

Update on Early Nutrition and Food Allergy in Children

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With growing evidence of an increase in the prevalence, food allergy has been emerged as a new public health problem. As treatment and management of food allergy remain challenging, more attention has been paid to the importance of prevention of food allergy. Although the exact mechanism of recent epidemic is not fully understood, it is suggested that nutritional exposure in early life may play an important role in food allergy development. The underlying hypothesis is that nutritional status or food exposure in the critical period of fetal development can affect the programming of immune system and modify the risk of immunologic reactions to foods in postnatal life. We review accumulating epidemiological studies to examine an association between nutritional exposure during pregnancy or early infancy and food allergy development in children. We also discuss recent advances in the studies of the genetic and epigenetic regulation of food allergy and evaluate the role of early nutrition in food allergy development to provide a new perspective on the prevention of food allergy.

Key Words: Food allergy, children, maternal nutrition, epidemiology, epigenetic regulation, immune tolerance

INTRODUCTION

Food allergy is defined as adverse health consequences mediated by abnormal immune reactions to innocuous food exposure.¹ It can be sometimes confused with food intolerance, which is different from food allergy. Food intolerance takes place in the digestive system without the body's immune response.² Prevalence of food allergy has not been accurately estimated due to lack of population-based data, especially from less developed countries. According to existing studies, the extent of prevalence varies considerably, depending on diagnostic methods such as self-report and oral food challenge (OFC) which is considered the gold standard test to confirm food allergy.³ In addition, predictive diagnostic decision point (DDP) values for specific immunoglobulin E (sIgE) antibodies are also widely used in clinical settings.^{4,5} A recent study based on OFC estimated that 1–10% of children under 5 years of age might

have food allergy.⁶ Another comprehensive review showed that 8% of children and 5% of adults were affected by some types of food allergies.⁷ Among Korean patients under 4 years of age who had suspected peanut and tree nut allergy, 31% were sensitized to walnut and 8% experienced anaphylaxis due to a small amount of walnut exposure.⁸ The severity of symptoms of food allergy can range from mild, in most cases, to life threatening in rare cases. Importantly, food allergy can negatively affect perception of one's health and limit family activities.⁹

Genetic predisposition and lifestyle changes including hygiene, sun exposure, smoking, and environmental pollutants are proposed risk factors for allergy development.^{10,11} As the development of immune system starts early gestation and the incidence of food allergy is highest during infancy or early childhood,¹² it has been hypothesized that nutritional exposure during the time of immune programming may play an important role in the development of food allergy. Although biological mechanisms remain to be explored, some studies have suggested that interaction between gene and nutrition may explain the increasing prevalence of food allergy. A limited but increasing number of studies attempted to find epigenetic evidence of food allergy in early life.

In this review, we discuss epidemiological studies to examine evidence of food allergy in infants and children, possibly associated with prenatal or early postnatal nutritional exposure. We focus on selective common food allergens (peanuts and tree

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nuts, cow's milk, and egg) and nutrients (vitamin D and n-3 fatty acids) that have been rather widely studied. We also evaluate evidence of gene and nutrition interaction, and epigenetic regulation of food allergy by nutrients. Lastly, we discuss potential opportunities in the prevention and intervention strategies using immunotherapy.

Allergic reaction and mechanisms of food allergy

Food allergy refers to a series of complex immune reactions to food allergen, particularly mediated by an immunoglobulin E (IgE) antibody, which plays a critical role in allergic diseases.¹³ In individuals without food allergy, antigen-presenting immune cells such as dendritic cells, macrophages, and T regulatory cells (Treg) process food antigen and mediate suppression of further immune response of adaptive immune system.¹⁴⁻¹⁶ But, in individuals with food allergy, food allergen promotes exaggerated response of T helper cells (Th2) and Th2 cytokines,¹⁷ and these consequently stimulate the generation of food sIgE antibodies from allergen-stimulated B cells.¹⁸ When food allergen binds to IgE antibody-bound basophils and mast cells, this triggers release of histamine from basophils and mast cells. This causes various allergic symptoms such as eczema, hives, and gastrointestinal problems.² In general, Treg prevent potentially dangerous hypersensitivity to harmless antigens and regulate immune homeostasis.¹⁹

Genetic evidence of food allergy

Genetic predisposition is a strong risk factor of food allergy. Family-based studies showed that the risk or prevalence of food allergy was greater in children with family history of allergy (parents, siblings, or relatives) than children without it.²⁰⁻²² Twin studies from China and the USA showed that the concordance rate of food allergy was higher with identical twins than with dizygotic twins.^{23,24} The familial aggregation and heritability of food allergy suggest that genetic factors may play a key role in developing susceptibility of food allergy. In addition, associations between genetic variants of nearly a dozen of candidate genes and food allergy were identified, although only few associations were reproduced by subsequent studies.²⁵ A recent genome-wide association study confirmed that two loci in the human leukocyte antigen (HLA)-DR and -DQ regions were associated with peanut allergy in children of European ancestor.²⁶ Collectively, the findings of familial aggregation, heritability and single nucleotide polymorphisms support the hypothesis that genes play a key role in the development of food allergy.

