects, criteria for diagnosis of food allergy, and duration of observation following food ingestion, among others.

Many food allergies will resolve in early childhood, and food allergy is not felt to be a common exacerbating factor of AD in older children and adults.[9] While some adult patients have exhibited eczematous reactions to foods that are cross-reactive to birch pollen[10] (such as green apple, carrot, hazelnut, celery, and pear), the prevalence of this type of reaction in unselected adult AD patients appears to be low.[11] With limited studies, however, this is an area requiring further study.

FOOD ALLERGY

The majority of food allergic reactions in the United States are triggered by peanuts, tree nuts, cow's milk, eggs, soy, wheat, seafood, and shellfish.[12] The term "food allergy" is frequently used by patients as well as the media. Some use the term to refer to anaphylaxis, while others use the term to refer to any type of reaction that occurs following ingestion of a specific food.

Due to the confusion surrounding food allergy, an expert panel was convened to publish clinical guidelines for the diagnosis and management of food allergy. The panel represented 34 professional organizations, federal agencies, and patient advocacy groups and was sponsored by the National Institute of Allergy and Infectious Disease (NIAID), a division of the National Institutes of Health (NIH).[13] Food allergy was defined by the panel as an "adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food." The term therefore encompasses several different types of reactions and includes both immunoglobulin E (IgE)-mediated and non-IgE mediated immunological reactions.

The panel, in reviewing the literature, noted that "multiple studies demonstrate that 50 to 90 percent of presumed food allergies are not allergies."[13] History, therefore, is often not a reliable indicator. Several diagnostic tests exist, but must be utilized and interpreted with care due to the high rate of false-positive testing and low predictive value for some tests when used alone.

Much of the confusion surrounding testing for food allergy is related to the concept of sensitization. The panel stated that sensitization is evidenced by allergen-specific IgE. However, patients can have sensitization without ever developing clinical symptoms upon exposure to these foods. Therefore, a diagnosis of IgE-mediated food allergy requires both sensitization and specific signs and symptoms following food exposure. In other words, a positive skin prick test (SPT) or serum IgE test alone is not sufficient to diagnose food allergy.

Complicating the clinical picture is the fact that food allergy can present as a single symptom or as a symptom complex, and these can develop anywhere from minutes to days following ingestion of foods.[12]

ATOPIC DERMATITIS AND IgE-MEDIATED IMMEDIATE REACTIONS

Immediate reactions are IgE-mediated and may include a wide spectrum of clinical findings. These may occur within minutes to hours of food ingestion and can present as a single symptom or a combination of symptoms. These reactions may involve a single organ system or multiple systems, including the cutaneous, respiratory, cardiovascular, and gastrointestinal systems. While immediate reactions can manifest as anaphylaxis, which is a rapid-onset, severe, and potentially fatal reaction, reactions may also vary widely in severity. Cutaneous findings may include pruritus alone or in combination with erythema, morbilliform eruptions, urticaria, or angioedema.

It has long been recognized that immediate reactions can lead to an exacerbation of AD due to pruritus and the resultant scratching. In 1936, Engman et al[14] described a child with AD, sensitive to wheat, whose symptoms improved on a wheat-free diet. When fed wheat again, the child developed pruritus, began scratching, and again developed eczematous changes.[14] While it has been suggested that immediate reactions may also lead to AD exacerbation via immune mediators, this requires further study.

One study of children with severe AD demonstrated that when foods triggering immediate reactions were eliminated from the diet, AD improved. In a study of 113 children with severe AD, SPT was performed and was followed by DBPCFC in children with positive tests.[15] Of these children, 63 experienced symptoms on food challenge. All symptoms occurred within two hours, with a recurrence of pruritus in some patients occurring 6 to 8 hours later. Cutaneous symptoms were seen in 84 percent

of challenges, with a diffuse erythematous macular or morbilliform rash and pruritus. It was notable that while most children had demonstrated reactions to multiple foods on SPT, most who reacted to the oral food challenge reacted to only one food. Of children with a documented food allergy followed by dietary elimination, most showed significant improvement of their AD, typically within 1 to 2 months.

