

Preventing Food Allergy

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In this review, we examine the critical periods of immune development and how these might be modified to prevent food allergy. The relevant dietary intervention studies, roles of microorganisms and their products, and other strategies are critically analyzed. Additionally, we highlight the potential importance of different routes of allergic sensitization and the role of oral tolerance induction in the pathogenesis and prevention of food allergy.

Introduction

There has been an increase in the incidence of allergic diseases, including food allergy, in the past two decades [1]. Genetic factors are clearly important, as demonstrated by twin studies [2], human lymphocyte antigen (HLA) linkages [3], and the positive relationship between food allergy and atopy in the individual and family [4]. However, it is unlikely that genetics can explain the recent increase in the prevalence of food allergy. Therefore, a considerable number of studies have been designed to determine the links between environmental or immunologic factors and food allergies.

Any review of this field is complicated by different phenotypic descriptions in the important studies. Some studies examine eczema, asthma, or rhinitis as end points. Other studies examine food allergies using different definitions, such as skin prick test or specific IgE. Very few studies use food challenge procedures, the gold standard for diagnosing food allergy. This is particularly problematic for cow's milk allergy, the most common food to be studied, because the allergy can be IgE or non-IgE mediated. Dietary intervention studies frequently use eczema as a marker for food allergy in infancy. However, some studies show an improvement in eczema but not in food allergy, suggesting that the two conditions are not necessarily linked.

Despite the limited, and often conflicting, data in this area, a great deal of public health advice is available. This advice involves maternal dietary avoidance during pregnancy and lactation, particularly in regard to peanut, and also infant dietary measures in respect to hypoallergenic formulas for

bottle-fed infants and delayed introduction of solids to 5 to 6 months of age. Some of these measures relate to a normal population, and some to a high-risk/atopic population (at least one or two parents or siblings with atopy). In view of the limited data, it is not surprising that the European and North American recommendations have some differences [5]. Taking the example of preventing peanut allergy, the 2000 American Academy of Pediatrics guidelines advise maternal peanut avoidance in pregnancy and lactation, and delayed peanut introduction into the infant diet until 3 years. These measures are similar to those recommended in the United Kingdom [6]. In contrast, the 1999 European Society for Pediatric Gastroenterology, Hepatology and Nutrition/European Society for Paediatric Allergy and Clinical Immunology guidelines recommend no maternal avoidance of peanut, and a delay of solids in the infant diet until 5 months, but no specific advice on infant peanut avoidance.

Fetal and Early Neonatal Immune Development

There has been considerable debate as to whether sensitization to food or inhalant allergens occurs in utero or in the postnatal period. There is evidence of antigen-specific immune responses in early fetal development. Furthermore, the opportunity for sensitization clearly exists, because food proteins can be transferred transplacentally and are present in amniotic fluid [7]. Prenatal sensitization with antigen-specific IgE has been reported, but seems to be uncommon, and limited to cow's milk [8]. None of the large birth cohort studies have demonstrated any specific IgE to foods in cord blood, including cow's milk, egg, and peanut, even in children who subsequently developed clinical or immunologic sensitization [9,10•], suggesting that sensitization is unlikely to be established in utero.

The absence of measurable, specific IgE in cord blood does not necessarily exclude the possibility that sensitization is initiated in utero. Allergen-specific T-cell and mononuclear cell responses have been demonstrated to ovalbumin, alpha-lactalbumin, and beta-lactoglobulin in cord and fetal blood [11]. The clinical significance of these T-cell responses is difficult to interpret in the absence of longitudinal data showing any predictive effect on the development of food allergy. Only a proportion of allergen-specific T-cell responses are derived from memory precursors; the rest come from naïve T cells and do not imply allergen sensitization [12]. In summary, there are no convincing data that sensitization is established or even initiated prenatally.

The potential for sensitization during lactation exists as small amounts of food allergens have been found in breast milk. Beta-lactoglobulin is found in the breast milk of 95% of mothers consuming cow's milk during lactation [13]. Peanut and other proteins have also been found in breast milk [14].

Irrespective of the timing of sensitization, by the time the infant presents with clinical allergy, there is evidence of both allergen-specific IgE and allergen-specific Th2-skewed immune response [15]. One study showed that resolution of peanut allergy is accompanied by a reversal of Th2- to Th1-skewed, allergen-specific, immune response [16]. This suggests plasticity within the immune system, raising the possibility of modifying the immune response, even after it has been established.

