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Title: Hydrolyzed Formula, Delayed Food Introduction, and Fatty Acids for Atopic Dermatitis Prevention in Infancy

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Short title: Preventative Measures for Atopic Dermatitis in Infancy

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Abbreviations: AD: atopic dermatitis, pHF: partially hydrolyzed formula, eHF: extensively hydrolyzed formula, n-3: omega-3, n-6: omega-6, PUFA: polyunsaturated fatty acid, r-TFA: ruminant trans fatty acids, RCT: randomized controlled trial.

Abstract:

Aim: The role of nutrition in preventing atopic diseases including atopic dermatitis has recently gained interest in the medical community. Caregivers of infants and children at an increased risk for developing atopic dermatitis often employ exclusion diets or other measures in hopes of preventing the development of this burdensome disease. This paper reviews the current literature in regard to the role of preventative dietary measures in the context of atopic dermatitis, with a special focus on the topics of hydrolyzed formula, early versus delayed introduction of certain foods, and fatty acid supplementation.

Methods: Literature pertaining to preventative dietary measures for infants at risk for atopic dermatitis was reviewed.

Results: Analysis of the literature suggests that hydrolyzed formula should not be routinely offered to infants for prevention of atopic dermatitis. Formulas utilized should contain concentrations of polyunsaturated fatty acids similar to that in breast milk. Finally, infant caregivers should not delay or restrict introduction of food, which can be more harmful than helpful to the patient.

Conclusion: Recommendations to caretakers providing for infants at risk for atopic dermatitis should include infant consumption of breastmilk, and avoid delayed introduction of foods.

Key notes

- In the context of atopic dermatitis prevention in infants, review of the literature suggests that hydrolyzed formula should not be routinely offered to infants.
- If formula is used, it should contain fatty acid concentrations similar to that in breast milk.
- In addition, restriction or delay of the introduction of certain foods is not advised, as it can cause harm to the infant.

Key words: atopic dermatitis; eczema; nutrition; prevention; infancy

Introduction

The role of early dietary modification for possible prevention of atopic dermatitis (AD) in the at-risk infant remains ambiguous to caregivers and physicians alike. The popular association made by patients or caregivers between the development and/or aggravation of atopic dermatitis due to food hypersensitivity may lead to unmonitored and unwarranted dietary exclusion, which can lead to malnutrition, growth stunting, vitamin deficiencies and even kwashiorkor.(1, 2) Thus, it is of great importance for the dermatologist to be able to provide evidence-based recommendations to caregivers of infants at high risk (i.e. positive family history for allergic diseases such as asthma, allergic rhinitis, or atopic dermatitis) for AD. The purpose of this review is to examine the role of AD prevention through dietary modifications in the infant, specifically in regard to hydrolyzed formula, early versus late introduction of foods, and fatty acid supplementation. We also provide evidence-based practical pearls for the dermatologist to utilize when counseling the caregivers of these patients.

Hydrolyzed Formula

Breast milk is the optimal source of nutrition for infants through the first year of life as it may reduce the incidence and severity of AD in high-risk patients.(3-5) Unfortunately, some infants are unable to breastfeed or may have a milk-protein allergy (i.e. food protein-induced proctocolitis). Hydrolyzed formula is an option for these infants. The purpose of hydrolyzing formula is to break down the cow's milk protein (i.e. casein, whey) in order to reduce the likelihood of a type-1 hypersensitive reaction from occurring. Hydrolyzed formulas are often marketed as completely hypoallergenic, however in actuality, they only reduce the chance of an allergic reaction from occurring.

Although hydrolyzed formula was designed for infants with confirmed cow's milk protein allergy, it has been thought to potentially prevent atopic dermatitis in at-risk infants who cannot breastfeed. In the last ten years, several systematic reviews were in favor of the use of hydrolyzed formula compared with standard cow's milk formula for the prevention of atopic dermatitis.(6-10) In contrast, Boyle et al. stated in a meta-analysis that there was no evidence to support the claim that hydrolyzed formula could reduce the risk of eczema or prevent allergy to cow's milk.(11) Importantly, the authors of this paper combined the data for all partially hydrolyzed formulas (pHF) and for all

extensively hydrolyzed formula (eHF), and grouped for age assessments without a scientific or clinically relevant rationale.(11) Similarly, a recent Cochrane systematic review showed that limited evidence supports the use of hydrolyzed formula compared with cow's milk formula to reduce eczema amongst babies and children at high risk of allergy.(12)