Diagnosis of immediate reactions can be challenging. SPT and allergen-specific serum IgE tests may be helpful in identifying potential food allergens, as they test for sensitization. However, neither test alone is diagnostic of food allergy. Studies have found that these tests exhibit multiple false-positive reactions and have low predictive value for food allergy. Therefore, positive test results must typically be confirmed via a food challenge test. The gold standard for diagnosis is the DBPCFC, in which the suspect food and placebo are administered in the clinic or hospital setting. In cases with a suggestive medical history, elimination of one or a few specific suspect foods may also be helpful in diagnosis.

ATOPIC DERMATITIS AND LATE ECZEMATOUS REACTIONS

Late eczematous reactions may occur anywhere from hours to two days following ingestion of a trigger food. Unlike an immediate reaction, the onset of late eczematous reactions is delayed. Following ingestion of a food, affected persons experience an exacerbation of AD. These eczematous reactions usually require at least six hours to develop,[6] and in one study occurred on average 24 hours later.[16] This has been described as "food responsive eczema."[16] While late reactions may occur in conjunction with immediate reactions, they may also occur as isolated reactions.

The overall prevalence of late eczematous reactions is unknown, but is likely underestimated, as studies of food allergy do not always evaluate for this type of reaction. Werfel et al[8] state that "a problem in most published clinical evaluations of food allergy in atopic eczema is that eczema which usually worsens on the day after the oral food challenge or even later was not scored systematically before and the day after oral food challenges." In other words, if a researcher is not specifically seeking this type of reaction, it will not be noted.

In one study, DBPCFC (with cow's milk, egg, soybean, or cereals) were administered to 73 patients with AD following SPT and patch testing. The food challenge triggered immediate onset exanthematous reactions in 22 cases and late onset eczematous reactions in 29.[17]

In another study, DBPCFC were administered to 106 children with AD. The foods included cow's milk, egg, wheat gluten, and soy.[16] In 46 percent of these food challenges, an allergic reaction resulted. Of these, 43 percent were immediate reactions, 45 percent were immediate symptoms followed by late eczematous reactions, and 12 percent were late eczematous reactions alone. The immediate reactions always included skin reactions, mainly erythema or urticaria. With late eczematous reactions, after an average of 24 hours, patients exhibited a flare of AD, typically a flare of pre-existing lesions.

Interestingly, a flare of eczema following ingestion of a specific food had only been suspected by the parents in 33 percent of patients.[16] In this study, patients also underwent testing for food-specific IgE and atopy patch testing. Both of these tests were often false positive, and therefore exhibited low positive predictive value.

The pathogenesis of late eczematous reactions remains unknown. In this study, 25 percent of patients with positive food challenges had negative tests for food-specific IgE, indicating that IgE may not be directly involved. In another study of DBPCFCs, 10 percent of positive food challenges were not associated with food-specific IgE.[18] This may also explain the results of a dietary exclusion trial, in which 60 percent of children with AD experienced significant improvement following exclusion of milk and eggs. In this DBPC trial, children with AD completed a trial of an egg and milk exclusion diet. AD in children on the exclusion diet improved significantly, based on number of areas affected, pruritus, and sleeplessness, as compared to controls.[19] Despite this improvement, no correlation was noted between a positive SPT and response to the trial diet.

While late eczematous reactions are broadly categorized as non-IgE-mediated, the pathophysiology is unclear. Due to this fact, no accurate laboratory testing is available at this time. While studies of DBPCFCs have confirmed that some patients exhibit food allergen-specific IgE on testing, the positive predictive value (PPV) is low. The PPV was only 33 percent for eczematous reactions as opposed to 57 percent for immediate reactions.[6]

T cells do play a role, as food allergen-specific T cells have been shown to be involved in late eczematous responses to food.[20] T-cell clones from patients with AD worsened by milk have shown higher proliferative responses than those from controls.[21,22] Patch testing is used to diagnose allergic contact dermatitis, another type of allergic reaction mediated by T cells. Researchers have therefore studied whether atopy patch tests (APT) with food allergens may be of utility in late eczematous reactions. While positive APTs have been noted in some patients with positive food challenges and negative food-specific IgE tests, results from different studies have indicated a great variation in PPV for this test. While this may be due to the types of reactions studied, as well as variations in allergen preparation, at this time APTs are not used routinely.