The Role of Maternal Diet

Several randomized studies have been performed in atopic populations to examine the effect of maternal dietary restrictions during pregnancy and/or lactation. These are summarized in Table 1 [17–21]. Using the end points of clinical food allergy and immunologic sensitization, there is no evidence from the available studies to suggest that dietary avoidance of cow's milk and egg in pregnancy reduces the risk of the infant developing food allergy to cow's milk and egg, in either normal or atopic populations. Similarly, maternal dietary avoidance of cow's milk, egg, and fish during lactation does not reduce the risk of infant allergy to cow's milk, egg, hazelnut, peanut, fish, and wheat.

Using eczema as the end point, which might have a link with food allergy in early childhood, these studies suggest a possible protective effect of maternal dietary restriction during lactation. The protective effect lasts for between 18 months and 4 years, with no effect being seen on 10-year follow-up [19].

One observational study has suggested a possible protective effect of maternal peanut avoidance in pregnancy and lactation in an atopic population [22]. This study was retrospective and uncontrolled, but suggested that the consumption of peanuts by mothers during pregnancy and lactation was associated with an earlier onset of peanut allergy in the children. There was no difference in the cumulative incidence of peanut allergy. An alternative explanation of the data is that the children of mothers consuming peanuts during pregnancy and lactation had the opportunity to consume peanuts earlier in life than those whose mothers did not eat peanuts. Furthermore, the findings of this study are not supported by two prospective birth cohort studies, one based on the Isle of Wight, UK [4], the other on Avon Longitudinal Study of Parents and Children (ALSPAC) [10•]. Both these studies showed no effect of maternal peanut consumption in pregnancy or lactation on the development of immunologic or clinical reaction to peanuts on follow-up at 4 to 6 years of age.

Maternal dietary polyunsaturated fatty acids (PUFAs) are known to have effects on immune function and inflamma-

tion, and, therefore, supplementing the maternal diet with anti-inflammatory n-3 PUFA might have potential in reducing allergic disease [23]. One recent study showed that maternal n-3 PUFA-rich fish oil supplementation from 20 weeks gestation until birth resulted in higher levels of n-3 PUFA and lower levels of interleukin-13 cytokine in neonatal plasma, indicating a T-cell response [24]. The clinical relevance in preventing allergy is unknown.

The Role of Infant Diet

In this section, we examine the effect of infant milk and timing of introduction of solids on the development of food allergy.

Breast-feeding

Numerous early studies, starting from 1930, have shown a protective effect of breast milk over unmodified cow's milk-based formula on the development of eczema in the first 12 to 48 months of life [25]. This was summarized in a recent meta-analysis [26]. Only some of these studies have looked at food allergy using clinical history and skin prick/specific IgE end points, as summarized in Table 1 [27–30]. Only one study was truly randomized [27]. The studies show no benefit of breast-feeding over cow's milk formulas on the development of food allergy to cow's milk, egg, and soy using skin prick testing, specific IgE, or food challenge definitions.

More recent observational cohort studies in normal populations appear to cast doubt on the protective effect of breast-feeding on the development of eczema. Indeed, two population-based, observational birth cohort studies from Germany and New Zealand have suggested the opposite effect that prolonged breast-feeding increases the risk of developing allergic disease, including eczema and asthma [31,32]. This discrepancy can be explained by "selection bias" and "reverse causality." Cohort studies that are not of the randomized interventional type (which is not ethically possible for breast-feeding) are difficult to interpret because of selection bias. Many atopic mothers choose to prolong breast-feeding and infants with early eczema may continue to be breast-fed for longer periods, on the advice of health professionals. Therefore, the recent observation that prolonged breast-feeding is associated with an allergic phenotype is most likely the result of reverse causality: genetic predisposition to atopy and early infant eczema modifies parental behavior and infant nutrition. A study by Sears *et al.* [31] corrected for parental atopy, but failed to correct for eczema in infancy. In the ALSPAC birth cohort, an association was found between a history of allergic reaction to peanut and prolonged infant breast-feeding, suggesting, erroneously, that breast-feeding might contribute to the development of peanut allergy, possibly through sensitization to allergens in breast milk. However, when infantile eczema was adjusted for in the regression analysis, there was no effect of breast-feeding on the development of peanut allergy.

