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Invited review article

Prevention of food allergy – Early dietary interventions☆

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IgE, Immunoglobulin E; WHO, World Health Organization; Th-2, T-helper type 2; FLG, Filaggrin; STAR, Solids Timing for Allergy Research; HEAP, Hen's Egg Allergy Prevention; EAT, Enquiring About Tolerance; BEAT, Beating Egg Allergy Trial; LEAP, Learning Early about Peanut Allergy; PUFAs, polyunsaturated fatty acids; SPT, skin prick test; OFC, oral food challenges; NNT, number needed to treat; ITT, intention-to-treat

ABSTRACT

The prevalence of food allergy has increased over the last 30 years and remains a disease, which significantly impacts on the quality of life of children and their families. Several hypotheses have been formulated to explain the increasing prevalence; this review will focus on the hypothesis that dietary factors may influence the development of food allergy. Historically, the prevention of food allergy has focused on allergen avoidance. However, recent findings from interventional studies have prompted a shift in the mind set from avoidance to early introduction of potentially allergenic foods. This review aims to facilitate a better understanding of contemporary research studies that make use of early introduction of common allergenic foods into infant diets as a preventative strategy against the development of food allergy.

Background

The prevalence of food allergy has been on the rise over the last 30 years with 6–8% of children being affected worldwide; the disease burden is higher for infants and preschool children.[2–4] Food allergy is primarily classified as immunoglobulin E (IgE)-mediated food allergy, non-IgE mediated food allergy or mixed IgE and non-IgE mediated food allergy.[5] IgE-mediated food allergies are type 1 immediate hypersensitivity reactions with a quick onset of symptoms usually within a few hours of exposure to a food antigen compared to non-IgE mediated food allergy where there is a delayed onset of symptoms following exposure to a food.[2] There is strong evidence showing the significant impact food allergies can have on the quality of life of the children affected and their families including emotional, psychological and financial burdens.[6–8] There is as yet no cure for IgE-mediated food allergy and the main treatment remains avoidance; thus, understanding the cause and developing strategies for the prevention of allergy has been at the forefront of current allergy research.

History of food allergy

In the 1960s, most infants were exposed to solids (complementary feeding) by 4 months of age[9]; however, in the 1970s new guidelines were introduced recommending a delay in the introduction of solids until after 4 months due to an assumption that early introduction of gluten was contributing to a rise in coeliac

☆ This review is a modified and updated version of a similar invited review that appeared in the Journal of Allergy and Clinical Immunology in April 2016.[1]

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disease which was observed at the time.[10] The World Health Organisation (WHO) recommended a further delay in the introduction of solid food in the 1990s to 6 months of age, and advised parents to delay the introduction of allergenic solids such as egg and peanut to 10 months and 3 years, respectively.[9] More specifically, in 1998 the UK Department of Health suggested that atopic pregnant and lactating women as well as children in the first 3 years of life should avoid the consumption of peanuts.[11,12] Despite these recommendations being intended for 'at risk' families they were more widely adopted.[13,14] A WHO systematic global review in 2002, which looked at exclusive breastfeeding for 6 months, reported no benefits of introducing complementary foods between 4 and 6 months of age for allergy prevention; despite this, recommendations for exclusive breastfeeding of infants in both developed and developing countries for the first six months of age were made.[15] A similar stance was adopted in the United States with a consensus document recommending that the optimal age for selected foods should be 6 months, specifically dairy products at 12 months, hen's egg at 24 months and at the earliest, peanut, tree nuts, fish and seafood at 36 months of age.[16]

Over the last few decades, despite these measures initiated to prevent allergy by delaying the introduction of allergenic foods, the prevalence of food allergy has continued to rise even in countries where dietary avoidance is practiced. Factors such as genetic variation, ethnicity, gender, hygiene, maternal diet in pregnancy and breastfeeding may all be contributing to the rising prevalence of allergy. Several hypotheses as to the cause for the rising prevalence of food allergies have been postulated and have been important in driving current research aimed at the prevention of food allergy. These hypotheses include the hygiene hypothesis, the vitamin D hypothesis and the dual-barrier hypothesis.

