# Food allergies in atopic dermatitis

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## Abstract

The relationship between Atopic dermatitis and food allergies remain controversial, it is not uncommon for patients and their care givers to question the possibility of allergy to food items acting as triggers for flare ups. This article seeks to examine the relationship between atopic dermatitis and food allergies and discusses the diagnosis of food allergy in patients with atopic dermatitis.

Key words: food allergies, atopic dermatitis

## Background

Atopic dermatitis, also known as eczema, is a chronic relapsing inflammatory skin disease characterised by skin dryness, erythema and lichenification. It is the most common chronic skin condition affecting approximately 5 to 20 percent of children and 2 to 5 percent of adults worldwide (1). The prevalence appears to be increasing (2), with the disease inflicting a high social and economic burden on society, especially as it starts in childhood and progresses into adulthood. It is estimated to cost over 5 billion dollars annually in direct and indirect costs (3). Treatment is often aimed at adequate prevention and management of flare ups.

## Epidemiology

Atopic dermatitis commonly starts in childhood, with 60% developing the disease within the first six months and 90% within the first five years (4). Children usually outgrow the disease, as around 60% will be disease-free by adolescence (1). It may present as the first in a series of atopic conditions such as food allergy, asthma and allergic rhinitis, the so-called “atopic march” (1). The prevalence is more in female children at a ratio of 1.3 to 1 (5), and it is more commonly observed in Asian and black patients (6).

## Pathophysiology

Atopic dermatitis is thought to arise from a complex interplay of genetics, barrier function, immunity and environmental factors, acting together and synergistically to drive barrier dysfunction, inflammation and disease progression (7).
Two theories have been proposed to explain the aetiology of atopic dermatitis. The first explains a primary barrier dysfunction leading to the penetration of allergens and microbes resulting in inflammation, whilst the second describes a primary immunological dysfunction leading to inflammation and subsequent barrier dysfunction. It is believed that both theories play a role in the aetiology of the disease (2).

The barrier function of the skin is in the stratum corneum. The permeability of the epidermis is determined by interactions between the keratinocytes on the skin surface, structural proteins such as filaggrin, regulatory enzymes and lipids (8). Filaggrin plays an important role in the development of barrier protein clusters, maintaining surface PH and retaining water in the cornified layer. Recent evidence suggests that a mutation in the filaggrin gene is responsible for up to 50% of atopic dermatitis, with the mutation resulting in epithelial barrier dysfunction (9). Defects in other proteins and enzymes in the stratum corneum and tight-junction related proteins in the stratum granulosa, have also been reported to contribute to epithelial barrier dysfunction (8,10).

Patients with atopic dermatitis have been shown to have a genetically predetermined imbalance in the T cells subsets with predominance of T-helper 2 cells (Th2) rather than T-helper 1 cells (Th1) (11). During the acute phase of the illness, allergen stimulation from the impaired epidermal barrier is thought to stimulate the dendritic cells to promote a Th2 driven immune response (12). The Th2 cells stimulate increased production of type 2 cytokines such as interleukins IL-4, IL-5 and IL-13, promoting IgE production, inflammation and subsequent epithelial barrier disturbance (13). As the disease progresses to a chronic stage, Th1/Th17/Th22 cells play an increasing role in the inflammatory process resulting in more keratocyte cell death, tissue remodelling and lichenification (14).

## Atopic Dermatitis and Food Allergy

Food allergy is an adverse immune response to certain food items, most commonly the protein component of the food (15). The prevalence of 20% in paediatric patients with atopic dermatitis is much higher than that of the general paediatric population at 4-5% (16). The prevalence increases with the severity of the disease, with studies reporting a prevalence of 15% in mild atopic dermatitis and 30-40% in moderate to severe atopic dermatitis (17,18). Food allergies are more commonly seen in children with atopic dermatitis compared to adults, with peanuts, eggs, soy, wheat, seafood and shellfish being the common culprits in children (19,20).

