



Atopic dermatitis and its relation to food allergy

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Purpose of review

To present the most recent evidence on atopic dermatitis and its relation to food allergy.

Recent findings

Atopic dermatitis is a chronic inflammatory disorder of the skin characterized by impaired skin barrier because of multifactorial causes including genetic factors, immune dysregulation, and skin microbiome dysbiosis. Infants with temporary skin barrier disruption and/or persistent atopic dermatitis are particularly at risk of developing food allergy (during the so-called atopic march), with up to half of patients demonstrating positive food-specific IgE and one-third of severe cases of atopic dermatitis having positive symptoms on oral food challenge. A high proportion of children with atopic dermatitis exhibit asymptomatic sensitization to foods, and skin testing to identify potential food triggers is not recommended unless the patient has a history suggestive of food allergy and/or moderate-to-severe atopic dermatitis unresponsive to optimal topical care. Indeed, indiscriminate testing can lead to a high proportion of false-positive tests and harmful dietary evictions. Promising strategies to prevent food allergy in children with atopic dermatitis include early skincare with emollients and treatment with topical steroid, and early introduction of highly allergenic foods.

Summary

Further studies are required to identify risk factors for atopic dermatitis to help prevent the development of food allergy in this high-risk population.

Keywords

atopic dermatitis, eczema, food allergy, skin testing

INTRODUCTION

Atopic dermatitis is the most frequent inflammatory disorder of the skin in children with an incidence of up to 30% in industrialized countries [1]. It is characterized by relapsing episodes of dry skin and pruritus, with frequent skin infections. It is associated with a high negative impact on the quality of life of patients and caregivers, because of chronic pruritus, lack of sleep and resulting limitations in social activities [2], as well as substantial loss of productivity at work in adults [3]. The pathophysiology of atopic dermatitis is complex, with a genetic predisposition and contribution of environmental factors. The major risk factors for atopic dermatitis include a familial history of atopic dermatitis and genetic mutations such as in the filaggrin gene [4]. Atopic dermatitis is considered the first step in the 'atopic march,' where there is a chronological progression of allergic conditions to food allergy, allergic rhinitis, and asthma [5]. Thus, atopic dermatitis is frequently associated with environmental and food allergen sensitization, and food challenge proven IgE (immunoglobulin E)-mediated food allergy is present in up to one-third of patients with

moderate-to-severe atopic dermatitis [6]. The majority of children with milder atopic dermatitis will outgrow the disease. However, a group of patients with more severe phenotypes may develop lifelong disease with frequent relapses [7]. This review will focus on the most recent evidence on atopic dermatitis and its relation to food allergy.

ATOPIC DERMATITIS ASSOCIATIONS WITH FOOD ALLERGY

Atopic dermatitis has clearly been shown as a major risk factor for food sensitization and the development of IgE-mediated food allergy [8,9]. Epidemiological

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KEY POINTS

- There is a strong association between atopic dermatitis, food sensitization, and food allergy.
- Food allergy may be present in approximately one-third of patients with moderate-to-severe atopic dermatitis. However, this requires a careful evaluation by specialists to confirm causality between foods and atopic dermatitis exacerbation as unnecessary dietary evictions may lead to loss of tolerance to allergenic foods and nutritional deficiencies.
- Strategies to prevent food allergy in high-risk patients with atopic dermatitis are currently being investigated, with promising results from early introduction of allergenic foods.

studies support the progression of the atopic march from atopic dermatitis to food allergy; skin barrier disruption (assessed by transepidermal water loss) and atopic dermatitis were shown to temporally precede the appearance of food allergy [17,18[¶]]. Recently, a Canadian birth cohort (CHILD study) found that sensitization and atopic dermatitis at one year of age was a strong risk factor for food allergy at three years (relative excess risk because of interaction: 15.11 [95% confidence interval, 4.19–35.36]) [18[¶]]. In addition, neonatal skin barrier dysfunction, even if transient, was associated with food allergy at the age of two [19,20[¶]]. A recent systematic review supports that atopic dermatitis with earlier onset is associated with the appearance of food allergy [9].