From a diagnostic standpoint, DBPCFCs remain the gold standard in diagnosis of late eczematous reactions. With late reactions, it is particularly important that the period of observation extends to two full days. A diagnostic elimination diet may also be utilized initially, in which a suspected food (based on history) is excluded for a period of 4 to 6 weeks.[8] Since improvement in AD symptoms may be coincidental, or due to placebo effect, suspect food allergies may still require confirmation via food challenge.

RECOMMENDATIONS FOR FOOD ALLERGY TESTING IN PATIENTS WITH ATOPIC DERMATITIS

While testing for food allergies is not warranted in all children with a new diagnosis of AD, it may be helpful in a specific subset of patients. The NIAID expert panel suggests that children less than five years of age with moderate-to-severe AD should be evaluated for a food allergy if they have intractable AD despite optimal management and topical treatment. Children should also be tested if they have experienced an immediate reaction following ingestion of a specific food.[13,23]

If suspecting an immediate reaction, testing may include SPT and allergen-specific serum IgE tests. However, as stated earlier, these test for sensitization only. Therefore, neither test alone is diagnostic of food allergy, and positive test results must typically be confirmed via food challenge test.

In cases of suspected late eczematous reactions, no accurate laboratory testing is available at this time, as the pathophysiology is unclear. Therefore, DBPCFCs remain the gold standard in diagnosis, with an observation period that extends to two full days. Some researchers have also recommended a diagnostic elimination diet, in which a suspected food (based on history) is excluded for a period of 4 to 6 weeks. Since improvement in symptoms may be coincidental or due to placebo effect, confirmation by food challenge may still be required.

FOOD ELIMINATION DIETS IN PATIENTS WITH ATOPIC DERMATITIS

In cases of confirmed food allergy, patients would expect that avoidance of that food would help with their dermatitis. Studies have confirmed this, in both IgE-mediated reactions and late eczematous reactions. In a randomized controlled trial (RCT) of 55 children with AD and possible egg sensitivity as identified by RAST later confirmed by food challenge, children in the egg exclusion group demonstrated, after four weeks, a significant reduction in eczema surface area and severity as compared to controls.[24] This has been demonstrated in multiple case reports and studies.[14,15,19,25]

While food elimination diets may be helpful in a subset of patients with AD, they must be recommended with caution, and only in specific cases. The National Institute of Allergy and Infectious Diseases (NIAID) expert panel recommends avoidance of the specific food allergen(s) in cases of documented food allergies concurrent with one or more atopic conditions, including AD, asthma, or eosinophilic esophagitis.[13] While avoidance of food allergens may reduce symptom severity, available evidence does not indicate whether avoidance will alter the pathological progression of AD, eosinophilic esophagitis, or asthma.[13]

Food elimination diets should not be recommended to all patients with AD. The effects of food restriction diets are difficult to quantify due to the multifactorial nature of AD development, the challenges inherent in compliance to diet, the need for patient education, and the shift to alternative foods that may have increased or decreased nutrients. However, a systematic review of nine RCTs, which investigated the effect of elimination diets on unselected AD patients, found little evidence to support dietary exclusions.[13] Restriction of more than three foods has shown no significant benefit in diminishing AD severity in the pediatric population, possibly secondary to alterations of vitamin and mineral stores.[26] While some dietary exclusion trials have suggested positive effects on AD even with negative SPT,[19] this type of testing alone is not sufficient to diagnose all cases of food allergy, and therefore, such results may be misleading.