Table 1. Dietary intervention studies

Study	Patients, n; type of study	Dietary intervention	Follow-up period, y	Definition of food allergy	Outcome
Kjellmann <i>et al.</i> [17] Falth-Magnusson <i>et al.</i> [18]	197–210; atopic population, birth cohort, randomized	Pregnancy: No egg and cow's milk in third trimester versus no restriction	1.5–5	Spt and specific IgE to cow's milk and egg	No difference
Hattevig <i>et al.</i> [19] Hermann <i>et al.</i> [20]	115–150; atopic population, birth cohort, one study randomized	Lactation: No egg, cow's milk, and fish during lactation versus no restriction	1–10	History of reaction to food (cow's milk and egg), spt and specific IgE to cow's milk, egg, hazelnut, peanut, fish, and wheat	Short-term reduction in eczema in intervention group in one out of two studies No difference in other outcomes
Lilja <i>et al.</i> [21] Hermann <i>et al.</i> [20]	150–162; atopic population, birth cohort, one study randomized	Pregnancy and lactation: No/reduced cow's milk and egg in third trimester and during lactation versus no restriction	1–1.5	Eczema Spt and specific IgE to cow's milk and egg	No difference
Lucas <i>et al.</i> [27] Chandra <i>et al.</i> [28] Oldaeus <i>et al.</i> [29] De Jong <i>et al.</i> [30]	75–1533; one preterm and three term studies, two population-based, two atopic population, only one study truly randomized	Breast milk versus cow's milk protein: Breast milk for few days to 4 months versus cow's milk	1.5–2	History Spt and specific IgE to cow's milk, egg, and soy Food challenge Eczema	Reduced eczema in breast-fed group in three out of four studies No difference in other outcomes
Chandra <i>et al.</i> [28] Schmitz <i>et al.</i> [34] Oldaeus <i>et al.</i> [29]	256–288; atopic population, birth cohort, randomized	Breast milk versus casein and whey hydrolysate: Whey/casein hydrolysate versus breast milk for few days to 4 months	1–1.5	History Spt and specific IgE to cow's milk, eggs, and soy Food challenge Eczema	Short-term reduction in eczema in breast-fed versus partial hydrolysate in one out of two studies No difference in other outcomes
Chandra <i>et al.</i> [28] Mallet <i>et al.</i> [35] Vandenplas <i>et al.</i> [36] Oldaeus <i>et al.</i> [29] VonBerg <i>et al.</i> [37]	58–945; atopic population, birth cohort, randomized	Cow's milk versus casein and whey hydrolysate: Whey/casein hydrolysate + breast milk versus cow's milk + breast milk for 4–6 months	1–7	Spt and specific IgE to cow's milk, egg, and soy Food challenge Eczema	Short-term reduction in cow's milk reactions and cow's milk IgE in hydrolysate group in one out of four studies Short-term reduction in eczema in hydrolysate group in all studies
Zeiger <i>et al.</i> [41•] Tariq <i>et al.</i> [4•]	120–288; atopic population, birth cohort, randomized, physician blinded	Pregnancy/lactation, infant milk and delay in solids: Maternal cow's milk, egg, and nuts ± fish exclusion during lactation ± third-trimester pregnancy, infant breast or soy/casein hydrolysate for 6 months, and delayed cow's milk and solids for 6 to 11 months versus no restrictions	4–7	Spt and specific IgE to cow's milk, egg, wheat, soy, peanut, cod, corn, and chicken/beef Food challenge Eczema	Reduced food allergy and cow's milk spt/sp IgE at 1 to 2 years in intervention group in one out of the two studies Reduced eczema to 1 to 4 years in both studies

In summary, the jury is still out as to whether breast-feeding protects or not against the development of allergic diseases. Indeed, a very recent observational birth cohort study, followed up to 4 years, suggested that breast-feeding protects against atopic disease, although not eczema or food allergy, in infants with an atopic family history. In contrast, breast-feeding increased the risk of atopic disease, including eczema, but not food allergy, in infants without an atopic family history, suggesting a dual role for breast-feeding [33].

Milk hydrolysates

Several studies have examined the role of milk hydrolysates in the prevention of food allergy and eczema. The studies compare the different hydrolysates and cow's milk formulas versus hydrolysates. Additionally, in other studies, mothers who either chose not to breast-feed or were unable to breast-feed exclusively were randomized to either a hydrolysate or cow's milk formula. These various comparisons are summarized in Table 1 [34–36].

Only one study in an atopic population shows a reduced specific IgE and clinical reactivity to cow's milk using a hydrolysate rather than cow's milk formula, an effect that disappeared in the infant after 6 months of age [36].

The studies show a protective effect of hydrolysed formulas over unmodified cow's milk-based formulas on the development of eczema in the first 12 to 48 months of life. Overall, the studies suggest a superiority of an extensively hydrolysed formula over a partially hydrolysed one. However, the recent German Infant Nutritional Interventional Program (GINI) study showed a reduction in eczema at 1 year of age that was greater with a partially hydrolysed whey formula and extensively hydrolysed casein formula than with an extensively hydrolysed whey formula, a finding that is hard to explain [37].

