Review article

The potential effect of dietary changes on the management of food allergies

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Abstract
Food allergy (FA) is a significant public health problem with symptoms ranging from mild urticaria up to severe anaphylaxis. The frequency of food allergy has been rising in the last decades particularly in children where nutritional compromise can ensue together with possible development of other allergic diseases. With the developing technology and knowledge, there has been improvement in the treatment of FA. Diet is a very important factor in the management and changes in the diet of both the child and mother affect the risk of developing food allergies. Consumption of some nutrients such as omega-3 fatty acids, vitamin D, folic acid may be beneficial in preventing FA. The mechanisms proposed are mainly related to their effects on regulating the immune system. Regulatory changes in the intestinal flora, such as dietary consumption and probiotic use, are also on the agenda and show promising results approaches. Although, it has been advised to remove the allergenic food from the diet, yet recently, it has been shown that processing of allergenic foods and early consumption of allergenic foods between 4th -6th months can cause food tolerance in infants. This review aims to provide updates on the effect of adding some nutrients and dietetic changes on the management of FA.
Keywords: food allergy, dietary changes, diet, food processing, early introduction.

Introduction

Food allergy (FA) is defined as an adverse health effect resulting from abnormal immune response following the consumption of food.[1] The pathophysiology of FA is complex. Briefly, when the gut (even skin) is exposed to the antigen, T-helper cells differentiate into Th2 cells that induce immunoglobulin E (IgE) resulting in one type of FA.[2,3] Nearly 170 foods are classified as allergenic, but most FA develops in response to consumption of egg, peanut, cow's milk, soy, nuts, shellfish, fish and cereals.[1,4] Children with FA have symptoms such as atopic eczema, gastrointestinal symptoms, and wheeze.[5] The prevalence of FA has been increasing recently, and it is estimated that it affects 1-10% of preschool children[6] and 5% of adults.[7]

Many factors involving hereditary, environmental and nutritional exposures can affect the risk of developing food allergies. Although many nutrients have been associated with allergy development, nutrition might also exert protective role against FA. In addition, many variables seem to be effective in the management of FA, such as the maternal diet, processing of allergens by cooking methods, early introduction of allergenic foods and the microbiota-regulating interventions. Thus, diet is the most important determinant of exposure to allergens and plays a very important role in both prevention and management of food allergy. This review aims to explore potential dietary changes that can make the diet more individualized and more effective in managing food allergies. [8,9]

Probiotics, prebiotics and FA

Intestinal microbiota and environmental microbial load play an important role in early immune development and thus can affect the development of allergies.[10-12] Increased incidence of allergic diseases has been associated with different factors that affect microbiota where increasing number of siblings was inversely correlated with the incidence of eczema.[13] Also, cesarean delivery was found to be associated with increased risk of FA, [14,15] and rural areas are characterized by lower frequency of asthma than the urban areas .[10,16] All these findings support that microbial development is associated with FA. The idea that microbial exposure has a protective effect against allergic diseases in the early life period

is known as the hygiene hypothesis.[17] Also, it is known that the intestinal microbiota of allergic and non-allergic children differ from each other,[18-20] the number of fecal *Bifidobacteria* is decreased in allergic children,[21]and the fecal bacteria diversity decreases in children with IgE-related eczema compared to non-atopic children.[22,23] Tan et al,[24] reported that a high fiber diet is protective against food allergy by regulating microbiota and increasing short-chain fatty acids (SCFA). Also, Roduit and colleagues found that atopic sensitivity was significantly lower in children with higher butyrate and propionate in their faeces.[25] It has been reported that probiotic supplementation may regulate the risk of developing eczema.[26] World Allergy Organization (WAO) recommends the use of probiotic in the treatment and prevention of allergic diseases.[27] Probiotics have been shown to regulate the innate immune system, providing differentiation of T-helper 1 cells and release of regulatory cytokines.[28,29] Nowadays, prebiotics are also being added to infant formulas and it has been shown that the number of *Bifidobacteria*[30] and *Lactobacillus*[31] increases in infants fed with food containing galacto-oligosaccharide (GOS)/fructo-oligosaccharide (FOS). These prebiotics have been shown to reduce the frequency of atopic dermatitis.[32,33] Human milk oligosaccharides (HMOs) are also a prebiotic effective ingredient that can positively affect early microbial development.[34] HMOs may have therapeutic potential in allergic disease.[35] However, precise information has not been obtained with prebiotics, and more studies are still needed.