Evidence from epidemiological studies

Although evidence from genetic studies is compelling, genetic factors alone cannot fully explain the increasing prevalence of food allergy. This naturally led to a hypothesis that considerable extent of the risk may be attributable to non-genetic factors. An increasing number of epidemiological studies have examined associations between early nutrition or food exposure and the

risk of food allergy development.

Vitamin D

The possible role of vitamin D in food allergy has been hypothesized because several observational studies reported varying food allergy incidence associated with geographic or seasonal variation (sun exposure). The prescription rate of epinephrine injection (anaphylaxis treatment) and the rate of hospital admission for food-induced anaphylaxis were higher in regions distant from equator in the USA and Australia.²⁷⁻²⁹ A study of multicenter medical records in the USA showed that children under 5 years of age born in fall or winter had 53% higher risk of food-related acute allergic reactions than children born in spring or summer. This study suggests that low sunlight and presumably suboptimal vitamin D status at birth is associated with food allergy development in childhood.³⁰ A large scale population-based study in Australia showed that infants with low serum 25-hydroxyvitamin (OH) D₃ levels (≤ 50 nmol/L) had almost 12 times and 4 times higher risk of developing peanut and egg allergies, respectively, in the first year of life than infants with adequate serum vitamin D level.³¹ However, another study conducted in Germany demonstrated that 25(OH)D₃ concentration in pregnant women's serum and in cord blood were positively associated with increased risk of food allergy development among children in the first 2 years.³² A recent randomized double-blind controlled trial showed that maternal vitamin D₃ supplementation for 6 weeks during lactation increased the risk of food allergy diagnosis by 3.42 times [95% confidence interval (CI)=1.02-11.77] among children of supplementation group compared to control group by 2 years of age.³³ Due to lack of robustly designed studies, a causal association between vitamin D status during prenatal and neonatal period and food allergy development in children remains inconclusive.

n-3 long chain polyunsaturated fatty acids

Because n-3 polyunsaturated fatty acids (n-3 PUFA) have anti-inflammatory and immunomodulatory functions,^{34,35} it is hypothesized that low fish intake or low n-3 PUFA exposure in early life may increase the risk of child allergic diseases.³⁶ A birth cohort study reported that fish consumption in the first year of life was associated with reduced risk of food sensitization by 24% in children by age 4.³⁷ In a randomized controlled trial of daily fish oil supplementation from birth to 6 months of postnatal period, fish oil supplementation in high-risk infants did not prevent allergy development, although the level of docosahexaenoic acid and eicosapentaenoic acid in erythrocytes of infants at 6 months was significantly higher in intervention than in control group.³⁸ In addition, there were 3 randomized controlled studies of maternal fish oil supplementation. Dunstan, et al.³⁹ reported that fish oil supplementation, from the 20 weeks of gestation until delivery, decreased risk of sensitization to egg [odds ratio (OR)=0.34; 95% CI=0.22-1.02], but not to peanut (OR=0.48; 95% CI=0.15-2.2) in Australian infants with high

risk of allergy at 12 months of age. Maternal n-3 PUFA supplementation, from the 25 weeks of gestation to 3–4 months of lactation, reduced the risk of positive results from skin prick tests for egg, milk, and/or wheat (OR=0.36; 95% CI=0.14–0.95) and risk of food allergy with clinical symptoms (OR=0.09; 95% CI=0.01–0.74) among Swedish infants with high risk of allergy at 12 months of age.⁴⁰ However, these two studies suffer from relatively small sample sizes (98 and 145, respectively). Maternal n-3 PUFA supplementation to more than 700 pregnant women during pregnancy in Southern Australia did not reduce clinical food allergy and peanut sensitization, but only egg sensitization [risk ratio (RR)=0.62; 95% CI=0.41–0.93] in one-year-old infants.⁴¹ Therefore, supplementation of n-3 fatty acids during pregnancy may protect specific food allergy development in children.

