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REVIEW ARTICLE

Dietary interventions for primary allergy prevention in infants

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Abstract: Allergy prevention remains a vexing problem. Food sensitization frequently occurs early in life and is often the first sign of future atopic disease. Therefore, interventions to prevent food allergies and the development of the atopic phenotype are best made early in life. The results of studies regarding the effects of breast-feeding and the prevention of allergy remain inconclusive. Several factors in breast milk either induce or protect against food allergies. Probiotic and prebiotic supplemented whey hydrolysate formulas need further research in order to determine the future of this intervention in the prevention of food allergies. Several dietary manipulations in infancy, such as prolonged breast feeding, maternal avoidance diets during pregnancy and lactation, the use of hypoallergenic formulas, have been proposed as ways of altering the Th1/Th2 balance in infants, with varying degrees of success. Studies have examined whether food atopy can be prevented by controlling the intake of highly allergenic foods by a high-risk infant from a variety of sources, that is, both direct ingestion and indirect ingestion through the breast milk. The previous studies showed that in high risk infants who are unable to be completely breast fed, there is evidence that prolonged feeding with a hydrolysed formula compared to a cow's milk formula reduces infant and childhood allergy and infant cow's milk allergy ,while other studies reported that an antigen avoidance diet for high risk mothers is unlikely to reduce the atopic diseases in their children substantially, and that such a diet may adversely affect maternal and/or fetal nutrition. Hippokratia 2011; 15 (3): 216-222

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Food sensitivity frequently occurs early in life and is often a first sign of future atopic disease therefore the prevention of food allergy remains a vexing problem and has been the subject of much current research. Infancy represents a time when an allergic phenotype may be determined. An infant's immune system can either have a T helper cell type 2(Th2)dominance with more secretion of interleukin (IL)-4 or a Th1 dominance with a cytokine balance toward interferon gamma (IFN-γ) production. Therefore, interventions to prevent food allergies and the development of the atopic phenotype are best made early in life. Several dietary manipulations in infancy, such as prolonged breast feeding, maternal avoidance diets during pregnancy and lactation, the use of hypoallergenic formulas, have been proposed as ways of altering the Th1/Th2 balance in infants, with varying degrees of success. The dietary manipulation has been the center of research over the past decades as a form of primary prevention of food allergy and hence atopic disease.

Immunomodulation

Immunomodulatory role of breast milk

The results of studies regarding the effects of breast-feeding and the prevention of allergy remain inconclusive. Even if maternal diets are devoid of allergenic foods, prevention of food allergy in infancy appears to be transient at best. Several factors in breast milk either induce or protect against food allergies (Table1)[1].

There is some suggestion that cytokine concentration in breast milk differs between allergic and nonallergic mothers, with IL-4,IL-5,and IL-13 being present in higher concentrations in the breast milk of atopic women. These are the cytokines known to be intimately involved with the IgE production and induction of eosinophils.The cytokine TGF-β,which is one of the predominant cytokines in human breast milk[2], has been shown to increase the ability of the infant to produce it's own IgA against β-lactoglobulin,casein, ovalbumin and gliadin[3].The soluble form of CD14, a cytokine that is thought to be central in the induction of a Th1 response by bacterial antigens[4], is found in very high concentrations in human breast milk[5], suggesting that this cytokine may play a role in the protective effect of breast-feeding on the development of allergy. A high arachidonic acid to eicosapentanoic acid ratio in human breast milk has been shown to increase the risk of allergic disease in the recipient[6]. The polyamines (including spermine and spermidine) present in breast milk decrease the permeability of the intestinal mucosa and thus are protective against the development of allergic disease in infants[7]. It is thus clear that milk has properties that allow it to be immunostimulatory and immunoprotective.