In summary, hydrolyzed formula should not be routinely offered to infants for prevention of atopic dermatitis (Table 1). Furthermore, hydrolyzed formula is often expensive and less palatable for infants, further justifying why it should not be used routinely unless necessary. It is important to keep in mind that not all hydrolyzed formulas are the same, with different heat, enzyme, and pressure treatments and fractions, which may lead to differences in each formula. Therefore, parents of infants with a proven milk allergy should consult a nutritionist or dietician familiar with alternative options for cow's milk formula to identify the best option for their infant. Other mammal milk alternatives such as goat and sheep milk have a high rate of allergy in infants with cow's milk allergy.(13) If an infant experiences a severe reaction (anaphylaxis which can either involved hypotension or respiratory distress) after ingestion of hydrolyzed formula, an allergist assessment is warranted, as even hydrolyzed formula may contain peptides of sufficient size to cause anaphylaxis.

Early versus Delayed Introduction of Foods

Early clinical practice guidelines recommended delaying the introduction of allergenic foods (i.e. peanuts, wheat, soy, fish, and egg) until the age of 3 years to prevent adverse reactions to feeding during infancy. Recently, there has been a paradigm shift in early food introduction due to findings suggesting that early introduction of allergenic foods is an effectual strategy for preventing rising rates of food allergy. Early introduction of allergenic foods to the largest immunologic organ in the body, i.e. the gastrointestinal tract, is thought to teach the naïve immune system not to react to food proteins as foreign. This concept is known as tolerance, and a failure to develop oral tolerance or a loss of oral tolerance is hypothesized to be the problem in food allergy.(14)

The landmark study eliciting the clinical implication of oral tolerance was “The Learning Early About Peanut Allergy” (LEAP) trial conducted in 2015, which provided high-level evidence regarding early

introduction of peanuts to high-risk infants with moderate-to-severe eczema and/or egg allergy.(15) Amongst infants with high-risk atopic disease, continued peanut consumption starting in the first 11 months of life, as compared with peanut avoidance, resulted in a significantly smaller percentage of children with peanut allergy at 60 months of age. Similarly, several systematic reviews since that time suggest that early introduction of allergenic foods may help in the prevention of food allergy development.(16, 17) In contrast, a meta-analysis by Ierodiakonou et al. found no consistent association between timing of allergenic food introduction and risk of atopic dermatitis.(18) Importantly, the assessment for publication bias in analyses of atopic dermatitis in particular was not possible because of the limited number of studies.

A recent large randomized controlled trial of 2,397 newborn infants in Oslo and Stockholm aimed to determine if either the application of early skin emollients or early complementary feeding reduced development of AD by 12 months of age in the general infant population.(19) Authors of this study found that atopic dermatitis developed in 16% of infants exposed to early food intervention, 16% of patients exposed to early skin emollient application, 15% of those with no intervention, and 12% in the combined intervention group. These results suggest that neither early food intervention nor early skin emollient application helped to reduce development of AD by age 12 months. Importantly, this study was done on infants in the general population and not those specifically at risk for AD. More insight on the connection between early introduction of allergenic foods and AD will develop upon completion of “The Preventing Atopic Dermatitis and Allergies in Children” study (ClinicalTrials.gov: NCT02449850). This is a European population-based prospective birth cohort randomization of about 2500 infants to either early introduction of 4 allergenic foods (egg, milk, wheat, and peanut) by age 4 months and regular emollient use. No data has been posted since the study anticipates continuing into adulthood.

There are specific guidelines for the introduction of peanuts in patients with atopic dermatitis(20), but not for other allergenic foods. With the current evidence, dermatologist may educate the caregivers of their AD patients that early food introduction has not been proven to reduce the risk of developing AD, however early food introduction seems to be important to prevent specific food allergy,

especially in children with AD. Families may be referred to work with allergy specialists to understand results and create customized plans for allergenic foods as needed. For high-risk children, education of signs and symptoms of a true allergic reaction is important as well as education about what should be done if a reaction does occur.(16)