Introduction of solids

There is a paucity of randomized, prospective studies in this area. A randomized, population-based study in Finland showed no difference in the cumulative incidence of fish and citrus allergy at 3 years of age between children with fish introduced early or late (after 1 year old) into the diet, although the children with earlier introduction reacted earlier in life [38]. In a prospective, nonrandomized study in an atopic population, eczema and a history of food allergy were reduced at age 1 year in the group fed solids after 6 months of age compared with those with solids introduced at 3 months. No food challenges or skin prick/IgE tests were performed in the first year, but at 5 years there was no difference between skin testing to fish, milk, and wheat; history of food allergy; and eczema between the two groups [39]. A prospective, nonrandomized study from a normal population showed a risk of chronic/recurrent eczema that was 2.9 times higher in those infants fed four or more solid foods before age 4 months compared with infants receiving no solid foods before 4 months of age. This difference was maintained until 10 years of age [40]. The risk of eczema in this study appeared

to be due to the diversity of the diet rather than to the particular food proteins introduced.

Therefore, the evidence to date suggests that delaying the introduction of a solid food will perhaps postpone rather than prevent the development of clinical food allergy, and might reduce the risk of eczema. There are no data suggesting that immunologic reactivity is affected. These observations are probably not surprising because a delay in the age at which clinical reactivity develops might simply reflect the timing of the food being introduced into the diet, thereby giving the individual the first opportunity to clinically react to the food.

Combined Maternal and Infant Measures

Two of the best trials in the field of dietary avoidance involve combined maternal and infant interventions [9,41•]. Both are prospective and randomized with assessments by physicians blinded to the randomization group in an atopic population, and are summarized in Table 1. In a study by Zeiger *et al.* [41•], a reduction in food allergy in the intervention group at 1 year of age was determined using a combination of clinical history, skin prick testing, specific IgE, and food challenge for diagnosis. These differences were almost entirely due to cow's milk allergy, so it is not surprising that the effect had disappeared by 2 years of age. No difference in skin prick testing or specific IgE was shown for the other food allergens tested, including peanut, which was the most common skin test-positive food allergen at 7 years of age, indicating that the beneficial effect of the dietary interventions was solely in reducing cow's-milk allergy. Both studies showed a reduction in eczema at 1 to 4 years of age but not thereafter. This effect is less likely to be associated with food allergy.

Routes of Sensitization, Cross-sensitization, and Oral-tolerance Induction

Dietary intervention studies have proved disappointing in the prevention of food allergy. Until recently, most of the focus has been on oral exposure to foods, rather than considering foods as environmental allergens. Food can behave as an aerosolized agent with early- and late-phase reactions [42]. In mice, preferential sensitization occurs through the skin and airways [43]. In the food industry, occupational exposure via the inhaled or cutaneous route seems to lead to sensitization. Therefore, of workers exposed to powdered egg or wheat, 5% to 20% of workers have been reported to develop asthma [44,45]. Similar sensitization has been reported in shrimp, crab, and oyster handlers [46]. We have recently explored nonoral routes of exposure in a longitudinal cohort of 13,971 preschool children followed from birth—the ALSPAC study [10•]. Forty-nine children up to the age of 38 months were identified with a history of peanut allergy; peanut allergy was confirmed in 23 of 36 children who underwent an oral peanut challenge. The results of this study showed a positive association between peanut allergy and eczema (odds ratio [OR],

2.6; 95% confidence interval [CI], 1.4–5.0), and a greater association with oozing, crusting rash (OR, 5.2; 95% CI, 2.7–10.2). There was an increased use of preparations using peanut oil in children with peanut allergy (OR, 6.8; 95% CI, 1.4–32.9), but this was limited to cutaneous rather than oral exposure. These findings suggest that sensitization to peanut and perhaps other allergens might occur through the cutaneous route if allergens come into contact with inflamed skin. This study suggests that sensitization to allergen occurs through environmental exposure to allergen rather than through consumption of allergen by the infant or mother. The study raises the question whether early aggressive treatment of eczema and complete environmental avoidance of the allergen (cutaneous and aerosolized allergen) would prevent the development of food allergy.

The same study [10•] suggests cross-sensitization as another potential mechanism by which food allergy might occur. This study showed that peanut allergy is independently associated with intake of soy milk or soy formula. Furthermore, the observation in a murine model of peanut allergy that desensitization with the soy homologue of Ara h 1 reduces peanut allergy supports the notion that cross-sensitization might contribute to the pathogenesis of peanut allergy [47]. In oral allergy syndrome, birch pollen sensitization can subsequently lead to the development of allergies to cross-reactive fruits.

