

Role of food allergy in atopic dermatitis

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Purpose of review

Food allergy and atopic dermatitis often occur in the same patient. Based on clinical data from the past few decades, it is clear that foods such as cow's milk and hen's eggs can directly provoke flares of atopic dermatitis particularly in sensitized infants, whereas inhaled allergens and pollen-related foods are of greater importance in older children, adolescents and adults. Because the role and immunology of food allergy in atopic dermatitis remain controversial, here we review data that mainly focus on skin eczema and food allergy.

Recent findings

Clinical studies have revealed that more than 50% of all children with atopic dermatitis that can be exacerbated by certain foods will react with a worsening of skin eczema alone or in addition to immediate symptoms. Adolescents and adults also react to foods, but reactions to 'classical' food allergens such as hen's eggs and cow's milk are not as common as in childhood. Subgroups of children and of adults with atopic dermatitis do, however, react to pollen-associated foods. Both immunoglobulin E associated and independent T-cell mediated responses appear to be involved in clinical eczematous reactions.

Summary

Food-induced eczema should be diagnosed only by a thorough diagnostic procedure, taking into account the patient's history, the degree of sensitization and the clinical relevance of the sensitization. More clinical and immunological studies are needed to unravel the pathophysiology and the different rates of clinical responsiveness to different foodstuffs in patients with atopic dermatitis.

Keywords

atopic dermatitis, cross-reactive foods, eczema, food allergy, oral provocation

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Abbreviations

APT	atopy patch test
CLA	cutaneous lymphocyte antigen
DBPCFC	double-blind, placebo-controlled oral challenge test
IgE	immunoglobulin E
PPV	positive predictive value

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Introduction

Atopic dermatitis is a chronic inflammatory skin disease that commonly begins in early infancy, runs a course of exacerbations and remissions, and is associated with a characteristic distribution and morphology of skin lesions. Furthermore, pruritus and subsequent sleeplessness are hallmarks of atopic dermatitis [1]. Numerous trigger factors for atopic dermatitis have been identified over recent decades, including inhalable respiratory allergens, food allergens, irritative substances and infectious micro-organisms such as *Staphylococcus aureus* and *Malassezia furfur*; T cells appear to mediate most hypersensitivity reactions in atopic dermatitis (Fig. 1) [2–4].

Food allergy and atopic dermatitis often occur in the same patient [5•]. Based on clinical data from the past few decades, it is clear that foods such as cow's milk and hen's eggs may directly provoke flares of atopic dermatitis in sensitized infants, whereas inhaled allergens and pollen-related foods are of greater importance in older children, adolescents and adults. Because the role and immunology of food allergy in atopic dermatitis remain controversial, here we review data that mainly focus on eczema and food allergy.

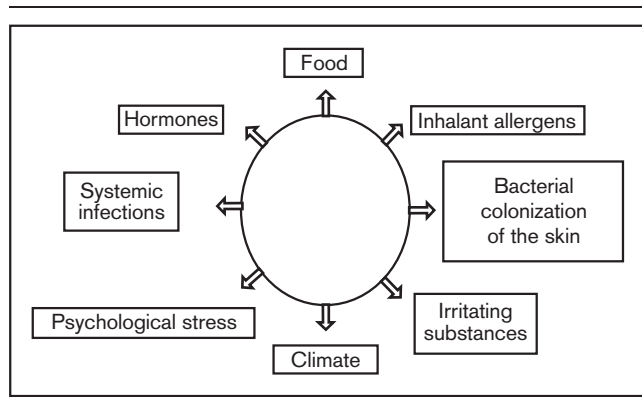
Patterns of clinical reaction to foods in patients with atopic dermatitis

Three patterns of cutaneous reactions to food may occur in patients with atopic dermatitis upon oral challenge [6]. In the first pattern immediate-type reactions, such as urticaria, angio-oedema and erythema, commonly occur a few minutes after ingestion of food, without exacerbation of atopic dermatitis. In addition, gastrointestinal, respiratory and cardiovascular symptoms may evolve. In the second pattern pruritus occurs soon after ingestion of food, with subsequent scratching leading to an exacerbation of atopic dermatitis. In the third pattern, exacerbations of atopic dermatitis occur after 6–48 h, and these are termed 'late reactions'. Late reactions may occur also after an immediate-type response.