In summary, food elimination diets may be helpful in a subset of patients with AD, but they must be recommended with caution and only in specific cases. The NIAID expert panel recommends avoidance of the specific food allergens in cases of documented food allergies concurrent with AD. In the absence of documented food allergies, dietary restrictions are not advised for patients with AD, as no evidence exists to suggest reduction of symptom severity. Even among those for whom there is proven benefit, care must be taken with food avoidance. Indiscriminate restriction of potentially allergenic foods may adversely affect growth and development and lead to nutritional deficiencies. Other risks of food elimination diets include social isolation, especially among children, and anaphylaxis following uncontrolled re-introduction of a previously restricted food.[27]

Food allergies among children tend to diminish with age, with the exception of nuts. Most children with food allergies eventually tolerate milk, egg, soy, and wheat, while allergy to peanuts and tree nuts is likely to persist.[28] Thus, after 12 to 24 months, restricted foods may be reconsidered for inclusion in the diet. It has been demonstrated with trials of allergen-restricted diets (duration ranging from 6 months to 4 years) that when a patient develops immunological tolerance to a food, re-introduction of the food is possible without a return of symptoms or exacerbation of existing AD.[13] In one study of 75 children with AD (ranging in age from 3 to 18 months), 60 percent of whom had at least one diagnosed food allergy, 26 percent of patients no longer exhibited food allergy in response to a food challenge test following 1 to 2 years of an allergen-restricted diet.[29] Patients who demonstrate co-morbid respiratory symptoms upon food challenge are much less likely to experience resolution of a food allergy relative to those with symptoms limited to the skin and/or gastrointestinal tract.[13]

SYSTEMIC CONTACT DERMATITIS

In persons with systemic contact dermatitis (SCD) due to dietary allergens, ingestion of specific foods can cause dermatitis. SCD is a specific immunological reaction, mediated by T cells, in which dermatitis occurs following systemic exposure to an allergen. The reaction requires sensitization to an allergen with subsequent systemic exposure.[30] This exposure may occur via several routes, including ingestion, inhalation, intravenous administration, or intramuscular administration. Our focus is on dietary exposure to allergens. Research indicates that in a subset of

patients with allergic contact dermatitis (ACD) to specific allergens, dietary elimination of these allergens will result in improvement of their dermatitis. Well-described allergens in foods that can trigger SCD include balsam of Peru (BOP) and nickel. Multiple reports have implicated other food allergens, including propylene glycol, chamomile, and formaldehyde.

ACD and SCD are related but have distinct immunological reactions. A subset of patients with ACD to a specific allergen will develop SCD following systemic exposure. Both reactions are T-cell mediated, and patch testing is used in both conditions to identify the causative allergens. Clinical presentation, however, may differ markedly. ACD occurs due to external allergen exposure that results in a local inflammatory response at the site of skin contact. SCD may have multiple clinical presentations. Some patients present with localized flares of dermatitis at sites of previous involvement, while others present with a non-specific exacerbation of their dermatitis.[31] SCD due to ingestion of BOP may result in either localized dermatitis, such as of the face, hands, or genitals, or a widespread dermatitis.[32] Nickel SCD often presents with acute vesicular hand dermatitis, while several allergens have resulted in a maculopapular rash. SCD may result from a number of oral medications, and may result in a specific cutaneous reaction pattern known as SDRIFE (symmetrical drug-related intertriginous and flexural exanthema).[33] This pattern was originally known as baboon syndrome, due to the symmetric erythematous eruption of the buttocks and flexural areas. Cutaneous reactions may occur within hours or days following allergen exposure.[31]

While both ACD and SCD are mediated by T cells, the pathogenesis of SCD is not well-understood. A key question is why only a subset of patients with ACD will react to allergens upon dietary exposure. No laboratory test is available to determine if a patient with ACD is also affected by SCD. Therefore, if a patient with ACD to nickel, BOP, or another well-recognized dietary allergen does not improve upon avoidance of cutaneous contact, dietary avoidance would be recommended for a period of 6 to 8 weeks. It is also important to note that SCD may occur in conjunction with AD. In these cases, dermatitis may improve with allergen avoidance, but not resolve, due to the underlying AD.

Balsam of Peru. SCD to BOP in foods has been recognized for decades.[34] BOP is obtained from the tree *Myroxylon balsamum pereirae* and consists of a mixture of potential allergens. These include chemicals such as cinnamates and vanillin that are related to or are found in flavorings, spices, and certain foods.[35] BOP serves as a marker of allergy to fragrance and is one of the most common allergens in North America.