Nutrition, Genetics and FA

It has been reported that the risk of developing FA is increased in children with a family history of the same disorder,[36,37] and higher risk of developing allergies has been reported among twins.[38,39] In addition, there loci in HLA-DR and -DQ gene region has been suggested to pose significant genetic risk for development of peanut allergy.[40,41] Epigenetic arrangements play a key role in maintaining T cell differentiation and TH1 / TH2 balance.[42] It has also been reported that differentiated DNA methylation in gene regions can affect the development of allergic diseases.[43-45] Irregularity of DNA methylation in genes associated with the mitogen-activated protein kinase (MAPK) signal during CD4 + T cell development may contribute to the development of FA by causing inadequate T lymphocyte responses in early childhood.[44] Also, polymorphisms in CD14 may increase the susceptibility to food allergies in children whose mothers have higher intake of baked and sugary products during pregnancy.[46]

Various nutrients may play a role in FA by affecting DNA methylation. For example, consumption of omega-6 causes altered DNA methylation in the promoter region of the TNF alpha gene, a candidate gene for allergic diseases.[47] A previous study demonstrated that vitamin D deficiency (VDD) was not associated with food sensitization (FS), however, VDD was found to have effect on FS among children with certain single nucleotide polymorphisms (SNPs) affecting IL-4 gene.[48] Similarly, SNPs in specific genes affecting innate immunity or TH1/TH2 balance was associated with increased FS among breast fed infants as compared to those who were never breast fed.[49]

The Relationship of Nutrients with FA

Nutrients can be classified as preventive or risk factors for the development of FA by regulating different mechanisms such as immune system, microbiota, antioxidant system and epigenetic regulations.

Vitamin D

Vitamin D plays a role in the Th1 / Th2 response,[50] Treg cell regulation.[51,52]In addition, expression of vitamin D receptor occurs in many immune cells.[53,54]Vitamin D intake[55] or supplementation[56] during pregnancy influences the immune system of the neonate. These relationships with the immune system make VDD a factor associated with FA. Moreover, vitamin D is really important to maintain intestinal homeostasis.[57-59]

There are two different approaches to Vitamin D: The first one is that insufficient vitamin D

levels increase FA also known as the vitamin D hypothesis, the second approach advocates the opposite. Allen et al showed that the risk of developing peanuts and egg allergies increases significantly in newborns with low vitamin D levels (<50 nmol / L).[60] In the German birth cohort study, high vitamin D levels during pregnancy were associated with an increased risk of FA.[61] Supplementing vitamin D during lactation has also been shown to increase the risk of FA.[62] Studies showing differences in the incidence of food allergies according to seasonal differences or geographic locations. It has been reported that epinephrine prescribing is more used in anaphylaxis treatment in countries far from the equator.[63,64] Another study found that food-related allergic reactions in children born in autumn or winter are 53% higher than those born in spring or summer.[65] In this way, it is stated that both high and low levels may be associated with food allergy.[66]

Folic Acid

Folic acid has been consumed for a long time with the discovery that it prevents neural tube defects, Folic acid is a nutrient that has a methyl donor and can show epigenetic effects by affecting DNA methylation. McGowan et al.[67] found that high levels of unmetabolized folic acid at birth are associated with an increased risk of developing FA. The researchers stated that this relationship may be due to increased synthetic folic acid in the body with the enrichment of nutrients with folic acid. Molloy et al.[68] measured the folate levels in 894 pregnant women in the 3rd trimester and no relationship was found between the folate levels of the mother and the development of FA in children at 1 year of age. In general, it is stated that food and dietary supplementation enriched with folic acid during pregnancy can cause allergies by raising folic acid levels.[69] However, studies investigating the relationship between folate levels in pregnancy and allergy development show conflicting results.