Prevalence of food allergy in atopic dermatitis

The prevalence of food allergy in infants with atopic dermatitis was reported to range from 20% to 80% in various studies, and may be estimated at 30% [7,8]. Hen's eggs, cow's milk, soy and wheat account for about 90% of allergenic foods in children with atopic dermatitis [8,9]. There is a perception that children are currently experiencing allergic reactions to an increasing range of

Figure 1. Trigger factors for atopic dermatitis



foods. Ellman *et al.* [9] compared two separate groups of children and young adults with atopic dermatitis who were evaluated a decade apart, and found no difference in sensitization rates or overall clinical reactivity to a variety of foods. Allergies to eggs, milk, wheat, soy, peanut, tree nuts and seafood accounted for approximately 90% of food-allergic reactions in that US study. Ingestion of foods at an early time-point in atopic individuals appears to enhance the risk for sensitization to these foods. Interestingly, sensitization to peanut protein may also occur in children via application of peanut oil to inflamed skin [10•].

About one-third of children will outgrow their food allergy after 1–2 years of allergen avoidance, depending on the kind of food [8,11]. In a placebo-controlled crossover study, Atherton *et al.* [12] observed a significant improvement in dermatitis in more than 50% of children during dietary exclusion periods (i.e. periods in which eggs and cow's milk were replaced with a soya-based substitute). Several open studies also described some benefit at various sites in subpopulations of patients with atopic dermatitis, but a major problem with these studies is their open design, which does not exclude placebo effects [13]. Immediate-type responses to foods are well characterized in studies using oral provocation tests among children with atopic dermatitis, but only few trials have examined true late eczematous responses, which require 6–48 h to develop and may occur only after repetitive ingestion of food.

Of all double-blind, placebo-controlled oral challenge tests (DBPCFCs), 46% resulted in an immediate and/or late eczematous reaction in a recent retrospective study conducted in children (aged 1–10 years) with atopic dermatitis (Fig. 3) [14•]. Based on this finding, food allergy was diagnosed in 64% of the investigated children. These high numbers might have resulted from the preselection of children investigated, who were

suspected of having food allergy because of their history, positive food-specific immunoglobulin E (IgE), or positive atopy patch tests (APTs).

Similarly, in a study conducted by Niggemann *et al.* [15], 51% of all challenge tests resulted in an allergic reaction and 81% of all patients reacted to at least one allergen. Sampson and coworkers found a frequency of food allergy of more than 60% in children with atopic dermatitis [5•,8,16]. The frequency of food allergy in children with atopic dermatitis was estimated at 30% in a study conducted by Burks *et al.* [17], who investigated infants who were not specifically referred for evaluation of food allergy. Children included in the study were older than those investigated in other studies.

Late eczematous reactions to foods in atopic dermatitis

Whether eczematous lesions can be induced by ingestion of food is still a matter for debate. The cutaneous inflammatory infiltrate in eczematous lesions of patients with atopic dermatitis consists mainly of CD4⁺ T cells, and food allergen-specific T cells have been shown to be involved in the late eczematous response to food [18–20]. Few reported studies have clearly differentiated food-induced eczema occurring after many hours from immediate-type reactions, which may be due to the fact that most investigators did not observe patients for longer than 1 day after challenge.

Because of the pathophysiological mechanisms that are involved in food-induced eczema, eczematous lesions usually need at least 6 h to develop, and therefore late eczematous reactions should be defined as occurring later than 6 h after ingestion of food. In order to distinguish eczematous responses clearly from early cutaneous reactions, the suspected food should be given over a period of 2 days. Ideally, the next food should be introduced after a challenge-free day. This provocation scheme was recommended for the detection of 'true' eczematous late-phase reactions by the German Society of Allergy and Clinical Immunology (Fig. 2) [21]. These recommendations differ from current proposals, which mainly address immediate reactions to food [22•].

Differences in the proportion of atopic dermatitis patients who react to food challenge in different studies may therefore be due not only to preselection but also to the method used for DBPCFCs. In a number of published studies the food was not given repetitively over 2 days [10•,15–17]. In some studies two challenges (verum/placebo) were administered within 4 h, and thus the patients could not be observed for longer than 1 day.

Similar to our study [14], cow's milk, wheat powder and soy milk were administered by Niggemann *et al.* [15].

Figure 2. Repetitive oral provocation tests for the detection of 'true' eczematous reactions in atopic dermatitis

Each column represents 1 day. The food or placebo is titrated on the first day. In the case of a negative reaction, an age-adapted full dose is given on the subsequent day.



Instead of egg powder consisting of egg white and yolk, as was administered in our study, those investigators used raw egg. Dehydrated food mixed with juice was used in other studies.