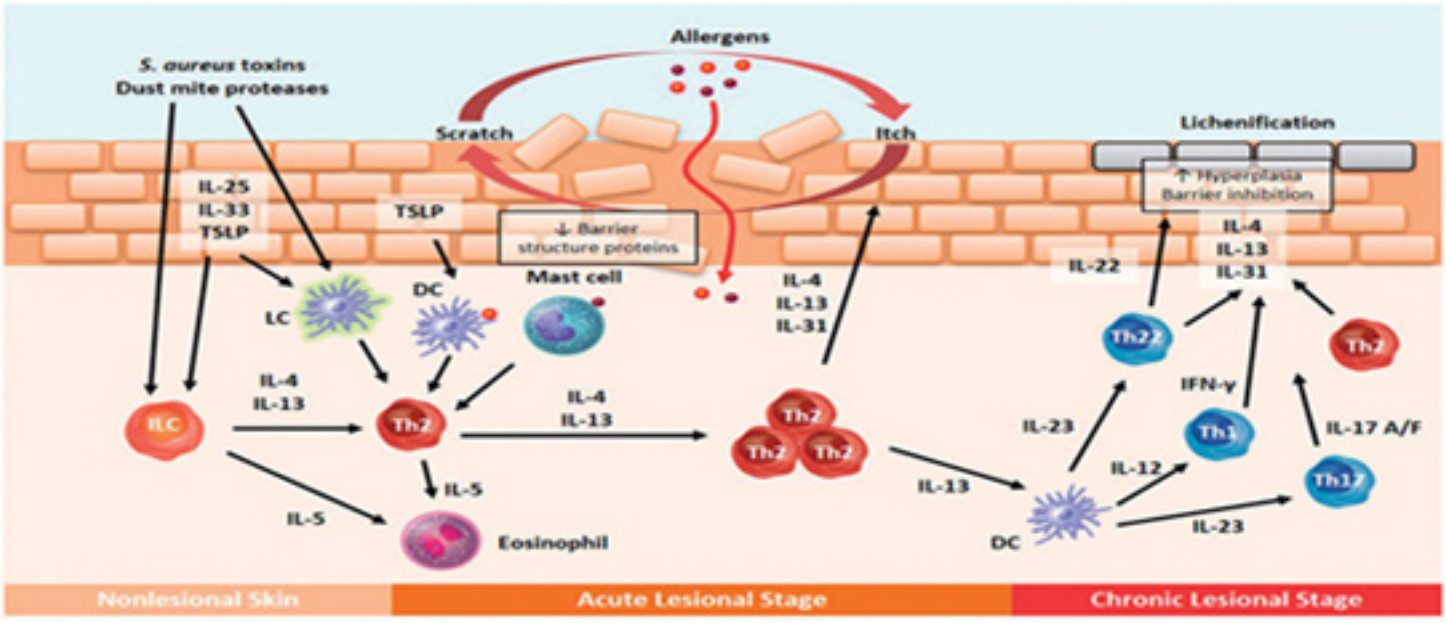


**Figure 1: Pathogenesis of atopic dermatitis.** Disrupted epidermal barrier and environmental triggers stimulate keratinocytes to release IL-25, IL-33 and TSLP, which activate dendritic cells and Langerhans cells. Activated dendritic cells stimulate Th2 cells to produce IL-4, IL-5 and IL-13 which leads to barrier dysfunction, decreased AMP production, impaired keratinocyte differentiation, and itch symptoms. Chronic AD is characterized by recruitment of Th1, Th22, and Th17 subsets, which results in epidermal thickening and abnormal keratinocyte proliferation.

AMP = antimicrobial peptide; DC = dendritic cell; IFN = interferon; IL = interleukin; LC = Langerhans cell; Th = T-helper type; TSLP = thymic stromal lymphopoietin.

The causal link between the two conditions remains a hypothesis. Several studies have reported an improvement in the skin symptoms of patients suffering from atopic dermatitis when suspected food items were eliminated from the diet, and a flare up of the symptoms with the reintroduction of the food items, strengthening the argument for a causal link (21).

Food allergens are thought to penetrate through the dysfunctional epithelial barrier in patients with atopic dermatitis, stimulating the production of IgE antibodies to one or more of the food allergens. The IgE antibodies bind to high-affinity receptors on the circulating basophils and tissue mast cells (22). Allergen from further consumption of the causal food binds to the IgE antibodies on the cell surface, triggering the release of mediators such as histamines, prostaglandins and leukotrienes that promote allergic inflammation. These mediators cause vasodilation, smooth muscle contraction and mucus secretion, which are responsible for the symptoms observed during acute allergic food reactions (15).

The cause of delayed eczematous reaction to food allergens is not currently completely clear although it is thought to be non-IgE related. There are reports of positive food challenge tests with negative food specific IgE tests supporting a non-IgE hypothesis (23). A trial reported an improvement in atopic dermatitis based on the number of areas affected, degree of pruritus and sleepiness when eggs and milk were excluded from the diet. The improvement did not correlate with skin prick testing, further supporting the non IgE hypothesis (24).

T-cells are thought to play a role; they have been shown to be involved in delayed eczematous food reactions. T-cell clones from patients with atopic dermatitis worsened by milk have shown higher proliferative responses than those from controls (25).