Fatty Acids

Omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFAs) have been implicated in the pathogenesis of atopy as they play diverse roles in the context of the skin. Metabolites derived from these fatty acids regulate inflammation and form part of the lipid-rich stratum corneum critical to an optimal skin barrier.(21) Furthermore, the proper n-6:n-3 ratio is thought to be an important aspect of immunological function, as n-3 fatty acids are typically associated with anti-inflammatory activity, while n-6 fatty acids regulate pro-inflammatory responses. Indeed, a recent cohort study showed that higher second trimester n-6 PUFAs were associated with atopic dermatitis in children of women with atopy.(22) Furthermore, a meta-analysis showed that higher n-6:n-3 ratio were associated with higher risk of AD.(23)

Studies tend not to be in support of infant fatty acid supplementation in prevention of AD. RCTs found no benefit of n-3 or n-6 PUFA supplementation in infants for the prevention of AD occurrence.(24-27) Results of meta-analyses are inconsistent. Zhang et al. found that increased intake of fish rich in n-3 PUFAs during the first year of life was associated with a lower risk of childhood atopic dermatitis.(28) In contrast, a meta-analysis showed that omega-3 fatty acids during childhood did not appear to significantly alter the risk of eczema.(29) A meta-analysis of 26 observational studies aiming to evaluate whether early life natural exposure to PUFAs and ruminant trans fatty acids (r-TFA) could affect AD risk found a protective effect only of vaccenic acid (an r-TFA) on eczema, but insufficient or no evidence was found for the protective effect of PUFAs on decreasing eczema risk.(23) Finally, a Cochrane Review of 17 clinical studies showed that PUFA supplementation in infancy did not affect infant incidence or prevalence of atopic dermatitis.(30) Importantly, the types of PUFAs used in each study were derived from different sources, and n-3:n-6 ratios were not similar across studies.

The current literature regarding PUFA intake in infancy is therefore ambiguous, with the majority of studies yielding no benefit. Importantly, PUFA consumption was never shown to be harmful. As breastmilk contains significant amounts of PUFAs, PUFA-supplemented formula should contain concentrations similar to that of breastmilk (Table III).(21) Because studies regarding this phenomenon are variable in trial design, dose, and other inconsistencies, further large-scale studies are required in order to determine the role of PUFA supplementation in infancy to reduce the prevalence and severity of AD.

Conclusion

Parents of children at an increased risk for atopy often struggle with the role of nutrition in preventing the occurrence of AD. In addition, due to the lack of consistent information, it can often times be difficult for the dermatologist to make evidence-based recommendations. This review sought to clarify common misconceptions and provide practical pearls regarding the role of hydrolyzed formula, early versus late food introduction, and fatty acid supplementation. If exclusive breastfeeding is not a viable option in infancy, cow's milk formula may be used as the role of hydrolyzed formula in AD prevention is inconclusive. Breastmilk substitutes should contain the same concentrations of polyunsaturated fatty acids as those present in breastmilk. Parents of AD infants should not restrict introduction of food, as this may be more harmful than helpful. Early introduction to peanut in at-risk children is recommended after appropriate screening for allergy.

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Conflict of Interest

There are no conflicts of interest to disclose.

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Table 1.

Practical Pearls: Hydrolyzed Formula	
◇	Exclusive breastfeeding should be encouraged as primary means of nutrition
◇	Infants unable to breastfeed, hydrolyzed formulas may have a role in atopic dermatitis but study results are inconclusive
◇	Hydrolyzed formula should not be routinely offered to infants to prevent atopic dermatitis
◇	Infants with diagnosed cow's milk allergy* should consult a nutritionist to explore alternative options for their infant

*Cow's Milk Allergy: Gold Standard Diagnosis by clinician-supervised, double-blind, placebo-controlled oral food challenge or Measurement of cow's milk-specific IgE

Table 2.

Practical Pearls: Early Introduction of Foods and Atopic Dermatitis	
◇	Parents of infants who are at risk for atopic dermatitis should not restrict introduction of food, as this may be more harmful than helpful

- Accepted Article
- ◇ Delay of introduction of peanut into the diet correlates with increased risk of developing peanut allergy as eczema severity increases

Table 3.

Practical Pearls: Fatty Acids	
◇	Literature-based evidence supporting the use of fatty acid supplementation in infancy is ambiguous, with several studies showing no benefit
◇	Infants at an increased risk for atopy should be breastfed in order to obtain adequate amounts of fatty acid concentrations
◇	Infants at an increased risk for atopy who cannot breastfeed should be provided with formula containing adequate amounts of polyunsaturated acids, similar in concentration to breastmilk