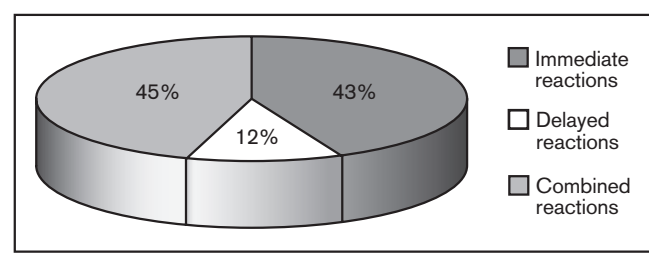
Rate of late reactions to challenges with foods

More than 50% of all positive oral challenges in children suffering from atopic dermatitis were associated with an exacerbation of eczema [14[•]]. Isolated eczematous reactions were seen in 12% of all positive challenges (Fig. 3). Of isolated eczematous reactions 50% occurred after challenge with wheat, but the limited number of patients reacting in this way might have biased these results.

Niggemann *et al.* [15] observed late reactions in 25% of positive provocation tests. In their study, late reactions were defined as symptoms occurring after more than 2 h. Other investigators did not describe true eczematous reactions upon DBPCFC [16,17], which might be due to the challenge method described above. In these studies, cutaneous symptoms such as pruritus and rash occurred within 2 h after challenge. Such immediate-type symptoms may be induced by mast cell degranulation with subsequent release of proinflammatory mediators such as histamine. Interestingly, in our study [14[•]] 19% of all immediate reactions occurred on the second challenge day after the highest dose had been tolerated on the first day. The pathophysiological mechanism of this phenomenon is not clear, but repetitive doses may boost the food-specific allergic response and may therefore reflect the normal situation in a more sensitive manner. Delayed immediate reactions, which occur after 2–6 h (16% of our patients), are thought to be induced by mediators derived from mast cells such as leukotrienes and cytokines, which lead to an influx of eosinophils, basophils and neutrophils [24,25].

Predictive values of diagnostic tools

Reliable markers for the identification of patients with food-responsive eczema are still lacking. Diagnosis of

Figure 3. Investigation into food-responsive atopic dermatitis in children: pattern of clinical reaction

immediate symptoms provoked by a food may be evident from a straightforward history and can be confirmed by diagnostic tests to detect food-specific IgE antibody; determination of the role played by food allergy in patients with atopic dermatitis is more difficult and may require additional diagnostic manoeuvres, including elimination diets and oral food challenges [26[•]]. Anamnestic data given by parents often do not correlate with the findings of an oral challenge, particularly with regard to eczematous reactions [12,27,28].

We found a low predictive accuracy of the personal history, particularly for eczematous reactions, which need several hours to develop [14[•]].

Specific IgE levels associated with a positive challenge test have been described to be significantly greater than specific IgE levels associated with a negative challenge [7,14[•]]. The fact that sensitivity, specificity and positive predictive value (PPV) for food-specific IgE are higher for immediate than for eczematous reactions underlines the importance of food-specific IgE, particularly for immediate reactions. From a physician's point of view the PPVs are of greatest interest because they indicate how likely it is that the patient will develop a clinical reaction to a certain food. The PPV of food-specific IgE was only 33% for eczematous reactions, which means that only one-third of all challenges associated with food-

specific IgE resulted in exacerbation of atopic dermatitis. The PPV of food-specific IgE was 57% for immediate reactions. This result is consistent with the findings of a previous study conducted by Sampson and Scanlon [11], who found the PPV to range from 18% to 57% for different kinds of food. The diagnostic accuracy of food-specific IgE was described to be lower in children who were older than 2 years than in younger children, which is probably accounted for by the fact that many children outgrow their food allergy, while food-specific IgE remains detectable [11]. The probability of a positive immediate reaction to food has been shown to depend on the level of food-specific IgE, and for foods such as cow's milk and hen's eggs it is possible to determine IgE levels that predict clinical reactivity with 95% certainty in children with atopic dermatitis [29,30].

Of all positive challenges 25% were associated with negative food-specific IgE in our trial [14•], and food-specific T cells may play a predominant role in the pathogenesis of these reactions. A relatively high number of patients without food-specific IgE, who had a history suggestive of food allergy or a positive APT, were included in our analysis, which might have resulted in the relatively high number of positive challenges associated with negative food-specific IgE. Thus, a suspicion of food allergy rather than detection of food-specific IgE should be the indication for DBPCFC in children with moderate or severe atopic dermatitis. Similarly to the findings of Niggemann *et al.* [31], who found that 10% of positive DBPCFCs were not associated with food-specific IgE, there were no differences in terms of age and total IgE levels as compared with children with food-specific IgE.