Hygiene hypothesis

The hygiene hypothesis describes the protective influence early-life microbial exposure has on the development of allergic diseases.[17] Strachen first proposed that having older siblings had a protective effect on the development of hay fever in younger siblings, possibly due to exposure to common childhood infections, but also maternal contact with older children in the prenatal period.[18] Since then, several studies have shown that various factors that increase exposure to pathogens, microbes and infections after birth can influence the host microbiome and immune defence system which plays a key role in the development of immune regulation as well as the development of oral tolerance.[19,20] Factors such as the mode of delivery, communal childcare, pets at home and birth order, which can influence exposure to micro-organisms, have been shown to influence the development of allergic disease.[19,21,22] The recent advances in our understanding of the role of the microbiome and gastrointestinal barrier function has led to a plethora of research in this area in relation to their role in food allergy.[23,24]

Vitamin D hypothesis

A more recent hypothesis has been that low vitamin D levels increase the risk of developing food allergy. Coincidentally, the rise in food allergy has occurred in conjunction with the increasing prevalence of vitamin D deficiency which has led to increased research into understanding the link between the two conditions.[25] In the HealthNuts population-based cohort study in Australia, vitamin D insufficiency was found to be associated with challenge-proven food allergy at 12 months of age.[26] More in-depth research into the genetic polymorphisms affecting vitamin D metabolism in this cohort has shown that altering the bioavailability of serum $25(OH)D_3$ could have a role in the development of food allergy.[27]

Dual-barrier hypothesis

The dual-barrier hypothesis has also played a key role in trying to explain the increasing prevalence of allergy. The most obvious and dominant route of food allergen exposure is through consumption, but allergen exposure may also occur through the skin and possibly the respiratory tract if inhaled. Atopic children experience a T-helper type 2 (Th-2) allergen specific immune response that occurs on exposure to a food allergen which results in the production of IgE antibodies for that specific allergen.[28] Non-atopic children absorb these foreign antigens without causing an immune host response, which allows for the development of oral tolerance.[28] The dual-barrier hypothesis suggests that early allergic sensitization to foods and environmental allergens occurs through a damaged or weakened skin barrier (i.e. eczema, filaggrin (FLG) loss-of-function mutations)[19,29]; thus there is a close relationship that exists between food allergy and eczema. A recent study showed that approximately 50% of children with eczema developed food allergy by 1 year of age.[30] Strid *et al.* had previously demonstrated that epicutaneous exposure to peanut protein in mice prevented the normal induction of oral tolerance but also enhanced Th2 responses including increasing IgE levels on gastrointestinal exposure.[31] This was further supported by Lack *et al.'s* paper which showed that use of topical peanut-oil based emollient preparations on children, which exposed them to peanut allergen through inflamed skin, was associated with peanut allergy.[32] Horimukai *et al.* also found that having eczematous skin increased allergic sensitization to egg white in the first 8 months of life.[30] Understanding the involvement of the skin barrier in food allergy has included further research into the role of FLG, which is known to play a vital role in epithelial barrier function and development of eczema. Brough *et al.* looked at the effect of environmental peanut exposure in a population-based birth cohort and found that children who carried a FLG mutation had an increased risk of peanut sensitization and allergy associated with early life environmental peanut exposure.[33] This is further supported by research from the Isle of Wight cohort for which there was a significant total effect noted of FLG mutations on the risk of food allergy later in childhood (10 years) but also an indirect effect between eczema and food allergy sensitization in early childhood.[34] Interestingly, recent work by Kelleher *et al.* demonstrate that a permeable skin barrier on day two of life is associated with food sensitization and allergy at 2 years of age, even in the absence of eczema.[29] Studies into improving the skin barrier in order to decrease the risk of food allergy in children are underway; indeed, in a pilot study Simpson *et al.* demonstrated in a cohort of neonates that daily emollient applied from birth resulted in a 50% relative risk reduction in the development of eczema at 6 months of age.[35]

The role of diet in food allergy

With the continual rise in prevalence of food allergy despite advisory measures of avoidance, the last 10 years have witnessed an increasing body of evidence based on epidemiological studies that challenge the idea of dietary avoidance for the prevention of food allergy.[36] This has led to research looking into the alternate strategy of early introduction of foods for the prevention of food allergy.