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Review suggests that the immunoregulatory and anti-inflammatory properties of allergenic foods can provoke oral tolerance if introduced early to infants' diets

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Short Running title: Early introduction of allergenic foods

ABSTRACT

For years, the advice was to postpone introducing allergenic foods, in order to prevent food allergies. However, food allergies have escalated rather than declined and our review of the latest epidemiological, immunological and nutritional research suggests that early weaning practices may be beneficial. The most allergenic foods, such as fish, eggs and peanuts, have proved to be inherently rich in tolerogenic substances that can play a significant role in preventing allergies.

Conclusion. We found evidence that the immunoregulatory and anti-inflammatory properties of allergenic foods can provoke oral tolerance if introduced early to both low-risk and high-risk infants.

Key words:

Allergy prevention, early food introduction, oral tolerance induction, tolerogenic foods, weaning practices

Key notes

- For years, the advice was to postpone the introduction of allergenic food, to prevent food allergies.
- However, the most allergenic foods, such as fish, egg and peanuts, are inherently rich in tolerogenic substances, which can play a significant role in preventing allergies.

- There is evidence that the immunoregulatory and anti-inflammatory properties of allergenic foods can provoke oral tolerance if they are introduced early to low-risk and high-risk infants.

INTRODUCTION

The increase in allergic diseases over the last few decades has led to the development of international guidelines that aim to provide primary prevention of food allergies. They are based on the premise that the infant gut mucosal barrier is immature and that the early introduction of solid foods may instigate sensitisation against foods and inhalants. Thus, the feeding recommendations issued up to 2012 proposed exclusive breastfeeding for the first six months in order to prevent allergic diseases in children (1-5). The suggested age for the introduction of fish or eggs differs considerably, with several countries recommending that they can be introduced from four to six months and others suggesting that it is best to wait until nine to 12 months or later (5). On the other hand, allergenic foods have been consistently introduced much later to high-risk children with moderate to severe eczema, food allergies or a positive family history (3,4). However, the rate of food allergies has escalated rather than declined in the past 10 years (6,7).

There is now mounting concern, and some new evidence, that recommending the delayed introduction of complementary foods, even to high-risk children, may have detrimental consequences, as early immune tolerance mechanisms will fail to develop. We know that the retarded immunological development of intestinal surface barrier maturity, on the one hand, and the persistent imbalanced immunoregulatory network, on the other hand, promotes allergies rather than tolerance (8). The first postnatal year of life seems to be a key period for programming of the immune system (9,10). Research has established that peripheral T regulatory cell induction is an antigen driven process and that mucosal exposure

to allergens is not the cause of the allergy epidemic. It seems that exposing the gut to allergenic foods seems to have preventive effects that subvert allergen restriction strategies (7).

Convincing data have emerged that support the concept of the early introduction of allergenic foods (8). In addition, depriving an infant with a rapidly developing organism of these nutrients with high biological value should only be advised on very solid scientific grounds. We have, therefore, reviewed the epidemiological, immunological and nutritional data concerning the tolerogenic role of the main allergenic foods, namely fish, eggs and peanuts.

Epidemiologic research on early food introduction, maternal diet and their impact on allergy prevention

Early consumption of fish has been associated with a lower prevalence of allergies in some birth cohort studies, mainly from Scandinavian countries (11-17). In a prospective Swedish and a Norway birth cohort study, lower levels of eczema and asthma was reported in low-risk and high-risk children given fish before the age of nine months (11,12). There was also a dose response effect, in that the earlier that fish was introduced into the diet, the greater the group-level protection. Other investigators have reported similar findings in respect to eczema (13,14). Furthermore, Kull et al reported less sensitisation and allergic disease at four years of age in children who were given fish before the age of one (15). In a Norwegian and Finnish birth cohort study, children given fish during the first year of life demonstrated a reduced frequency of asthma and allergic rhinitis at four years of age (16,17). Moreover, the Finnish study, confirmed the earlier observation of the Swedish group that the age when fish was introduced to the diet, even among atopic families, was inversely related to the risk of allergic rhinitis. Furthermore, the late introduction of fish was associated with allergic sensitisation to any food or inhalant allergen (17). Similarly, a number of studies have not

supported the theory that the delayed introduction of the most potentially allergenic solids beyond the sixth month decreases the prevalence of allergic diseases and sensitisation.

These were the Influences of lifestyle related factors on the immune system and the development of allergies in childhood cohort study (LISA), the German infant nutritional intervention cohort study (GINI) and the Generation R study from the Netherland (13,14,18).