Zinc

Chronic inflammatory changes have occurred in children who are constantly exposed to allergens, and these children have been shown to have low zinc levels.[70] The fact that zinc serves as a cofactor for superoxide dismutase enzyme and many enzymes, which are responsible for maintaining antioxidant / oxidant balance, suggests that adequate zinc intake may be beneficial in children with FA.

Dietary Fats

Nowadays, in addition to the high oil consumption increased with the Western diet, the widespread use of vegetable-based oils in the food industry has led to a significant increase in the dietary omega-6 / omega-3 ratio.[71] Westernization of diet which contains high omega-6 and saturated fats negatively affect the microbiota and intestinal barrier function[72,73] and could increase allergy development.[74,75] Hussain et al.[76] showed that in mice fed a high-fat diet, mice became more susceptible to FA, regardless of obesity.

It is thought that n-3 fatty acids have protective effects against allergies, although the evidence for omega-3 fatty acids is limited and contradictory (Table 1). The regulatory effects of polyunsaturated fatty acids (PUFAs), eicosanoids and resolvins synthesized from PUFAs on the immune system and its potential relationship with food allergies have been studied in detail in previous reviews.[77,78] In a randomized controlled study, daily administration of fish oil supplements from birth to 6 months did not prevent the development of allergies in high-risk infants.[79] In a systematic review, it was reported that PUFA supplementation does not affect the incidence of food allergies in infants.[80] On the contrary, regular fish consumption in the first 12 months of life has been shown to be associated with reduced food sensitivity. The fact that this study is observational, and the FA is not confirmed are the limited aspects of the study.[81]

Diet during pregnancy and lactation period

The role of the maternal diet in the development of FA is a complex issue due to many interacting variables, including genetics, environment and lifestyle. Diet during pregnancy can alter the epigenome and microbiota, and these interactions could affect

immune programming.[82-86] Netting et al.[87] showed in their systematic reviews that there was no relationship between mother's diet and atopic outcomes in their children. However, they stated that the Mediterranean diet could be beneficial. The importance of a healthy balanced diet should be emphasized in mothers, but it should be remembered that wrong elimination diets have nutritional risks for both mother and child. It is stated that in high-risk women, a diet that includes the elimination of commonly allergenic food during lactation may reduce the risk of developing atopic eczema in the child, but more data are needed to confirm this.[88] Studies investigating the relationship between maternal and lactation diet and FA are highly heterogeneous and provide contradictory results (Table 1). Researching the entire diet may yield more beneficial results than studies of a single nutrient in studies.[89] In general, it is not recommended to adopt a restrictive diet approach during pregnancy and lactation period, and to consume an adequate and balanced diet.[1,90] Also, omega 3 supplementation might be useful, but this is not clear yet.

Hypoallergenic formulas

Formulas can be classified as non-hydrolyzed, partially hydrolyzed, extensively-hydrolyzed and amino acid based. In extensively hydrolyzed foods, milk proteins are divided into small peptide particles and take on a form that shows almost no allergic, while partial hydrolyzed foods contain larger peptides. These formulas can be used to prevent or treat FA in children, as the allergen properties of formulas are reduced by extensively or partial hydrolysis of milk proteins. Protein based extensively hydrolyzed formulas are used as the first alternative for the treatment of cow's milk allergy.[113] It is thought that tolerance to allergen can be achieved with extensively hydrolyzed formulas and this effect can be enhanced with probiotic bacteria and other components.[114-116] When breastfeeding is not possible, the use of whey-based partial hydrolyzed formula instead of cow's milk-based formula has been reported to reduce the risk of developing atopic symptoms, including atopic dermatitis in the general infant population.[117] In the German Infant Nutritional Intervention Study, infants with an allergy history in their family were divided into groups as cow milk-based formula, whey-based partial hydrolyzed formula, whey-based extensively-hydrolyzed formula and casein-based extensively-hydrolyzed formula. At the end of the study, whey-based partial hydrolyzed formula and casein-based extensively-hydrolyzed formula significantly reduced allergic manifestations.[118] Protective effect of hydrolyzed formula has been reported to last up to 10 years.[119] Although meta-analyses confirming the protective effect of hydrolyzed formula for atopic dermatitis have been published,[120,121] in a Cochrane review, it's stated that the benefits of hydrolyzed formula compared to cow milk-based formulas are limited.[122] In addition, Goldsmith et al.,[123] showed that using partial hydrolyzed formula instead of cow's milk does not reduce the risk of FA.