Table 1: Factors in breast milk that either induce or protect against food allergies

Factors	Inducing	Protective
Antigens	Sensitizing allergens	Tolerizing allergens
Cytokines	IL-4	TGF-β
	IL-5	sCD14
	IL-13	
Immunoglobulins		s-IgA to ovalbumin
Polyunsaturated fatty acids	Arachidonic acid	Eicosapentanoic acid
		a-Linoleic acid
		n-3 Polyunsaturated fatty acids
Chemokines	RANTES	
	IL-8	
Polyamines		Spermine
		Spermidine

IL, Interleukin; TGF-β: Transforming growth factor-beta; RANTES: regulated on activation, normal T cell expressed and secreted

Probiotics and Prebiotics

Probiotics are generally called the Lactobacilli and Bifidobacteria. Much of the current research lately has focused on the immunomodulatory effects of probiotics and prebiotics. In vitro studies have shown down regulation of Th2 cytokine production by stimulation of Th1 cytokines (IL-12,INF-γ) or regulatory cytokines(IL-1)[8]. In vivo studies regarding the effect of probiotics in atopic dermatitis (AD) are inconclusive. There are studies that show upregulation of the Th1 cytokines[9,10,11] without accompanying down regulation of Th2 cytokines[12,13]. Several other studies do not show any effect on cytokine production[14-19].

In regards to the immunomodulatory effect of prebiotics, the proposed mechanisms of action are the following: They are thought to stimulate the activity of lactic acid bacteria, such as lactobacilli and bifidobacteria,which have immunomodulatory qualities. A second mechanism of action is that fermentation of prebiotics by lactic acid bacteria enhances Short Chain Fatty Acids (SCFA)[20], which act as energy substrate for colonocytes[21]. It has been shown that SCFA stimulate IFN-γ and IL-10 production[22].

Several Randomized Controlled Trials (RCTs) have investigated the effect of probiotics on the prevention of AD.A study of the year 2007[23] showed no reduction of the incidence of AD. A recent study of the year 2008 showed that Lactobacillus rhamnosus, but not Bifidobacterium animalis,significantly reduced the incidence of AD with almost 50% compared to placebo, without any effect on sensitization[24]. In contrast two prevention studies did not show a reduced AD incidence[25,26].

A systematic review of RCTs of the year 2009 evaluating the efficacy of probiotics for treating eczema showed that currently probiotics cannot be recommended for treating eczema.[27]

In regards to the immunomodulatory effect of prebiotics in AD prevention a recent study showed that the incidence of atopic dermatitis was significantly lower in the intervention group than in the placebo group[28]. In a more recent study the incidence of AD at the age of 2years was still significantly reduced as were the recurrent wheezing and allergic urticaria. Although these results seem very promishing, a limitation of the study was the large percentage (more than 20%) of infants that were lost to the follow-up during the intervention period [29].

Exposure to infection

The "hygiene hypothesis" suggests that exposure to common respiratory infections early in infancy may actually decrease the risk of allergic diseases such as asthma by preferentially selecting a Th1-predominant immune system rather than a Th2-predominant atopic immune system[30-32]. Early infections such as respiratory syncythial virus may predispose infants to develop asthma later in childhood. Much data has been accumulating that children who are either placed in daycare early or have older siblings have higher rates of wheezing during early infancy but lower rates of asthma after age 6[30,33]. It has been suggested that intracellular microorganisms have a particularly strong immunomodulatory effect in that they are able to induce a strongly polarized Th1 response and a long-lived memory immunity[31]. There is also an association of frequent use of antibiotics in infancy with an increased odds ratio for the development of subsequent asthma[34]. In a similar vein, bacterial endotoxin may also have a protective effect against the develpoment of allergies, but may sensitize people who are already atopic[35]. This hypothesis is appealing because it may help to explain the increasing incidence of asthma over the past few decades, although tertiary prevention of asthma involves limiting exposure to infection.

Autoimmunity and atopic disease

The autoallergens represent mainly intracellular proteins, but some of them could be detected as IgE immune complexes in sera of sensitized patients. Several relatively recent findings led to the concept that IgE autoreactivity may play a pathogenetic role in severe and

chronic forms of atopy. It was reported that patients predominantly with severe and chronic manifestations of atopy (eg. atopic dermatitis) contain IgE autoantibodies against a variety of proteins. It is suggested that at least two pathomechanisms could play a role in autoallergy. First, autoallergens may cross-link effector cell-bound IgE autoantibodies and, by release of inflammatory mediators, lead to immediate-type symptoms. Second, IgE-mediated presentation of autoallergens may activate T cells to release proinflammatory cytokines contributing to the magnitude of the allergic tissue reaction[36].