Because APT lesions resemble spontaneous lesions both clinically and histologically, it is likely that APTs mimic the mechanisms that are involved in food/aeroallergen-responsive atopic dermatitis [32,33]. In our study [14•], 75% of patients with an isolated eczematous reaction had a positive APT. In five patients with a positive challenge who had no food specific IgE, an APT was performed that resulted in a positive reaction, suggesting a major role of food-specific T cells. However, we calculated a low specificity and PPV for the APT in our study. A high rate of false-positive APT reactions was seen, particularly after application of wheat proteins, and this was possibly caused by irritation. In contrast, the APT with cow's milk allergy had a PPV of 95% in a study conducted by Roehr *et al.* [34]. The combination with positive food-specific IgE of any level resulted in a PPV of 100% for early and late reactions. Isolauri and Turjanmaa [35] also found a very good correlation between positive patch test results and late reactions to cow's milk. Other investigators, however, found a markedly lower PPV of 40% for immediate reactions to cow's milk, but they did

not investigate late reactions [36]. In another study focusing on wheat allergy the PPV was 63% [37]. To date, the APT is not well standardized, and different methods for preparing the test solutions are likely to yield controversial results. Therefore further studies are needed before the APT may be used as a routine tool for the diagnosis of food allergy.

Taken together, the personal history, food-specific IgE and APT are not sufficiently reliable for identification of clinically relevant foods, particularly when eczematous reactions are concerned. Therefore, food challenges are still necessary for appropriate diagnosis of food allergy in patients with atopic dermatitis. Elimination diets based solely on in-vitro or skin tests are inadequate, if the history is not convincing. A negative open challenge may confirm the absence of food allergy; in positive cases a DBPCFC is recommended.

Allergen specific T-cell responses in atopic dermatitis

Early studies conducted in passively sensitized individuals demonstrated that immunologically active food proteins can enter the circulation and are distributed throughout the body, including skin sites. Food antigens taken up this way can directly interact with specific IgE, which is bound to Fc receptors on Langerhans cells, mast cells, monocytes and basophilic granulocytes, but also on skin-infiltrating T lymphocytes.

Since eczematous lesions are probably triggered by T lymphocytes, both new diagnostic approaches and a deeper understanding of immunological mechanisms may come from the characterization of allergen-specific T-cell parameters in atopic dermatitis [3]. We found significant differences in the proliferative response of blood lymphocytes between the patients who reacted to milk with worsening of atopic dermatitis and control groups, and we were able to generate casein-specific T-cell clones from the blood of these patients [18–20]. Higher proliferative responses to lipopolysaccharide-depleted casein – the major protein fraction in cow's milk and thus the main protein source for many individuals – were observed both in atopic children and in adults who reacted to oral provocation with a worsening of eczema. Although this method cannot be recommended for routine purposes, it may be used as the basis for novel T-cell-based specific tests.

As mentioned above, specific IgE to food antigens is detectable in most investigated children with atopic dermatitis who react with clinical symptoms [18]. In contrast, we found food-specific IgE in less than 50% of adult patients who reacted to oral provocation with cow's milk. A type 1 cytokine pattern (i.e. production of interferon- γ but not of interleukin-4) was detectable in

the majority of food-specific T-cell clones from the latter patients. Moreover, no correlation between specific lymphocyte proliferation and specific IgE was found [20]. Considerable evidence suggests that non-IgE-mediated mechanisms may be involved in food allergy [38*]. Results from atopic dermatitis studies indicate that IgE-independent mechanisms may be involved in the eczematous reaction to food in some patients, stressing the potential pathophysiological role of allergen-specific T lymphocytes in atopic dermatitis.

T cells that express cutaneous lymphocyte antigen (CLA), a unique skin-homing receptor, are known to play an important role in atopic dermatitis. Milk-induced eczema is associated with a higher rate of CLA-positive lymphocytes on in-vitro stimulation with casein [39]. However, expression of CLA is not unique to milk-induced inflammation in the skin of patients with atopic dermatitis and milk allergy because it has recently been described also for milk-induced urticaria [40].

Li *et al.* [41] established a murine model of food-induced atopic dermatitis, which confirmed the important role of food-specific T cells in eczema. In this model female C3H/HeJ mice were sensitized orally to cow's milk or peanut and then subjected to low-grade allergen exposure. An eczematous eruption developed in approximately one-third of mice after low-grade exposure to milk or peanut proteins. Histological examination of lesional skin revealed spongiosis and a cellular infiltrate consisting of CD4⁺ lymphocytes, eosinophils and mast cells. Interleukin-5 and interleukin-13 messenger RNA expression was elevated only in the skin of mice with the eczematous eruption.