Numerous population-based studies have found an association between atopic dermatitis and food allergen sensitization. The likelihood of food sensitization in infants with atopic dermatitis is up to six times higher than healthy controls at the age of three months [9]. In addition, up to 53% of children with atopic dermatitis have demonstrable positive food-specific IgE (sIgE) and/or positive skin prick tests (SPTs) with up to 15% demonstrating signs of food allergy on oral food challenge (OFC) [9], compared with 0.1–6% food allergy prevalence in the general population [10]. One important large population-based study highlighting these findings is the Health-Nut study, which showed that one in five Australian infants with atopic dermatitis had a food allergy compared with one in 20 without atopic dermatitis ($n = 4453$) [11]. Patients with atopic dermatitis were six times more likely to have an egg allergy, and 11 times more likely to have peanut allergy.

In interventional studies, rates of food allergy in children with moderate-to-severe atopic dermatitis with food allergy confirmed by double-blind, placebo-controlled food challenges (DBPCFC) or open

food challenges generally range from 33 to 38.7% [12–14], with occasional studies having higher rates up to 81% [15,16]. Thus, confirmed food allergy is more frequent in more severe phenotypes of atopic dermatitis.

Finally, the effect of atopic dermatitis on tolerance acquisition to foods is not clearly understood and complex. Atopic dermatitis was associated with persistent egg allergy in some studies [21,22]. Severity of atopic dermatitis at age of diagnosis was inversely associated with timing of resolution of milk allergy [23]. On the other hand, in one recent study, the presence of atopic dermatitis did not seem to affect the natural history of cow's milk allergy [24]. These discrepancies likely depend on confounding factors including severity of atopic comorbidities, baseline SPT and sIgE levels to foods.

MECHANISMS OF SENSITIZATION TO FOODS IN PATIENTS WITH ATOPIC DERMATITIS

Atopic dermatitis is characterized by impaired skin barrier and immune dysregulation [6,25[¶],26]. Enhanced absorption of allergen through disrupted skin barrier is thought to lead to a T helper 2 (Th2) response, IgE-class switching, and subsequent clinical food allergy [27,28]. Food allergens penetrating the top layers of the skin (stratum corneum) and exposed to keratinocytes are taken up by local dendritic cells (Langerhans cells), which migrate to local lymph nodes where they induce a Th2 immune response [29]. Moreover, murine studies have shown that innate immune cells (eosinophils and basophils) accumulate in the skin in response to exaggerated thymic stromal lymphopoietin production after cutaneous application of food allergens [30[¶]]. Interleukin-4 produced by basophils and eosinophils promotes dendritic cell activation and presentation of food antigens to naïve T cells, which leads to Th2 polarization [30[¶]] and ultimately intestinal IgE-mediated food allergy in mice [30[¶],31]. This is corroborated by the fact that epicutaneously sensitized mice display intestinal mast cell expansion and subsequent anaphylaxis upon exposure to the food allergen [32].

These in-vivo findings are supported by clinical studies, where epicutaneous sensitization was shown to occur by application of peanut oil on eczematous skin [33] and through environmental exposure to peanuts [34,35]. In addition, exposure to hydrolyzed wheat protein in facial soaps was shown to be a risk factor for a special phenotype of wheat allergy [36]. On the other hand, ingestion of allergens by the oral route generally promotes tolerance [28].

Genetic factors underlying skin barrier disruption have been associated with increased risk of food

allergy. In particular, filaggrin loss-of-function mutation is a risk factor associated with peanut sensitization in children with atopic dermatitis via environmental exposure to house dust peanut protein [35]. Interestingly, filaggrin mutation was shown to be a risk factor for peanut allergy but not for other food allergens in preschool children [37]. Furthermore, missense mutations in serine peptidase inhibitor Kazal type 5 (SPINK5) have been associated with food challenge-proven food allergy [38].

Skin microbiome dysbiosis also plays a role in predisposing food sensitization in patients with atopic dermatitis by contributing to skin barrier dysfunction [28]. Staphylococcal superantigens (such as Staphylococcal enterotoxin B) were shown to enhance peanut epicutaneous sensitization in mice [39]. In addition, higher rates of food allergy were found in children with atopic dermatitis colonized with *Staphylococcus aureus* [40].