The role of T regulatory cells in allergy prevention

It is believed that T regulatory cells are involved in tolerance acquisition. Human studies reinforce the hypothesis for a key tolerogenic role of regulatory T cells, as children having outgrown food allergy with mostly gastroenterologic symptoms have increased number of $CD4^{+}CD25^{+}$ T-regulatory cells in their gut mucosa. Clearly, promoting the IL-10 rich environments in the gut seems to be an option to prevent or even treat food allergy[37].

Predictors of allergy

When attempting primary prevention of food allergy the first question that needs to be asked is which children should be the target of any intervention or manipulation of diet or lifestyle. Several factors have been investigated as predictors of the develpoment of atopic disease, including family history of allergy and cord blood IgE.Numerous genes have been uncovered that can predict allergy in some populations.These genes may prove to have more and more utility in predicting which patients may be candidates for certain interventions,including which infants might be candidates for immunomodulation or dietary manipulation to prevent food allergy.

“Allergy Genes”

An atopic phenotype may be linked to certain polymorphic genetic markers. Numerous genes have been shown to be associated with allergy[38]. Some loci appear to show linkage with allergy in certain ethnic groups whereas other loci appear to be more universal susceptibility markers.These regions include 11q13, which encodes the beta chain of high-affinity IgE receptor[39,40]; 5q31-33, which contains a cytokine gene cluster; and the genes for the β-adrenergic and steroid receptors CD14 and fibroblast growth factor,12q[41], which contains the gene for IFN-γ and 6p21.Total IgE shows evidence of linkage to chromosome 6p21. This region contains several important genes that are biologically relevant to IgE regulation. Linkage has fount for eosinophil count in a genome screen of atopic families. In Caucasian sib pairs, there was evidence for increased allele sharing for markers on 6p21.3.23. Another linkage is with TNF genes, which is important in mediating inflammatory responses, as is HLA in antigen presentation. A study of the year 2006 showed an association between various cytokine polymorphisms with hay fever as well as with increased total and specific IgE levels. The study established IL-4, IL-10, IL-6 and IL-18 as candidate genes for atopic health outcomes[42]. Although linkages between these genes and allergies have been well documented ,the usefulness of this knowledge in determining which children might be candidates for intervention to prevent food allergy is not yet clear.

Family History and Cord Blood IgE as Predictors of Allergy

Although a genetic test for allergy risk remains elusive, family history remains in practice the most clinically useful determinant of risk of atopy in a child.Studies performed since the 1970s have estimated the risk of atopy to be between 38% to 58% in an offspring with one allergic parent and as high as 60% to 80% in a child born to two allergic parents.A child with a negative family history has about a 5% chance of developing allergy[43].

Cord blood IgE, a less practical indicator to obtain, was only 26% sensitive in determining the risk of atopy, whereas it was 74% specific.

Dietary manipulation during pregnancy, lactation and early infancy

Dietary manipulation during pregnancy

Studies which have examined the prophylactic effect of maternal avoidance of highly allergenic foods such as milk and egg during pregnancy in high risk groups showed no beneficial effects in the development of food allergy,if the infant was otherwise maintained on a hypoallergenic diet after birth.It is therefore now widely accepted that maternal avoidance diets during pregnancy should not be recommended as way to prevent allergic disease in children and may be potentially harmful in light of the increased risk of maternal malnutrition[1].

Breast-Feeding

Undoubtedly**,** breast feeding is the best nourishment for infants.It is also clear that there is a risk of exposing a child at risk of atopy to highly allergenic foodstuffs through breast milk. It has long been known that β-lactoglobulin, casein and bovine gammaglobulin, three of the most common milk antigens, as well egg, wheat antigens have been detected in breast milk 2-6 hours after ingestion.Peanut proteins may be detected only 1-2 hours after ingestion in lactating women[44]. Studies so far have been controversial.Studies performed in the 1980s showed that breast feeding had no protective effect on the development of food allergy as compared to formula feeding[45-48].

A more recent meta-analysis of prospective studies of breast feeding and it’s effect on the development of atopic dermatitis from 1966 to 2000 revealed a significant protective effect against the development of atopy by breast feeding[49].