In an attempt to prevent allergies, many diet interventions during pregnancy have also been investigated. One randomised controlled study was designed to evaluate clinical symptoms in infancy after maternal omega 3 long chain polyunsaturated fatty acids (LPUFA) supplementation during both pregnancy and lactation. It found that there was a decrease in food allergies, less allergic sensitisation and immunoglobulin E associated eczema in the first year of life of infants with a family history of allergic disease (19). A retrospective cohort study indicated that the children of non-allergic mothers, were less likely to have positive skin prick tests at five years of age if their mothers ate fish frequently during pregnancy. The same was not true for the allergic mothers (20). In a study of maternal fish intake during pregnancy, fish was found to be protective against both childhood current and ever asthma at the age of seven years (21). Moreover, two systematic reviews found no benefit in restricting common food allergens among pregnant women (22,23). In contrast, another review concluded that the mother's antioxidant status during pregnancy, on the one hand, and their children's consumption of antioxidants, on the other, protected against the development of allergic disease (24).

As far as egg consumption is concerned, in 2008 the German LISA and GINI cohort studies suggested that there was no evidence to support the delayed introduction of eggs, but they reported an increased risk of doctor-diagnosed eczema in the avoidance group when eggs were first consumed after the first year (13,14). In addition, the Finnish birth cohort study, as well as other review studies, have suggested that the introduction of eggs at

an age younger than 11 months, in addition to a free maternal diet during pregnancy and lactation, decreased the risk of sensitisation to all the specific allergens and prevented atopic diseases (17,22-25).

With regard to peanuts, it has been reported that high levels of environmental skin exposure to peanuts during infancy, due to household peanut consumption, appeared to promote sensitisation, whereas maternal peanut consumption during pregnancy or lactation had no hazardous effects (26,27). Interestingly, it has been reported that Jewish children in the UK had a 10-fold higher prevalence of having a peanut allergy than Jewish children in Israel. This difference was not accounted for by differences in atopy, social class, genetic background or peanut allergenicity. It was attributed to the fact that Israeli infants traditionally consume peanuts in high quantities in the first year of life, whereas UK infants avoid peanuts (28). Moreover, the Learning Early About Peanut Allergy (LEAP) study suggested that the early introduction of peanuts to sensitised children significantly decreased the frequency of a peanut allergy developing and modulated their immune responses to peanuts (29). Lastly, Perkin et al randomised 1,303 exclusively breast-fed infants to receive either all the allergenic foods from three months onwards or to maintain exclusive breast-feeding until the age of six months (30). They reported a significantly lower overall incidence of food allergy in the group that received the allergenic food than in the exclusively breast-fed group. This was accounted for by a lower incidence of peanut and egg allergies. However, that was not the case for cows' milk, white fish, sesame seeds and wheat.

Interestingly, the diversity of complementary foods in the first year of life has been shown to reduce the risk of atopic dermatitis (31). This effect was not only observed in a proactive way. Conversely, less food diversity during the first year of life might be linked to a higher risk of developing asthma and allergies in childhood (32,33).

Immunologic research on the effect of allergenic foods on tolerance induction

The normal, physiological immune response to eating food proteins is a state of systemic immunological hypo-responsiveness, known as oral tolerance. This is based on the pivotal role of the T regulatory cells that downregulate the Th₂ inflammatory response. Moreover, an increased diversity of foods in the first year of life might also be associated with the increased expression of T regulatory cells, mirrored by the increased expression of forkhead box protein 3 and a decreased expression of Cε germline transcript (33). The underlying allergy-protective mechanism of early food introduction is only speculated on in the literature, as it is mainly in vitro studies that have showed some indirect evidence. Fish and eggs are rich in many main healthy nutritional components, such as omega 3 LPUFA, antioxidants, vitamin A and D. Omegas 3 LPUFA, known as decosahexaenoic acid and eicosapentaenoic acid, have immunoregulatory and anti-inflammatory properties through the bioactive lipids lipoxins, neuroprotectines and resolvins (34). On the other hand, omega 6 LPUFA such as arachidonic acid, are major constituents of human inflammatory cells, with the ability to stimulate mediators from the family of eicosanoids and produce inflammatory cytokines. What is important is the fact that omega 3 and omega 6 LPUFA act as feedback inhibitors for the same enzymes (35). Eicosapentaenoic acid can compete with arachidonic acid and counteract the immunoglobulin E stimulatory and pro-inflammatory action of the arachidonic acid -derived prostaglandin E₂ and leukotriene B₄. In addition, eicosapentaenoic acid and decosahexaenoic acid cause changes in immune cell membrane fluidity and decrease the content of arachidonic acid, which influences cell responsiveness to exogenous stimuli (36). Thus, the increase in the consumption of food rich in a high omega 3/omega 6 ratio can reduce the omega 6 metabolites, attenuating inflammation. This is supported by studies that showed that a diet with omega 3 LPUFA increased placental decosahexaenoic acid levels