Peanut or tree nut

Peanut (ground nut) and tree nuts (i.e., almond, walnut, hazelnut, cashew, Brazil nut, and pecan) are common food allergens that can cause life-threatening anaphylaxis in severe cases.⁴² The prevalence of peanut and tree nut allergy ranges from 1–6% and 0.05–5%, respectively, according to population-based studies based on history of allergic reaction and clinical diagnosis, although these estimates are predominantly from industrialized western countries.^{43–45} In Korea, the parent-reported incidence of peanut allergy is 0.68% in infants and 0.34% in early childhood.^{46,47} The peanut and tree nut allergies develop in early life and generally persist through adulthood.⁴⁸ Because of the severity in clinical symptoms and a long natural history, peanut and tree nuts have been most frequently studied among food allergies. A study showed that frequent maternal consumption of peanuts during pregnancy increased the risk of peanut sensitization among atopic infants in a dose-dependent manner.⁴⁹ On the other hand, some studies found no associations between maternal nut consumption during pregnancy or lactation and the risk of peanut sensitization among children, although these population-based studies may be underpowered due to a small number of infants with food allergy.^{50,51} Du Toit, et al.⁵² reported that the risk of peanut allergy was nearly 10 times higher (RR=9.8; 95% CI=3.1–30.5) in Jewish children living in the UK where peanut consumption in the first year of life is not as frequent as Jewish children living in Israel where peanut is introduced early and consumed frequently. Frazier, et al.⁵³ reported that the risk of peanut or tree nut allergy diagnosis was almost 70% lower (OR=0.31; 95% CI=0.13–0.75) among children born to non-allergic mothers who consume peanut or tree nuts more often during peri-pregnancy (≥ 5 times vs. < 1 time per month). Recently, Kim, et al.⁵⁴ showed that DDP of peanut-sIgE level may be useful predictor of the outcomes of OFC in Korean children suspected of peanut allergy. Ara h 2 is the most important allergen in Korean children with peanut allergy. They suggested the cutoff levels for peanut (10.3 kU/L) and Ara h 2 (4.0 kU/L) in the diagnosis of peanut allergy in Korean children. A

randomized trial showed that the prevalence of peanut allergy among children assigned to consume at least 6 gram of peanut protein per week until 60 months of age was significantly lower than that of children assigned to avoid peanut consumption (1.9% vs. 13.7%, $p < 0.001$) among 640 infants with severe eczema, egg allergy, or both.⁵⁵ Although the results from observational studies are inconsistent, the result of the study with a robust experimental design suggest that early consumption of peanuts or tree nuts may prevent nut allergy development. Due to a long natural history, more randomized controlled trials with multiple long-term follow-ups need to validate this finding.

Cow's milk, egg, and others

Cow's milk and egg are relatively common food allergens.⁵⁶ Because cow's milk is usually introduced to infants earlier than any other foods, it is the earliest food allergen among others.^{57,58} The estimated incidence of cow's milk and egg allergies in infants and children are relatively high (0.3–3.5% and 0.5–8.0%, respectively), but most children ($> 80\%$) outgrow the allergies.⁵⁹ A large prospective study showed that the average age of cow's milk introduction to infant feeding was significantly later among Israeli infants with cow's milk allergy than infants without it (116.1 days vs. 61.6 days, $p < 0.001$).⁶⁰ One randomized controlled trial showed that partially hydrolyzed whey formula and extensively hydrolyzed casein formula, as opposed to the standard cow's milk formula, reduced the risk of any allergic diseases by 13% (RR=0.87; 95% CI=0.77–0.99) and 17% (RR=0.83; 95% CI=0.72–0.95), respectively, among high-risk children aged 7–10 years.⁶¹ However, there is insufficient evidence of preventive effect of certain type of cow's milk formula on childhood food allergies.⁶² In a population-based study in Australia (HealthNuts), introduction of egg to egg-sensitized infants at 10–12 months and after 12 months of age increased the risk of egg allergy by 1.6 times (95% CI=1.0–2.6) and 3.4 times (95% CI=1.8–6.5), respectively. They suggested that introduction of cooked egg at 4 to 6 months of age might protect against egg allergy in these infants.⁶³ Studies showed similar protective effects of early introduction of cereal, grain, and oligosaccharides against food allergy development.^{64–66}

Evidence of gene and nutrition interaction

Few studies examined the modulatory effect of gene and nutrition interaction on food allergy development. In the Boston birth cohort study, cord blood vitamin D deficiency [25(OH)D concentration < 11 ng/mL] was not found to be associated with food sensitization to eight common food allergen in children.⁶⁷ However, when individual genetic variant of 4 candidate genes involved in IgE synthesis and vitamin D metabolism were jointly considered, there is a statistically strong gene-vitamin D interaction ($P_{\text{interaction}} = 9 \times 10^{-6}$) on food sensitization. In the same birth cohort study, children who were ever breast-fed had 1.5 times (95% CI=1.1–2.1) higher risk of food sensitization to any of 8 common food allergens than children who were never

breast-fed.⁶⁸ This association was significantly modified by individual or joint 3 single nucleotide polymorphism (SNP) in the *IL12RB1*, *TLR9*, and *TSLP* genes. These genes are related to innate immunity or Th1/Th2 balance. These studies identified functional genetic variants that could modulate the risk of food allergy in children related to early nutrition. Because there is an insufficient number of studies, more studies with a systemic approach are needed to support the effect of genetic variation on the associations between early nutrition and food allergy development in childhood.