Food allergies are broadly categorised into those mediated by IgE antibodies and those caused by other immunological mechanisms. IgE-mediated reactions are the most common form of food allergy, occurring in 40-60% of cases (26) and usually manifest with a rapid onset of symptoms. They occur within minutes of food consumption and can involve single or multiple organs. Skin manifestations can include eruptions such as urticated plaques, angioedema-like appearance, excoriations, erythema and morbilliform appearance. These reactions can cause pruritus which worsens the atopic dermatitis. Non-dermatological features include vomiting, diarrhoea, abdominal pain, rhinitis, asthma and anaphylaxis. These manifestations are independent of the atopic dermatitis.
Delayed eczematous reactions occur hours to days after the ingestion of a trigger food, often manifesting as flare ups of eczema on the pre-existing areas of atopic dermatitis (27). The true prevalence is unknown possibly because delayed reactions are often not included in published studies of food allergy in atopic dermatitis. They can occur in isolation or together with acute food reactions. A combined picture of acute and delayed reaction is said to occur in about 40% of children with positive oral food challenge (28).

## Allergy Testing

The high prevalence rates of food allergies in patients with atopic dermatitis, makes it impractical to screen all patients. The National Institute of Allergy and Infectious Diseases in the United States of America suggested allergy testing in children less than five years old with moderate to severe atopic dermatitis and a reliable history of immediate reaction to a specific food or persistent symptoms despite optimal treatment (17). Similarly, countries like Japan and Germany have produced guidelines in the context of general food allergy with some focus on atopic dermatitis patients; both suggesting investigating for food allergies when the history is indicative (29,30). The diagnosis of food allergy involves a three-step process; careful history taking, identification of sensitisation to specific food items and confirmation of the food allergy, often with oral food challenges.

A careful history is essential to establishing a temporal relationship between symptoms and specific foods, with the aim of determining the pre-test probability of food allergy. It is reasonable to suspect food allergies in patients presenting with a sudden flare up of atopic dermatitis within minutes to hours of ingesting food, or those who experience symptoms of food allergy on one or more occasions after consuming specific food items. The positive predictive value of history is however lower with delayed eczematous food reactions, with only 35-50% of parent-diagnosed food allergies being confirmed by food challenge (31). There are various environmental factors that play a role in the remitting and relapsing nature of atopic dermatitis that can confuse dietary involvement.
When the pre-test probability of food allergy is deemed significant, allergy testing helps to identify sensitisation to the suspected food allergens. The testing can either be through in vivo testing (skin prick tests) or in vitro testing (specific IgE measurement). The choice of food items being tested should be influenced by the history and the common food allergies in the population because many patients with atopic dermatitis will be sensitised to several food allergens without any clinical significance (27).

**Skin prick tests**

Skin prick testing detects the presence of allergen specific IgE on the surface of patients' cutaneous mast cells by introducing food allergens either through a skin prick or by intradermal route. The intradermal route, although more sensitive, is not commonly performed clinically because it carries a high risk of systemic allergic reaction and gives an unacceptably high false positive result (34).The allergen binds to allergen specific IgE antibodies if present on the patient's mast cells, activating the mast cells, with subsequent degranulation and release of inflammatory mediators, such as histamine, tryptase, chymase, and carboxypeptidase (32). Histamine mediates a localised skin reaction characterised by a central oedema (wheal) surrounded by erythema (flare). A positive result is most commonly defined as a wheal equal or larger in size to that associated with the histamine control, with the histamine control normally producing a wheal of at least three

millimetres in diameter when measured 15-20 minutes after the introduction of the allergen.

The general sensitivity and specificity of skin prick testing for the diagnosis of food allergy is estimated to be greater than 90% and 50% approximately (33). The larger the wheal the greater the likelihood of a clinical allergy, although the size of the wheal does not correlate with the severity of a reaction (34). The negative predictive accuracy of 90-95% makes it useful for excluding IgE mediated food allergy (35).

It should be undertaken in the clinics with resuscitation facilities and appropriately trained medical staff because of the risk of anaphylaxis, and clinicians should be cautious with patients at high risk of systemic reaction, such as poorly controlled asthmatic patients or those with a history of previous anaphylaxis.

**Serum specific IgE blood tests**

Serum specific IgE testing involves using immunoassays to measure interactions between antigens and antigen-specific antibodies. Enzyme-linked immunosorbent assays (ELISA) use antibodies linked to enzymes. When the substrate of the enzyme is added, the reaction generates a coloured product. Variations of the basic ELISA technique include fluorescent enzyme immunoassays (FEIA) and chemiluminescent immunoassays, which also use antibodies linked to enzymes, although when the substrate of the enzyme is added, the reaction generates a fluorescent or chemiluminescent product.