Based on the previous data the American Academy of Pediatrics (AAP), the European Society for Paediatric

Allergology and Clinical Immunology (EAACI) and the European Society for Paediatic Gastroenterology Hepatology and Nutrition (ESPGHAN) strongly recommend exclusive breast feeding for at least 4 months and should be continued till the 6th month of age as a hallmark for allergy prevention.

Maternal avoidance diets during lactation

Several studies have attempted to determine whether sensitization to highly allergenic foodstuffs could be prevented in high risk infants if lactating mothers avoid these foods.

The recommendations of the American Academy of Paediatrics (AAP) present the view of a Cochrane database systematic review (Osborn DA, Sinn J) [50]. The previous study has shown that in high risk infants who are unable to be completely breast fed,there is evidence that prolonged feeding with a hydrolysed formula compared to a cow's milk (CM) formula reduces infant and childhood allergy and infant cow's milk allergy.

The recommendations of the European Academy of Allergy ane Clinical Immunology (ESPACI) were based on a 2006 Cochrane review (Kramer MS & Kakuma R)[51] including 4 trials and 451 participants which reported that an antigen avoidance diet for high risk mothers is unlikely to reduce their children's of atopic diseases substancially,and that such a diet may adversely affect maternal and/or fetal nutrition.

Because of these contradictory recommendations, maternal avoidance diets during lactation should be instituted on a case by case basis only after evaluating the degree of risk for atopy and the motivation of the family. Care must be taken to make sure that the mother's food intake remains balanced during such a diet to prevent maternal malnutrition. If cow's milk is avoided, one must take care to ensure that the mother is ingesting sufficient calcium, up to 1500mg of elemental calcium daily.

Soy Formula and prevention of allergic disease

There is some evidence that up to 10-15% of children with cow's milk allergy have IgE antibodies to soy. Therefore, although soy formula is certainly nutritious and not deleterious to non-allergic infants, soy formula cannot be recommended for primary prevention of the disease[52]. It can, however be recommended as a safe alternative to cow's milk formula in the majority of infants with cow's milk allergy after screening documents indicate no coexisting soy allergy.

Hypoallergenic formulas and prevention of allergic disease

The ideal protein hydrolysed formulas should not contain peptides larger than 1,5KD,should contain no intact proteins, should demonstrate no anaphylaxis in animals, and should reveal protein determinant equivalents less than 1/1,000,000 of original protein[53]. Most importantly, the formula must be demonstrated safe in milk allergic infants by both double-blind placebo-controlled food challenge and by open challenge.

Acceptable hypoallergenic formulas need to be extensively hydrolyzed in order to be composed of small enough peptides to be considered truly safe in children with milk allergy. Partially hydrolyzed formulas have numerous peptides of more than 4 KD and can cause allergic reactions in 40% to 60% of children with IgE mediated cow's milk allergy and can therefore not be considered a safe alternative for these patients[54].

Partially hydrolyzed and extensively hydrolyzed formulas have been studied for their ability to prevent atopic disease for more than 15 years. Most studies of these formulas have focused on infants at high risk of developing allergy.

In studies of infants at high risk of atopy who are not exclusively breastfed for 4 to 6 months, there is modest evidence that the onset of atopic disease may be delayed or prevented by the use of hydrolyzed formulas compared with formula made with intact cow milk protein, particularly atopic dermatitis[55].

A relatively recent systematic Cochrane meta-analysis (Osborn DA and Sinn J) regarding the use of hydrolysed proteins on allergy prevention has concluded that in infants at high risk for allergy who are unable to be completely breastfed there is limited evidence that feeding with a hydrolysed formula compared to cow's milk formula reduces allergies[50].

Recommendations of AAP and ESPACI/ESPGHAN (2008) regarding the hypoallergenic formulas

Both the AAP and ESPACI/ESPGHAN commitees recommend the use of protein hydrolysate formulas in primary prevention of allergy in high risk infants who are bottle -fed.

The AAP recommends extensively hydrolyzed formulas or possibly partially hydrolyzed formulas whereas the the European committee suggests a formula with confirmed reduced allergenicity[56,57].

The AAP recommendations take into account the higher cost and lower palatability of extensively hydrolyzed formulas that limit their usefulness.The lower palatability may be overcome by their early introduction to infants, before the child has developed a taste for other formulas. Therefore,if cost is not an issue,an extensively hydrolyzed formula should be used in infants at high risk for atopy if they are to be exclusively bottle-fed or if breast feeding is to be supplemented.