In patients allergic to BOP, some do not improve with external avoidance of fragrance additives. In these patients, BOP avoidance diets may be effective. In one study, patients who underwent patch testing and were found to be fragrance-allergic, but who did not improve with avoidance of external fragrance allergens, were asked to follow a BOP avoidance diet. In these 45 patients, 47 percent either cleared or had substantial improvement.[32]

Major related foods to avoid include citrus fruits, tomatoes, and certain spices. Since spices, such as cinnamon, vanilla, and cloves, are related to BOP, patients must be careful with baked goods, certain condiments, and certain liquors. Other potential triggers include chocolate and colas.

Nickel. Nickel is the most common allergen in North American patients undergoing patch testing. While many patients are aware that nickel may trigger ACD via jewelry, watchbands, or other metal objects in contact with the skin, fewer patients are aware that dietary nickel can lead to dermatitis. Acute vesicular hand dermatitis in particular has been associated with dietary nickel.

In one DBPC trial, patients were asked to ingest nickel in capsule form. Some nickel-allergic patients reacted to levels that would be expected in a normal diet. In contrast, patients who were not sensitive to nickel did not react to high-nickel doses.[36]

Other studies have found that compliance with a low-nickel diet leads to skin improvement.[37] Use of an oral nickel-chelating agent, disulfiram, has also shown benefit. In a study of nickel-allergic patients with hand eczema, use of disulfiram led to significant improvement in 8 of 9 patients.[38]

Patients with dyshidrotic hand eczema and allergy to nickel may therefore benefit from a low nickel diet. Avoidance for 6 to 8 weeks may be required to see improvement. Guidelines for a low-nickel diet have been published,[31,39–41] but these recommendations can only serve as guidelines. Studies have found that nickel content of foods can vary in different parts of the country, based on such factors as local soil conditions and the use of fungicides.[31] Individual factors also play a role, as dietary absorption of nickel from food and water can vary significantly.

Foods that are higher in nickel include certain grains, including whole wheat bread and oatmeal. Vegetables that are higher in nickel content include beans, lentils, peas, soybeans and soy products, and some canned vegetables. Shellfish, processed meats with fillers, and canned meats or fish are also included. Other sources of dietary nickel include chocolate, nuts, seeds, black tea, and canned foods in general.

Other causes of SCD. A number of other allergens found in foods or dietary supplements can trigger SCD. Propylene glycol (PG) is one such allergen, found in some artificial food products.[42] PG is an excellent humectant and solvent, and therefore is found commonly in many skin and hair care products as well as topical medications. It is also used in various industries and is found in anti-freeze and brake fluid. Interestingly, this same substance is also found in many commercially prepared food products. It may be found in a diverse range of commercial food products, including such items as salad dressings, barbecue sauce, snow-cone mixes, food colorings, and sour cream.[39] A review of a website listing ingredients of more than 75,000 foods (www.foodfacts.com) found that propylene glycol was found in 2,001 food products.[43] Its presence is indicated on the

ingredient list of these foods.

Some ingested herbs and flowers may also trigger SCD. One example is chamomile, a member of the *Asteraceae* plant family whose members contain sesquiterpene lactones. These can act as allergens and have resulted in SCD following ingestion of chamomile tea.[44]

Formaldehyde and formaldehyde-releasing preservatives are commonly used in skin and hair care products, but can be found in some foods as well. Foods that contain formaldehyde have triggered dermatitis, such as eyelid dermatitis, due to formaldehyde derived from ingested aspartame.[45]

CONCLUSION

While the cutaneous manifestations of exposure to food allergens vary in terms of the underlying immunological reaction, clinical presentation, severity, and time course, it is clear that multiple food allergens may serve as triggers for dermatitis. In patients with AD, food allergens may lead to an exacerbation of dermatitis. In patients with SCD, food allergens may be the cause of the dermatitis. In selected patients with AD, avoidance of specific dietary allergens has resulted in improvement of signs and symptoms of chronic dermatitis. In patients with SCD, avoidance of allergens, as identified by patch testing, has resulted in resolution of the dermatitis. Increased awareness of potential food triggers, in conjunction with the appropriate diagnostic testing, can facilitate early identification of allergens, thus reducing the morbidity associated with chronic dermatitis and improving quality of life.

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