PATTERNS OF CLINICAL REACTIVITY TO FOODS IN PATIENTS WITH ATOPIC DERMATITIS

Children with atopic dermatitis present with three types of reactions to foods on OFC: immediate IgE-mediated reactions, delayed exacerbation of atopic dermatitis (thought to be non-IgE mediated) [41], or a mixed presentation [42]. Immediate reactions generally occur within 2 h and display typical characteristics of IgE-mediated food allergic reactions: skin symptoms including urticaria/angioedema, respiratory symptoms, digestive symptoms, cardiovascular or neurologic symptoms [43]. The majority of patients with atopic dermatitis present with cutaneous symptoms. On the other hand, delayed reactions generally occur within 6–48 h after OFC [42] and consist of atopic dermatitis flare-up. Finally, up to 40% of patients present with initial immediate reactions, followed by delayed exacerbation of atopic dermatitis [1].

DIAGNOSIS AND DIETARY MANAGEMENT OF FOOD ALLERGY IN PATIENTS WITH ATOPIC DERMATITIS

Diagnosis and management of patients with atopic dermatitis suspected of food allergy should follow established international guidelines [44[¶],45,46]. Skin testing and/or sIgE should be performed in patients with a history compatible with an immediate IgE-mediated reaction to the suspected allergen(s). In addition, selected food skin testing/sIgE can be considered in patients with moderate-to-severe atopic dermatitis under the age of five unresponsive to topical treatments and other skincare

treatments. Atopy patch testing has been studied to evaluate foods responsible for atopic dermatitis flare-ups in children with atopic dermatitis [47,48]. Although promising, they are not standardized and not suggested in routine diagnosis of food allergy in patients with atopic dermatitis. DBPCFC may be necessary in some instances to confirm food allergy; many patients with atopic dermatitis present with asymptomatic sensitization and these challenges may help guide which allergens may be clinically relevant. Finally, an elimination diet trial based on results of conclusive food challenges may be indicated, on the basis of evidence that this may reduce the severity of atopic dermatitis in these patients [49[¶]]. Unselected elimination diets are not recommended because of possibility of loss of tolerance to introduced foods [50,51] and can be associated with other complications such as nutritional risks and growth restriction [49[¶],52[¶],53].

FOOD ALLERGY PREVENTION STRATEGIES IN PATIENTS WITH ATOPIC DERMATITIS

Numerous recent studies have focused on optimal strategies to prevent food allergy in high-risk infants with atopic dermatitis.

EARLY TREATMENT WITH EMOLLIENTS

Treatment of atopic dermatitis with emollients and topical antiinflammatory medication aims at reducing inflammation and repair skin barrier defects [28]. Many studies have evaluated the effect of aggressive emollient treatment in infancy and development of atopic dermatitis and food allergy. A recent study group in the United Kingdom performed a pilot randomized, parallel, single-blind controlled trial of the effect of twice-daily application of ceramide emollient for the first six months of life on the incidence of atopic dermatitis and skin barrier function in 80 high-risk infants up to 12 months of age [54]. There was no significant effect on development of food sensitization and atopic dermatitis, although a trend toward improvement was seen. Another large multicentric study is ongoing in Japan (Prevention of Allergy via Cutaneous Intervention study) to determine whether early aggressive treatment of atopic dermatitis with emollients and topical corticosteroids can prevent development of food allergy [55].

EARLY INTRODUCTION OF ALLERGENIC FOODS

Early introduction of allergenic foods for prevention of food allergy in patients with atopic dermatitis has

been investigated for peanuts [56,57], eggs [58,59], and multiple foods [60^{***}]. The Learning Early about Peanut Allergy (LEAP) study was the first interventional study to address the issue [56]. This landmark study consisted of a double-blind placebo-controlled trial in which high-risk infants 4 to 11 months of age (moderate-to-severe atopic dermatitis and/or egg allergy) were separated in high peanut consumption or no consumption groups for 60 months. A much lower incidence of peanut allergies was seen in the group with high peanut consumption (1.9%) when compared with the avoidance group (13.7%), suggesting that infants with allergic potential became tolerant to peanuts after early peanut exposure. A follow-up study with the same cohort (LEAP-On) showed that a 12-month period of peanut avoidance at five years of age was not associated with an increase in prevalence of food allergy in the high consumption group, suggesting that primary prevention was sustained rather than a temporary phenomenon. Similar positive results were found in high-risk groups with atopic dermatitis with early introduction of egg [58,59] and recently with multiple foods [60^{***}]. In the Enquiring About Tolerance (EAT) study, infants with moderate-to-severe atopic dermatitis developed significantly less food allergy to one or more foods, and less egg allergy with early introduction of allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat) at the age of three months compared with standard introduction at six months [60^{***}]. This trial had previously been unsuccessful at preventing food allergy using an intention-to-treat analysis in infants recruited from the general population [61]. One caveat of early introduction is the safety of performing such a task, as some infants with atopic dermatitis may already be allergic at time of introduction. This is highlighted by the Solids Timing for Allergy Research trial where a high rate of allergic-reaction in egg-sensitized children at the age of four months forced an early termination of the trial [58]. Thus, guidelines generally suggest performing SPTs and/or sIgE before early introduction of allergenic foods in children with moderate-to-severe atopic dermatitis [62,63]. In addition, real-life parents' assiduity at regularly introducing allergenic foods may not be as stringent as in the aforementioned study protocols (patients were instructed to eat three times a week), depending on family's personal dietary habits, which could ultimately limit the benefit of early introduction. Further studies are needed to better determine the best approach of introducing these allergenic foods in these high-risk patients for the prevention of food allergy.