All these factors taken together make dietary avoidance very difficult. Furthermore, children with proven food allergies continue to react, on average, once every 2 to 3 years due to accidental exposure, despite specialist advice, including dietician input. If avoidance strategies are destined to failure, other strategies must be explored. It has been observed in animal studies using cow's milk and egg that the dosage and timing of oral allergen exposure determines whether rodents become sensitized or tolerant [48]. High-dose early exposure to food antigens usually results in tolerance to the antigen. Although there are no human studies, there are two relevant observations in humans. Both US and UK guidelines advise against feeding peanut to infants and young children. Both countries have rates of peanut allergy up to 1%. In contrast, in countries such as China, South Africa, and Israel, where there are no guidelines on peanut avoidance, peanut consumption is high, and an important part of the infant's diet. However, peanut allergy is rare, affecting only 0.04% of young children in Israel [49,50]. This low rate in Israel might be explained in part by the fact that peanut allergy was assessed only in children under the age of 2 years. Peanuts in Israel are consumed in the roasted form, and, therefore, the mode of processing cannot account for the lower prevalence. The second observation comes from our outpatient practice, where we are seeing increasing food allergy, particularly to peanuts, in ethnic populations in whom peanut allergy was not a problem 5 to 10 years ago. In terms of timing, this appears to coincide with increasingly restrictive dietary practices in these populations in line with public health advice, with the UK guidelines on avoidance of peanuts being introduced in 1998 [6]. Prior to

that time, we did not see much peanut allergy in non-white children born in London. It is only since the guidelines on the avoidance of peanuts that we have witnessed a steep rise in peanut allergy in this group of children. We hypothesize that in societies in which there is high-dose, early exposure to peanuts in infancy, the normal immunologic response is tolerance. In contrast, in societies in which there is high consumption of peanut but the introduction is delayed, the predisposed infant will become sensitized through lower-dose environmental exposure.

The Role of Micro-organisms in Preventing Food Allergy

Many observations have provided support for the "hygiene hypothesis," whereby cleaner environments fail to provide adequate type 1 stimulation for suppression of the type 2 allergic response, leading to a higher rate of allergic disease [51]. Furthermore, commensal gut microflora, rather than infection, might promote potentially antiallergenic processes, such as type 1 immunity, IgA production, and generation of transforming growth factor- β , which might suppress the type 2 response. There has, therefore, been a recent interest in the administration of bacterial products for allergy prevention. Much of the work has centered on the use of probiotics [52]. In a recent mouse model of food anaphylaxis, the intraperitoneal administration of lactobacillus strain induced interleukin-12 responses and suppressed the development of IgE-responses and anaphylaxis [53]. In humans, there has been one randomized, placebo-controlled study of probiotics in an atopic population [54]. Mothers were given lactobacillus GG antenatally, and their infants lactobacillus for 6 months postnatally. Those treated with probiotic had a reduced risk of eczema at 2 years of age. However, no differences in skin prick testing or specific IgE to food allergens, including cow's milk, egg, wheat flour, wheat gluten, cod, and soy were seen, nor were there any differences in total IgE between the two groups.

Mycobacteria are potent type 1 immunostimulants, and have been investigated as vaccine candidates for the prevention of allergic disease [55]. Intradermal administration of mycobacteria has been used with some success in reducing the severity of eczema [56], but there are no studies showing a benefit for prevention of allergy in humans.

Conclusions

There is no doubting the advances made in the understanding of the immune response in the fetus and into early childhood. This understanding has yet to translate into strategies that have shown significant protection against the development of food allergy. The dietary intervention studies have been hampered by a lack of end points that can truly be considered to be representative of food allergy. The literature to date offers some evidence that breast-feeding and type of infant milk, maternal diet during lactation, introduction of

solids, and a combination of measures might have some effect in reducing food allergy. However, future studies conducted to clarify this area will have to adopt the stricter definitions of food allergy, particularly food challenges, because a proportion of food allergy, such as cow's milk allergy, can be both IgE and non-IgE mediated. Further studies are also needed to establish whether avoidance of solid foods reduces the risk of developing allergies to the avoided food allergens, and to other food allergens. To achieve total avoidance requires a full understanding of the routes of exposure by which sensitization might occur, and recent data suggest that both oral ingestion and environmental exposure might be important. To restrict environmental exposure, stricter avoidance regimens are required. The alternative possibility of high-dose-tolerance induction in the infant also deserves more consideration.

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Papers of particular interest, published recently, have been highlighted as:

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