The presence of allergen specific IgE is interpreted as evidence that the patient is sensitised to that allergen and may react upon exposure. The likelihood of clinical reactivity is influenced by the degree of positivity and the patient's clinical history. Patients with higher levels of antibody are more likely to experience symptoms upon exposure to the allergen, although strongly positive tests do not necessarily predict that anaphylaxis is more likely to occur (36).

Serum specific IgE blood test can be advantageous over the skin prick test as it can be performed in cases where skin testing is limited by severe dermatitis and does not carry the risk of anaphylaxis. They are also not affected by medications such as antihistamines. On the other hand, skin prick tests are cheaper, and results are available in a quicker time. Serum specific IgE blood tests, as with skin prick tests, have been reported to have low positive predictive values but high negative predictive values making them useful tools in excluding food allergies. Lemon-Mulé et al reported that less than 40% of patients with positive skin specific igE and skin prick tests had oral food challenge-proven food allergy (37).

**Patch testing**

Patch testing has been studied as a possible tool in evaluating people with possible delayed eczematous reactions. It is based on the principle that primed antigen-specific T lymphocytes of the Th1 phenotype circulate throughout the body in sensitised individuals and can recreate a delayed-type hypersensitivity reaction when non irritating concentrations of the antigen are applied to normal skin (38).

The allergen is placed on the upper back under occlusive bandage and left in place for 48 hours to allow for penetration of the allergen. The skin is reassessed at 72 to 96 hours. Papules, erythema and vesicles are observed under the area of contact with positive allergen. Patch testing has been found to have a greater sensitivity than skin prick tests and specific IgE measurement in cases of delayed eczematous reactions (39). The lack of standardisation and controversy around reproducibility means that it is not currently recommended in routine clinical practice for assessing delayed food reactions in patients with atopic dermatitis (23).

**Diagnostic trial elimination of food**

Elimination of suspected foods can be a helpful practical guide in the diagnosis of delayed eczematous food reactions. Food diaries can help to identify potential trigger foods and elimination of the suspected food item followed by gradual reintroduction after a few weeks can help evaluate diagnostic relevance. However, this may not be fully reliable because of its placebo effect. Long term food elimination in patients without proven food reactions is not advised because of the risk of nutritional deficiencies (17).

**Oral food challenge**

An oral food challenge is the gold standard for confirming food allergies (27). It is performed when a diagnosis remains uncertain from the history, allergy testing and/or diagnostic elimination of food item.

Food challenges are conducted after a period of eliminating the suspected food from the diet, to ensure that the food is cleared from the system and does not interfere with the interpretation of results. Patients are gradually fed with suspected food items whilst observing for signs and symptoms of food allergy.

There are generally three types of oral food challenges. The open food challenge involves gradually feeding a patient with food in its natural state, with the patient and observer being aware of the nature of the food. It is easy to perform but prone to patient and observer bias. The patient- blind challenge involves hiding the taste of the food usually by mixing it with another food to eliminate patient bias, although it is still open to observer bias. The double-blind placebo-controlled challenge (DBPCFC) is the most reliable way of confirming food allergy (27), the patient is fed two meals with one containing the food being tested with the taste disguised. Neither the patient nor the observer is aware of the content of the meals to eliminate patient and observer bias. It is ideal to observe for symptoms up to 24-48 hours after the challenge because delayed food reactions can take that long to develop.

It should be undertaken in an adequately resourced clinic or hospital setting, under close supervision by appropriately trained medical staff with access to facilities for emergency treatment of anaphylaxis and resuscitation.

We propose this algorithm to support the diagnosis of food allergies in patients with atopic dermatitis.


**Proposed algorithm for the diagnosis of food allergy in patients with atopic dermatitis**

## Conclusion

Although, there has been some controversy on the link between food allergies and atopic dermatitis, evidence shows that the prevalence of food allergies in patients with atopic dermatitis is higher compared with that of the general population. Food allergies manifest either in an acute IgE mediated manner or as a delayed reaction, thought to be mediated by cellular mechanisms.

A suggestive history of food allergy should prompt further tests to detect sensitisation to the suspected food allergen. Skin prick tests and specific IgE blood tests are commonly used to identify sensitisation to food allergens, although these tests are not diagnostic of food allergies on their own. Negative skin prick tests and specific IgE blood tests are however useful in ruling out food allergies. Measuring total IgE is unhelpful and does not add any diagnostic value because a significant proportion of patients with atopic dermatitis will have raised serum total IgE levels independent of allergies. Whilst diagnosis can be made in a lot of cases based on the suggestive history and confirmation of sensitisation, oral food challenges remain the gold standard for diagnosis and will be needed when the diagnosis remains uncertain. Random elimination of food items from the diet without confirmation of food allergy is discouraged because of the risk of nutritional deficiencies.

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