BREASTFEEDING/HYDROLYZED FORMULAS

Guidelines generally recommend exclusive breastfeeding till the age of four months in high-risk infants, with hydrolyzed formula recommended in infants who are unable to breastfeed [44^{***}]. There is however a lack of robust data supporting the prevention of food allergy and/or atopic dermatitis in high-risk patients with breastfeeding. Some data suggests breastfeeding may prevent cow's milk allergy by the age of two [64,65]. On the other hand, a higher proportion of egg sensitization was found in breastfed infants with atopic dermatitis compared with non-breastfed infants [66]. Confounding factors such as length of breastfeeding, as well as variability in personal and familial atopic risk may explain heterogeneous data in the literature. Although some individual studies have suggested hydrolyzed formula may prevent eczema in high-risk infants [67], a recent Cochrane metaanalysis found only very low-quality evidence that short-term use of an extensively hydrolyzed formula compared with cow's milk formula (CMF) for the prevention of cow's milk allergy [68^{*}], with no evidence to support a hydrolyzed formula compared with a CMF for prevention of allergic disease. This is supported by a recent large population-based study ($n = 11\,720$) which found a higher risk of food allergy at two years in at-risk infants using partially hydrolyzed formula with hypoallergenic labels compared with nonhydrolyzed formula [69^{***}]. Guidelines may be changed in the future [70].

PREBIOTICS/PROBIOTICS/VITAMINS

Prebiotic and probiotic supplementations for the prevention of food allergy in children (with or without atopic dermatitis) are not currently recommended because of inconsistent evidence [44^{***},45]. One recent study evaluated the effect of combining emollients and synbiotics (mixture of probiotics and prebiotics) alone or in combination from birth to the age of six months. Unfortunately, this strategy had no effect on prevention of food allergy at the age of one year [71]. On the other hand, a recent two-center randomized placebo-controlled trial showed that supplementation with *Lactobacillus rhamnosus* (HN0001) or *Bifidobacterium lactis* (HN019) during end of gestation, in breastfeeding mothers, and in infants till the age of two reduced the incidence of atopic disease including atopic dermatitis and food allergy at the age of 11 [72^{***}]. Further data is needed. Finally, a recent systematic review concluded that there is insufficient data to support vitamin D supplementation to prevent atopic dermatitis and food allergy [73].

CONCLUSION

Atopic dermatitis is frequent disorder of childhood which poses a strong risk factor for the development of food allergy. A large amount of evidence in recent years supports epicutaneous sensitization to food allergens via defective skin barrier in atopic dermatitis. Genetic factors, skin microbiome dysbiosis, as well as innate immunity dysregulation are all implicated in the pathogenesis of atopic dermatitis, and play a role in transcutaneous sensitization. Food allergy may be present in approximately one-third of patients with moderate-to-severe atopic dermatitis, and dietary evictions may be warranted in such patients. However, this requires a careful evaluation by specialists to confirm causality between foods and atopic dermatitis exacerbation as unnecessary dietary evictions may lead to loss of tolerance to allergenic foods and nutritional deficiencies. Strategies to prevent food allergy in high-risk patients with atopic dermatitis are currently being investigated, with promising results from early introduction of allergenic foods. Further studies are required to precise the optimal strategy and timing of introduction and whether this may be applicable to other allergenic foods. Ultimately, further studies on the pathophysiology of atopic dermatitis and its role in the development of food allergy will help to define better therapeutic targets for both the primary prevention and treatment of food allergy.

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There are no conflicts of interest.

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- of special interest
- of outstanding interest

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