and reduced placental interleukin-6 production (36,37). Interestingly according to a significant Cochrane study, maternal omega 3 LPUFA supplements, in contrast to individual consumption during pregnancy and lactation, did not significantly reduce immunoglobulin E-associated allergic disease (38).

Fish are also rich in several types of endogenous antioxidants, which can inhibit the oxidation of their own lipids. These include antioxidant enzymes such as glutathione peroxidases, amino-acids, peptides, ascorbic acid, carotenoids and natural phenolic compounds, such as resveratrol, tocopherols and ubiquinones (39). Eggs are also an important antioxidant food, as they contain various natural compounds, including the proteins ovalbumin, ovotransferrin and lysozyme in egg white, as well as phosvitin, carotenoids and free aromatic amino acids in egg yolk. In addition, lecithin, a major component of egg yolk, is a major dietary source of phosphatidylcholine, which is necessary for infant brain function and acts synergistically with primary antioxidants like tocopherols. The bioactivity of egg antioxidants can be enhanced by gastrointestinal digestion, as new antioxidants in the form of free amino acids and peptides are formed (40). With respect to peanuts, a study has highlighted the antioxidant capacity of peanuts, which are rich in resveratrol, phenolic acids, flavonoids, phytosterols, zinc, selenium, phosphorus, magnesium and vitamin E (41). Antioxidants play a pivotal role in redox homeostasis. Concentrations of glutathione in the epithelial lining fluid of the respiratory tract, normally exceed those of plasma levels by 100-fold, enhancing cell tissue responses to oxidative stress and reducing airway damage to reactive oxygen radicals (42). On the other hand, it has been found that increased glutathione expression in the eosinophils of asthmatic patients, compared to non-asthmatics, provide protection from the reactive oxygen species generated by these cells (43). Moreover, antioxidants reduce fractional exhaled nitric oxide in asthmatic children and modulate both mast cell degranulation and cytokine gene expression (44,45).

Fish and eggs are also rich in fat-soluble vitamin A and D, which have been implicated in several diverse allergy prevention studies, albeit with weak evidence (46). However, in murine models, fatty acids and vitamin A and E influenced oxidative stress, reducing tumor necrotic factor- α , interleukin 1 β , interleukin 6 and prostaglandin E₂ production (47). Moreover, in animal models, the consumption of ovomucoid, a major allergen present in hens' eggs, resulted in oral tolerance induction, measured as both a reduced ovomucoid-specific spleen cell proliferation and antibody response. This tolerogenic response was not abolished by simultaneous consumption of ovomucoid, peanuts and peas (48).

However, the effect of food exposure on tolerance induction is not explained solely by their anti-inflammatory and antioxidant components, but possibly by specific antigen-driven immune responses. Thus, in the LEAP study, increases in the levels of peanut-specific immunoglobulin G4 antibodies occurred predominantly in the children exposed early to peanut allergens, while elevated titres of peanut-specific immunoglobulin E antibodies were noted in the avoidance group (29). These findings suggest that the early introduction of allergenic food can manipulate the immune system in a similar way to immunotherapy. This tolerogenic immune response seems to be food specific, as shown with peanuts and eggs and to a lesser extent with milk, fish, sesame seeds and wheat (30). Concerning the maintenance of tolerance induction with early weaning practices, Du Toit et al showed that when children who faced a high of allergies avoiding peanuts for 12 months, having eaten them during the first year of their life and until five years of age, they did not experience an increase in their prevalence for a peanut allergy. This suggests that their previous consumption had a long-term effect (49). In contrast, when a group of children received oral immunotherapy, only a minority of the subjects achieved sustained unresponsiveness to peanut after discontinuation of the immunotherapy.