Evidence of epigenetic regulation of food allergy

An increasing number of studies suggest that epigenetic regulation plays a critical role in the development of allergic diseases.⁶⁹ Syed, et al.⁷⁰ found that CpG sites in forkhead box protein 3 in antigen-induced regulatory T-cells were differentially demethylated between children with immune tolerance of peanut allergy and children without tolerance. They suggested that modifications at the DNA level of antigen-induced T-cells may be predictive of clinical immune tolerance during peanut oral immunotherapy. In the HealthNuts study by Martino, et al.⁷¹ DNA methylation profiles in CD4+ T-cells were examined in 24 infants with and without IgE-mediated food allergy diagnosed at 12 months. The authors suggested that dysregulated DNA methylation at genes involved in mitogen-activated protein kinases (MAPK) cascade during early CD4+ T-cell development may affect T-cell response and IgE-mediated food allergy in early childhood.⁷² Hong, et al.²⁶ conducted the genome-wide association study of food allergy in the USA population. They found that loci in the HLA-DR and -DQ gene regions were associated with peanut allergy in children. Differential DNA methylation might partially mediate the identified genetic risk factors of peanut allergy. The results of these studies suggest that differential DNA methylation in the regions of genes related to T-cell differentiation and balance between Th1 and Th2 during the critical period of early life may be potential mechanisms of allergic disease development.⁷³

Epigenetic regulation by nutrients

Although possible roles of prenatal folate, n-3 PUFA, and vitamin D in immune programming have been suggested,^{34,74} only a limited number of studies examined epigenetic regulation by these nutrients as a potential biological pathway of allergic diseases. An animal study showed that maternal methyl-rich diet taken during pregnancy changed methylation level at 82 gene-associated loci that are related to allergic airway disease in offspring mice.⁷⁵ This study suggests that excessive DNA methylation by prenatal exposure to methyl donors reduces transcriptional activity of genes, which negatively regulate allergic airway disease. Lee, et al.⁷⁶ showed that maternal docosahexaenoic acid supplementation (400 mg/day) during pregnancy changed DNA methylation levels of genes IFN- γ and IL-13 in mononuclear cells in the cord blood. Since IFN- γ and IL-13 are Th1 and

Th2 cytokines respectively, the findings support the role of n-3 PUFA in T-cell differentiation. In a genome-wide study, a high level of 25(OH)D₃ in the cord blood was associated with low DNA methylation in the enhancer region of *TSLP*. This study showed that prenatal vitamin D-mediated epigenetic regulation in *TSLP* increased the risk of wheezing in children.⁷⁷ More human studies are needed to substantiate the role of epigenetic regulation by nutrients in the growing epidemic of food allergy.

Induced immune tolerance

Treatment of food allergy mainly relies on strict avoidance of specific food allergen, although complete avoidance of allergenic food can be hardly practiced. Recently, immunotherapy has been suggested as an emerging intervention that ameliorates allergic reactions or permanently desensitizes food allergen.⁷⁸ Mechanisms of induced immune tolerance are not fully understood. The key idea is to induce immune tolerance by promoting non-responsiveness of adaptive immune system to innocuous food antigen through the activation of antigen-specific Treg cells or deletion of Th2 cells.^{18,19} In oral immunotherapy, patients are gradually exposed to a small but steadily increasing amount of specific food allergen until they are desensitized to it and sustain non-responsiveness after discontinuation of the therapy. Recent meta-analysis of 18 randomized and 3 clinical controlled trials showed that oral immunotherapy showed a protective effect against food allergy (RR=0.21; 95% CI=0.12–0.38).⁷⁸ Oral immunotherapy also increased average risk of systemic adverse reactions although it was not statistically significant (RR=1.08; 95% CI=0.97–1.19). Although immunotherapy is not currently recommended for practice because of safety issue, more experimental studies with a larger sample size and longitudinal follow-ups are required to provide efficacy and safety of immunotherapy.

CONCLUSIONS

Based on accumulating evidence, prolonged avoidance of allergenic foods during pregnancy, lactation, and delayed introduction of allergenic foods in infant feeding are effective in preventing food allergy development. Epidemiological studies suggest that exposure to food allergens in early life may prevent food allergy development among high-risk individuals. Individual genetic variants and differentially methylated DNA at certain genes help us to understand potential biological pathways of food allergy. Epigenetic studies provide our knowledge of mechanisms of food allergy and insights into new approaches to the prevention and management of food allergy. As controlling food consumption during pregnancy and lactation is relatively possible, as opposed to controlling other environmental exposures, early nutrition deserves more attentions as a primary target of further food allergy research.

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