Pollen-associated food allergy in atopic dermatitis

Patients sensitized to pollen allergens often develop an IgE response to cross-reactive food allergens. Of adolescent or adult patients with birch pollen reactive pollinosis, 50–70% also exhibit immediate symptoms upon ingestion of birch pollen related foodstuff. An abundance of food has been identified as being birch pollen related over recent years, including a multitude of plant families such as rosaceae, solanaceae and umbelliferae. Among these apple, hazelnut, carrot and celery most often induce allergic symptoms, such as the oral allergy syndrome, urticaria, angio-oedema, rhinoconjunctivitis, asthma, or even anaphylactic shock. Most patients avoid these foods when they become aware of their allergenic character.

The major allergen of birch pollen, Bet v1, is mainly involved in the development of cross-reactive IgE antibodies to apple, celery and hazelnut [42]. Furthermore, the highly conserved protein profilin Bet v2, a

60 kDa plant panallergen, and the isoflavone reductase-related protein, which is now named Bet v6, have been identified as cross-reactive minor birch pollen allergens. Relatively high levels of specific IgE to birch pollen and Bet v1/Bet v2 are often detected in the sera of patients suffering from atopic dermatitis in Northern England, whereas lower levels of food-specific IgE are found in most patients at the same time.

Although cow's milk, hen's eggs, wheat and soy are frequent food allergens in children with atopic dermatitis, pollen-related foods are of greater importance in adults. In a pilot study [43] we showed that birch pollen related food may lead to an exacerbation of eczema in a subpopulation of adult patients with atopic dermatitis. Thirty-seven patients with a sensitization to birch pollen, who had no history of immediate reactions to birch pollen related foods, were investigated. These patients were challenged with birch pollen related food in a double-blind, placebo-controlled setting after 4 weeks of an elimination diet. Nearly half of the patients exhibited late eczematous reactions following oral provocation after 24 h, and most of them had not been aware that this kind of food played a role in their skin disease. Interestingly, a birch pollen specific T-cell response could be detected in the lesional skin of the responding patients.

The presence of serum IgE antibodies to inhalant allergens increases with age. A sensitization to inhalant allergens commonly develops at about 3–4 years of age, and some children become sensitized to pollen as early as in the first months of life. Children with respiratory allergy sensitized to birch pollen allergens often suffer from immediate symptoms to pollen-related food. In contrast to adults, the importance of birch pollen-related food with regard to the induction of immediate symptoms/late eczematous reactions is still not clear in children with atopic dermatitis.

In a recent study [23*] we showed that birch pollen-related food may induce allergic symptoms in a subgroup of children with atopic dermatitis sensitized to birch pollen, even in the absence of a history suggestive of food allergy. Four out of 12 (33%) patients with moderate to severe atopic dermatitis, who were aged 3–9 years and who were sensitized to birch pollen, reacted with late eczematous reactions upon oral challenge with birch pollen-related food. Moreover, in another three children worsening of atopic dermatitis might have been suppressed by systemic corticosteroids, which had to be administered because of immediate symptoms.

These data show for the first time that children with atopic dermatitis who are sensitized to birch pollen may also develop late eczematous responses upon ingestion

of birch pollen-related food. Both in adults and in children, the deterioration in dermatitis presented as a flare up of pre-existing lesions 24 h after ingestion of food. Patients who experienced a worsening of dermatitis upon oral challenge did not differ significantly from the other patients in terms of total IgE, birch pollen specific IgE, history of respiratory allergy, age, or severity of atopic dermatitis. However, in order to select patients who may react to birch pollen related food with a deterioration in dermatitis, a history of seasonal respiratory atopy and immediate reactions to this kind of food, and determination of birch pollen specific IgE might be helpful.

Conclusion

Food-induced eczema can be diagnosed only with a thorough diagnostic procedure, taking into account the patient's history, the degree of sensitization and the clinical relevance of the sensitization. Clinical studies revealed that more than 50% of all children suffering from atopic dermatitis that can be exacerbated with foods will react with a worsening of skin eczema alone or in addition to immediate symptoms. In addition, we and others have shown that older patients with atopic dermatitis also react to foods, although reactions to 'classic' food allergens such as hen's eggs or cow's milk are not as common as they are in childhood. Subgroups of children and adults with atopic dermatitis can also react to pollen-associated foods. Both IgE-associated and IgE-independent T-cell-mediated responses appear to be relevant in clinical eczematous reactions. More clinical and immunological studies are needed if we are to unravel the pathophysiology of clinical responsiveness to different foodstuffs in patients with atopic dermatitis.

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