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Reviews

The skin as a target for prevention of the atopic march

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Key Messages

- Childhood allergic diseases are common and cause a substantial health burden.
- Atopic dermatitis (AD)/skin inflammation may increase risk of other allergic diseases.
- Routine use of emollients from infancy halves the risk of AD.
- Trials will determine if emollient use reduces risk of food allergy and asthma.

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ABSTRACT

Objective: Allergic diseases have increased dramatically in the developed world during the past few decades, yet the understanding of risk factors and effective prevention approaches remain limited. In this review, we summarize the evidence supporting the hypothesis that skin-barrier impairment and early-life atopic dermatitis (AD) could play a causal role in the development of sensitization and subsequent food allergies and allergic airways disease (allergic asthma and rhinitis). We further discuss the potential to target the skin barrier as a means to lower the incidence of allergic disease.
Data Sources: Review of published literature.
Study Selections: Narrative.
Results: There is a strong link between AD and sensitization, food allergy, asthma, and allergic rhinitis, particularly AD that is severe and commences in the first 6 months of life. There also is emerging evidence that regular use of prophylactic emollients can significantly decrease the expression of AD, at least while treatment continues. Studies are exploring whether decreased AD expression might modulate the allergic response at a more fundamental level and potentially alter the association between early-life AD and subsequent development of food allergy and allergic airways disease.

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Conclusion: Although at this point there is only indirect evidence that early-life emollient use might prevent AD and food allergy, early studies are encouraging. The results of high-quality prevention trials that are in progress are eagerly anticipated. If found to be effective, then neonatal emollient use could be a simple public health measure to lower the incidence of AD, food allergies, and allergic airways disease in future generations.

Introduction

The "atopic march" is a clinical sequence that begins with atopic dermatitis (AD) and progresses to food allergy followed by subsequent development of respiratory allergies (asthma and/or allergic rhinitis).[1,2] The increased prevalence of allergic diseases in Westernized societies during recent decades has sparked considerable interest in whether early-life intervention might prevent the evolution of the atopic march.

Allergic diseases are common in Westernized countries and cause substantial health, social, and economic burdens. There are dramatic differences between geographic areas in the prevalence of these conditions and prevalence shifts over time,[3] making it difficult to provide accurate estimates of prevalence. AD, also known as atopic eczema or simply eczema, is the earliest manifestation of the atopic march and affects approximately 20% to 30% of infants.[4] Another common and early manifestation of allergic disease is food allergy. Recent reports have suggested that food allergy affects 5% to 10% of infants in early life,[5–7] and there has been a relatively recent and dramatic increase in the rate of hospital admissions for food-induced anaphylaxis in young children in several countries including Australia,[8] the United Kingdom,[9] and the United States.[10] Although allergic diseases can resolve in some individuals with time, there are currently no cures for these conditions. These conditions are a major health concern, because they are the most common chronic illnesses affecting children in Western societies.

To date, most research into strategies for the prevention of allergic disease has been disappointing. Reviews covering these studies are already available for food allergy[11] and AD.[12] There is growing awareness of the role of epithelial barrier dysfunction in the pathogenesis of allergic disease,[13] and there is mounting evidence that impaired skin barrier and inflammation associated with AD could be a precursor to allergic sensitization and other forms of allergic disease.[1] The strong link between AD, particularly AD that is early onset and severe, and other forms of allergic disease, including food allergies and asthma, has been well recognized for some time.[14–16] This observation has led to the atopic march hypothesis, in which it is argued that AD might actually be a cause of the subsequent increase in risk of food allergy and allergic respiratory disease. Furthermore, the dual-allergen exposure hypothesis (or Lack hypothesis, authored by Gideon Lack[17]) in part suggests that epicutaneous allergen exposure in early life might promote allergic sensitization as the first step in the allergic march.

The aim of this review is to explore the theoretical basis and supporting evidence for the hypothesis that skin inflammation and/or epithelial barrier dysfunction might be critical in the development of allergic sensitization, food allergy, and allergic airways disease. Then, we consider the implications of this hypothesis on disease prevention. In particular, we describe previous and current studies testing the effect of skin-barrier improvement interventions on primary and secondary prevention of allergic disease. Further, we explore key issues pertinent to the design and interpretation of existing and future studies concerning the potential prevention of the atopic march.

Dual-Allergen Exposure Hypothesis

The dual-allergen exposure hypothesis, which could explain the increase in food allergy prevalence,[17] posits that exposure to environmental food allergens can lead to induction of sensitization and subsequent food allergy if early-life skin barrier function is poor or if there is skin inflammation, such as occurs with AD. However, early oral ingestion of food allergens can abrogate this risk by helping to promote immune tolerance to foods. This hypothesis has a number of important implications.

The first implication is that early oral exposure to food allergens could help promote immune tolerance. The Learning Early About Peanut (LEAP) trial showed that regular exposure to peanut allergen from 4 to 11 months of age in children at high risk of peanut allergy (due to severe eczema or egg allergy) resulted in an absolute decrease in the cumulative incidence of food allergy of 11.8% (13.7–1.9%).[18] Although trials evaluating a similar strategy for other allergens, including egg,[19–22] have not been as definitive, when the results from multiple studies are pooled together, there is evidence that early introduction of egg (at 4–6 months of age) is effective at lowering the risk of egg allergy.[23] In contrast, no consistent evidence exists for an effect of age of introduction to cow's milk on cow's milk allergy.[23] These protective effects of early food allergen exposure appear to be allergen specific; early introduction of one allergen does not prevent the development of allergy to other allergens. Effects on other allergic disease outcomes, including eczema, are not clear.[23]

The second implication of the dual-allergen hypothesis, and the primary focus of this review, is that if the skin barrier can be improved and/or the inflammation of AD can be proactively prevented, then the incidence of food allergy and possibly other forms of allergic disease also might be decreased. This represents a substantial shift in thinking concerning the target organ for food allergy prevention. We will describe the evidence to support this hypothesis and the research that is currently underway in this field.

Can the Skin be the Site of Initiation of Sensitization and Subsequent Allergic Disease?

It has been hypothesized that sensitization to allergens can occur through damaged skin associated with AD, which then increases the risk of food allergy and other forms of allergic disease.[1] The skin is a very important barrier to the external environment; this barrier is initially more permeable (in infancy) and becomes more effective with increasing age.[24] The decreased barrier function of infants is, at least in part, due to low concentrations of ceramides in the stratum corneum, with ceramide concentration increasing in the weeks after birth.[25] Eczematous skin also is characterized by decreased ceramide levels.[26] Skin barrier is impaired in AD, even in asymptomatic skin.[26] Impaired skin barrier function in the first week of life is associated with an increased risk of AD by 12 months of age, even when the effect of family history and null mutations in the filaggrin (*FLG*) gene are taken into account.[27] Interestingly, increased transepidermal water loss can be detected at day 2 of life in infants who develop food allergy at 2 years of age.[28] Impaired skin barrier is associated with innate immune activation that results in dysregulated immune responses to innocuous environmental antigens, such as allergens and bacteria, and then to unwanted skin inflammation, leading to the development of allergic sensitization.[13] These dysregulated immune responses in turn lead to further impairment of the barrier function and thereby establish a feedback cycle of ongoing inflammation and injury.[29]

There are accumulating data supporting the concept that allergic sensitization can occur through an impaired skin barrier. Studies of mice have shown that epicutaneous disruption followed by ex-