Nutritional analysis of the main allergenic foods

Our nutritional analysis was based on the United States Department of Agriculture National Nutrient Database for Standard Reference Release (50). A portion of 100 grams of cooked Atlantic cod provides 105 calories, 22.83g of protein and 0.86g of fat, as well as 55mg of cholesterol. Since cod is so low in fat, it isn't a good source of omega 3 fats, as it only provides about 221mg per 100g of this essential fat. However, fish with a high fat content, such as salmon and swordfish, provide much higher amounts of omega 3 and omega 6 fatty acids. Peanuts are not true nuts, as they belong to the legume family, but they are a good source of protein. A portion of 100g of raw peanuts contains 567 calories, 25.8g of protein and 16.13g of carbohydrates, of which 8.5g are fibres. However, they also contain high amounts of monosaturated and polyunsaturated fats, up to 49.24g, mainly in the form of ω 6 fatty acids. Eggs are an important source of high quality protein, namely 12.58g, because of their essential amino acid content profile and the high digestibility of their proteins. The fat content of an egg is 10.6g, and this is almost entirely contained in the yolk in the form of monounsaturated (45%), polyunsaturated (25%) and saturated (30%) fatty acids. Eggs are a good source of ω 3 long chain fatty acids, mainly in the form of decosahexaenoic acid and eicosapentaenoic acid albeit much lower than fish. Interestingly, the omega 3/omega 6 ratios in cod, salmon and swordfish are 36, 3.4 and 28, respectively, whereas the same ratio in eggs and peanuts are 0.06 and zero, respectively. Moreover, eggs are rich in cholesterol, lecithin and vitamins, with the exception of vitamin C. They provide all the B vitamins, particularly B12 and B2, and are an excellent source of folate and fat-soluble vitamins A and D. Phosphorus, iron and zinc are found in lower concentrations. Vitamins B complex are the only vitamins found in significant amounts in cod which is also a good source of phosphorus and selenium. Fatty fish contains much higher amounts of all the vitamins in the vitamin B complex. Peanuts are high in vitamin E, folate, niacin, vitamin B₆ and almost all minerals, especially iron, phosphorus, magnesium, selenium and zinc.

International weaning practices guidelines

Up to 2012, the international allergy societies had advised delayed weaning practices. But much earlier, in 2008, the European Society for Paediatric Gastroenterology Hepatology and Nutrition had proposed a different approach. In their position paper, the authors claimed that there was no convincing scientific evidence that avoiding or delaying the introduction of potentially allergenic foods, such as fish and eggs, reduced allergies, either in infants who did, or did not, face an increased risk of developing allergies (51). Later, the Reactions to Foods Committee of the American Academy of Allergy, Asthma and Immunology recommended no avoidance diets during pregnancy and lactation, exclusive breast-feeding for at least four months, and up to six months, and the introduction of all complementary foods between four and six months of age (25). Similarly, The European Academy of Allergy and Clinical Immunology position paper on preventing food allergy, reported that there was no need to avoid introducing complementary foods beyond four months, irrespective of atopic heredity (52). In 2014, the guidelines issued the German Society for Allergology and Clinical Immunology suggested that the introduction of solid foods should not be delayed as a means of allergy prevention (53). What is more, a mini consensus report based on the LEAP study claimed that there was no scientific evidence to recommend the early introduction of peanut products into the diets of high-risk infants (54).

CONCLUSION

As tolerance to food allergies appears to be driven by early exposure to allergenic food proteins during a critical early window of development, dietary avoidance strategies in infants are not justified. Although the optimal weaning timing is not clear, the current evidence suggests that this opportunity window is most likely to be between four and six months, preferably while the child is still being breast fed. The same recommendations have been suggested for children with a history of eczema or those who are sensitised to food

allergens, but without clinical allergy disease. There is evidence, based on epidemiological, immunological and nutritional data, to suggest that fish, eggs and peanuts are beneficial nutrients with a possible privileged role towards oral tolerance induction. This occurs mainly through their ω 3 fatty acids and antioxidants content, on the one hand, and their antigen specific tolerogenic effect, on the other hand. These weaning practices seem to have long-term effects on tolerance. However, new studies in different populations, that address the role of early exposure to allergenic foods, rather than avoidance, are urgently needed both in high cases and non high-risk cases. Moreover, the clear designation of high-risk cases must be revised, to help health professionals and parents to overcome the old guidelines. Studies are needed to challenge many long-held concepts, in order to redefine the pattern of weaning based on both the immunogenicity and nutritional value of the different foods. Until then, no general recommendations can be given and it seems advisable to introduce all foods early, as a weaning practice, based on their beneficial lipid and antioxidant prevention properties.

Abbreviations

LPUFA, Long chain polyunsaturated fatty acids; LISA, Influences of lifestyle related factors on the immune system and the development of allergies in childhood cohort study; GINI, German infant nutritional intervention cohort study; LEAP, Learning Early About Peanut Allergy;

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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