Although amino acid-based formulas are not the first alternative, they are recommended for use in cases where hydrolyzed formulas do not work. Even it is not recommended for use in children with cow's milk allergy under 6 months,[124] soy-based formulas are also used as an alternative.[125] It can also be used in rice-based hydrolyzed formulas in children with cow milk allergies in recent years.[126,127] Although partial or extensively-hydrolyzed formulas are effective in treating FA, there is insufficient evidence that these alternative formulas can prevent atopic diseases in newborns and children even they are at high risk.[128]

Table 1. The possible impact of maternal diet during pregnancy and lactation period on development of FA in the offspring.

Maternal Periods	
Diet, Foods and Nutrients	**Effect**
Omega-3	Reduced risk of eczema and allergic sensitivity to nutrients[91]
	Reduced risk of eczema and allergic rhinitis Atopic outputs are unchanged[92]
	No reduction in IgE-mediated allergies at 6 years of age[93]
	Reduced the absolute risk of persistent wheeze or asthma[94]
	Evidence for the protective effect of supplements given during maternal and lactation periods against food allergies is limited[95]
	Decreased egg sensitivity No changes in food allergies[96]
	Providing oral tolerance by decreasing Th-2 cytokines and increasing TGF-Beta[97]
Vitamins E and zinc	Decreased risk of wheeze[89,98]
Consumption of foods containing vitamin D	Reduced risk of allergic rhinitis[99]
Folic acid	Increased consumption may be associated with food allergy[100]
	No evidence of an association between maternal folic acid supplement use (compared with no use) in the pre-pregnancy period through the first trimester and asthma in childhood[101]
	A high dose of folic acid supplementation for mother during pregnancy was associated with an increased risk of infant asthma, whereas supplementation with a relatively low dose was associated with a decreased risk of infant asthma. [102]
	Maternal folate intake during pregnancy could increase infant asthma risk[103]
	Maternal intake of folate in a dosage higher than recommended (> 0.4 mg/day) was more often observed in the group of allergic subjects[104]
Copper	Protective effect against allergies[89]
Peanut	Peanut consumption in early maternal period is negatively related to allergy and asthma risk[105]
	Early allergen exposure increases tolerance and lowers risk of childhood food allergy[106]
	Peanut consumption in maternal and lactation periods is associated with an increased risk of allergies[107]
	Maternal peanut consumption is associated with peanut sensitivity[108]
Celery and citrus consumption	Increased risk of reaction to cow's milk, eggs and peanuts[109]
Diet rich in seafood	Decreased allergen sensitivity[110]
Lactation Period	
Diet, Foods and Nutrients	**Effect**
Omega-3 Supplementation	Decreased risk of food allergies[111]
Vitamin D Supplementation	Increased risk of food allergies[62]
Dairy restriction in allergic mothers	Decrease in the prevalence of atopic dermatitis[112]

Early consumption of allergen foods

Management of FA was based on not consuming the allergen foods until the age of 1-3 until the 2000s. Despite this restrictive approach, the increase in the frequency of food allergies caused this approach to change. The results obtained from the studies where the allergens are introduced to the baby in the early stages of life show that instead of avoiding the allergens, early and regular consumption may be more effective in reducing the risk of food allergies. Du Toit et al.[129] observed that Israeli children had a much lower incidence of peanut allergies than children in the United Kingdom, and they stated that the reason for this is that peanuts are routinely consumed in early life of Israeli children. Compared to children who started peanut consumption at 4-11 months and children who started at the age of 5 years, it was reported that peanut allergy was less common in children who started peanut consumption earlier.[130] Similarly Joseph et al.[131] found that starting complementary feeding before 4 months reduced peanut sensitivity. Data from observational studies showed that starting solid foods before 4 months