Delayed introduction of solid foods

Although not conclusive, several studies suggest that early introduction of solid foods might lead to an increased risk of eczema. The nutritional committees based on more recent data published the following recommendations.

The revised AAP report of the year 2008 suggests that solid foods should be delayed until 4 to 6 months of age[55].

The European committees suggest that complementary foods should be introduced after 17 weeks but no later

than 26 weeks and concluded that there is no convicing evidence that avoidance or delayed introduction of potentially allergenic foods, such as fish and eggs, reduces allergies in infants either at risk or not.

Table 2 offers an approach to prevention of food allergy in children that incorporates the guidelines of both organizations[56, 57].

Table 2: Recommmendations on primary prevention of Food Allergy, incorporating current Guidelines of the ESPACI / ESPGHAN 2008

Interventions	Recommendations
Immunomodulation	Still experimental
Pregnancy diet	Not recommended
Breast feeding	Exclusive breast-feeding strongly recommended for at least 4 months and should be continued till the first 6 months of life.
Lactation diet	Milk and egg avoidance is not routinely recommended but may be offered on a case-by case basis to highly motivated families;if instituted ,mother must take supplemental calcium
Soy formula	Not recommended
Protein hydrolysate formula	A formula with confirmed reduced allergenicity is strongly recommened if infant is to be bottle-fed or as a supplement to breast milk.
Delayed introduction of solid foods	Solid food may be added at 6 months (after 17 weeks but no later than 26 weeks)

Combined Infant and Maternal Avoidance of Allergenic foods

Studies have examined whether food atopy can be prevented by controlling the intake of highly allergenic foods by a high-risk infant from a variety of sources ,that is,both direct ingestion and indirect ingestion through the breast milk.In prenatally randomized ,physician-blinded ,parallel-controlled study the effect of multiple food allergen avoidance in both the lactating mothers and their infants was compared to standard feeding practices in children with positive family history of allergy.This study found that children whose intake of allergenic foods from a variety of sources was restricted showed significantly lower incidence of allergic diseases such as atopic dermatitis at 1 year of age because of a lower incidence of food allergy and lower specific IgE to cow's milk up to 2 years of age compared with acceptable infants. There was no effect on the occurance of respiratory allergy or sensitization to environmental allergens from birth to 7 years.

These studies suggest that, whereas food allergies can be avoided in the first 1 to 2 years of life by carefully limiting the dietary intake of highly allergenic foods for more than 6 months, this is not followed by a reduction of allergic disease later in childhood [58].

Maternal ω-3 Fatty Acid Supplementation during Pregnancy and Lactation

A recent study investigated whether previously reported preventive effect of maternal ω-3 fatty acid supplementation on IgE-associated allergic disease in infancy may be mediated by facilitating a balanced circulating Th2/Th1 chemokine profile in the infant. Pregnant women, at risk of having an allergic infant, were randomized to daily supplementation with 1.6 g eicosapentaenoic acid and 1.1 g docosahexaenoic acid or placebo from the 25th gestational week through 3.5 month of breastfeeding. Infant plasma was analyzed for chemokines (cord blood, 3, 12, 24 months). High Th2-associated chemokine levels were associated with infant allergic disease. In infants without, but not with, maternal history of allergy, the ω-3 supplementation was related to lower chemokine Th2/Th1 ratios. Furthermore, in non-allergic, but not in allergic infants, ω-3 supplementation was linked with higher Th1-associated chemokine levels. Thus, the prospect of balancing the infant immune system toward a less Th2-dominated response, by maternal ω-3 fatty acid supplementation, seems to be influenced by allergic status[59].

Conclusions

Following the above immunomodulation is still experimental. Pregnancy diets are not recommended.Exclusive breast feeding is strongly recommended for at least the first 4 months of life and should be continued till the first 6 months of life[60]. Diets during lactation should be recommended only on a case by case basis to highly motivated families. Soy formulas are not recommended. Hydrolysate formulas with confirmed reduced allergenicity are strongly recommended if the infant is to be bottle fed or if breast feeding is to be supplemented.Solid food should be added at 6 months of life(after the 17th week and not before the 26th week of life).

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