was not protective against FA, and data from randomized controlled studies showed that starting egg 4-6 months and starting peanut between 4-11 months reduced egg and peanut allergy.[132] In a systemic review and meta-analysis involving randomized controlled trials, introducing eggs between 4-6 months has been shown to reduce the risk of egg allergy by 46%, and peanuts from 4-11 months to reduce the risk of peanut allergies by 71%.[133] Based on the previous studies, early introduction of peanut into the diets of high-risk infants has been recommended.[134] However, studies investigating early consumption of egg showed contradictory results.[135-137] Another meta-analysis involving randomized controlled trials showed an association between the early introduction of egg and a lower risk of egg allergy.[138] Apart from egg and peanut, Katz et al.[139] showed that early consumption of cow's milk reduced the incidence of cow's milk allergies.

With the increasing number of evidence that early consumption of allergenic foods may be beneficial, the guidelines of the authorities are also changing in this direction and they suggested that starting allergenic foods should not be postponed after 4-6 months.[90,140] It should be remembered that the start of solid foods before the 6th month contradicts the World Health Organization's suggestion that only breast milk should be consumed for 6 months. In addition, it has been shown in various studies that increasing the food diversity that are introduced to the child in the first year of life may be beneficial in the development of immune tolerance and thus preventing allergic diseases.[141,142]

Processing of allergenic foods

Dietary management of FA requires completely avoiding the consumption of allergenic food. However, passing the allergen food through various cooking processes can alter the reaction to the allergen. For example, there are studies showing that the tolerance to eggs used in baked foods such as cakes or muffins in children who are allergic to eggs varies between 64% to 84%.[143-146] Similarly, for the milk, a high level of tolerance was achieved when baked or heat-treated milk is used.[147-150] The boiling process can also reduce allergen activity. In a study where milk was boiled at 100 ° C for 2 hours, it was reported that milk's allergen activity decreased.[151] It has been shown that the allergen activity does not change when the egg is boiled at 100 ° C, but the allergen activity decreased by traditional Chinese cooking methods such as steaming, spicing and tea boiling.[152] However, there is no standard regarding which children can benefit from these procedures or how the food process should be.

Conclusions

As a result, some dietary changes may be an alternative method of preventing and treating food allergies, as they have regulatory effects on the immune system. Although it is difficult to build up conclusion due to the heterogeneity of studies and contradictory results, several different dietary approaches can be recommended in the management of FA-based on the authors' vision and analytical opinion about these studies:

- Omega-3 and vitamin D is important to regulate microbiota and immune system. Omega-3 intake may reduce allergy risk, but more studies needed to confirm this. Also, both inadequate and high levels of vitamin D may increase the risk of developing food allergies. In general, in both mother and child healthy diet containing high food diversity consumption could be benefit. There is limited evidence on the benefits of elimination diets during pregnancy and lactation period.
- There is increasing numbers of evidence that delaying the onset of introduction of commonly allergenic foods will increase the risk of FA in these children. The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommends starting allergenic foods at/after 4 months of age.[140] This approach might be useful especially in high-risk infants and peanut allergy.
- Hypoallergenic formulas could be used to reduce risk of developing FA in high-risk infants as well as to treat allergic manifestations in already affected children. This effect may be enhanced by probiotic or prebiotic.
- Although it has been shown that allergic foods can be tolerated by methods such as baking and boiling in children with FA, these methods have not been standardized yet and should be applied under surveillance if they are to be tried.
- The effects of nutrients such as omega-6, vitamin D and folic acid on DNA methylation can have an impact on FA. There is not enough evidence yet about the effect of nutritional-genetic interaction on FA.
- Regulation of microbiota and maintaining intestinal health is another prominent issue in preventing food allergies. Dietary approaches to increase microbial diversity and probiotic and prebiotic supplements are a promising approach in the management of FA. In parallel, prebiotic

supplements have also been added to infant formulas. Although the benefits of probiotics and prebiotics were demonstrated, more studies are needed to determine the correct strains and number of organisms.

Declaration of competing interest

The authors declare no competing interest.

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