Management of food allergy: vitamins, fatty acids or probiotics?

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The dietary approach to allergic disease in infancy is evolving from passive allergen avoidance to active stimulation of the immature immune system, the aim of which is to support the establishment of tolerance. This may include probiotics providing maturational signals for the gut-associated lymphoid tissue and by balancing the generation of pro and anti-inflammatory cytokines in addition to their capacity to reduce the dietary antigen load by degrading and modifying macromolecules. Probiotics have also been shown to reverse the increased intestinal permeability characteristic of children with food allergy and to enhance specific IgA responses frequently defective in children with food allergy. The promotion of gut barrier functions by probiotics also includes the normalization of the gut microecology, alterations in which have been demonstrated in allergic individuals. Dietary lipids, especially long-chain polyunsaturated fatty acids, regulate immune function and may modify the adherence of microbes in the mucosa thereby contributing to host–microbe interactions. The properties of specific dietary compounds in optimal combinations and the joint effects of nutrients can be exploited in the development of specific prophylactic and therapeutic interventions. To meet these targets, rigorous scientific effort is required to elucidate how the food matrix and the dietary content impacts on the complex cascade of interrelated immunological mechanisms in food allergy. *Eur J Gastroenterol Hepatol* 17:1305–1311 © 2005 Lippincott Williams & Wilkins.

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Introduction

The basic foundation of nutrition lies in a healthy, balanced diet to meet the needs for growth and development in children. The first goal here is directed towards the prevention of diet-related deficiencies, and the second target may be ascribed to reducing the risk of disease. The mainstay of the treatment of food allergy is strict avoidance of the offending antigen. However, empirical elimination diets have hitherto been used, albeit with little success, in an attempt to prevent allergic diseases. Therefore, accurate diagnostic procedures to identify the specific food allergies in affected children and to avoid unnecessary elimination diets that carry a constant risk of inadequate nutrition form the backbone of the management of food allergy. Furthermore, dietary manipulations in this population may influence adult size, performance and health, as markers of early nutrition have been linked to the risk of chronic diseases such as atherosclerosis, diabetes, hypertension and obesity. Data are accumulating to suggest that early nutrition also governs the development of atopic diseases.

On this basis, current research interest is directed towards the identification of active dietary compounds modulating specific target functions in the gut and the immune system with specific effects in health promotion beyond the nutritional impact of food. For this purpose, the demonstration of a consistent effect attached to specific dietary compounds and supplements across well-controlled clinical studies is required in the defined target population. For the exploitation of scientific efforts in clinical practice it is further necessary to elucidate the interactions of the compounds and the dietary context, i.e. the presence or absence of potentially active substances in the usual diet.

Impaired gut barrier function: the target of treatment in food allergy

The mucosal surface forms the largest area of the body in contact with the external environment. Protection against potentially harmful agents is ensured by two opposing functions of the intestinal mucosa: a barrier excluding antigens and the controlled transfer of antigens evoking local antigen-specific immunity. The continuous exposure of antigens such as food and microorganisms places high demands on the defence barrier. The immaturity of this barrier, the intestine's antigen exclusion, elimination and immune regulation mechanisms, may lead to aberrant

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antigen transfer (see Heyman, present issue), thus explaining the increased proneness of infants to inflammatory responses to intraluminal antigens. Consequently, allergies could be ascribed to the lack of physiological anti-inflammatory processes.

There are several active mechanisms through which mucosal tolerance is established and maintained (see Mayer, present issue). Distinct regulatory mechanisms effecting both T helper types 1 and 2 cells have recently been discovered with suppressive and regulatory functions. These T helper type 3 and T regulatory type 1 cells exert their effects via the production of cytokines, mainly transforming growth factor beta (TGF-β) and IL-10, respectively. TGF-β with suppressive effects on both T helper types 1 and 2 responses [1] has been implicated in the establishment and maintenance of oral tolerance, and infants with food allergy have been reported to display a defect in TGF-β-producing cells in the intestine [2]. In addition, TGF-β is the initial trigger for the production of IgA antibodies [3,4], frequently defective in children with food allergy [5].

The intestinal microbiota also constitutes an important aspect of the mucosal barrier in carrying specific metabolic activity and trophic effects on the intestinal mucosa. The establishment of the gut microbiota of a newborn is dependent on genetic factors, maternal microbiota, the mode of delivery and the birth environment [6], and it is characterized by specific stages of development: early colonization by facultative anaerobes such as enterobacteria, coliforms and lactobacilli, succeeded by anaerobic genera such as *Bifidobacterium*, *Bacteroides*, *Clostridium* and *Eubacterium* [6]. The greatest difference in the microbiota of breast-fed and formula-fed infants lies in the numbers and species composition of bifidobacteria. *Bifidobacterium breve*, *Bifidobacterium infantis* and *Bifidobacterium longum* are species frequently found in faecal samples from breast-fed infants, whereas later in life *Bifidobacterium adolescentis* becomes more common. After weaning the microbiota becomes more diverse, resembling that of adults.

The innate immune system is the first line of defence against invading microorganisms. To sense the myriad of microorganisms found in the gastrointestinal lumen, the gastrointestinal epithelium is equipped with pattern recognition receptors, including Toll-like receptors (TLR), which recognize specific conserved pathogen-associated molecular patterns on their surface. Signalling pathways here result in the production of proinflammatory cytokines. These structures are not unique to pathogens. Therefore at the level of TLR pathogens and commensals cannot be distinguished. Several molecular characteristics of the gut epithelium have been thought to prevent inappropriate immune responses towards indigenous gut microbiota such as a negative regulator of TLR signalling, Toll-interacting protein, which may mediate some tolerogenic effects of commensal microbes [7]. The maturation of dendritic cells carrying commensals and the subsequent secretion of cytokines and chemokines then influence the polarization of T helper cells and thereby the adaptive immune responses, ensuring a local IgA response [8], which contributes to intestinal barrier function and the anti-inflammatory tone in this milieu.

Food allergy: the patient

Food allergy is defined as an immunologically mediated adverse reaction to dietary antigens. Cow's milk allergy frequently comprises the first major allergy to manifest itself, because cow's milk proteins represent the first source of antigens encountered in large quantities in infancy. Cow's milk allergy can affect several organ systems, and an infant with cow's milk allergy may show more than one symptom or show symptoms in more than one organ system. The symptoms arise from the gut, skin and respiratory tract. The factors that determine the site of the clinical symptom, type of reaction or clinical outcome remain unexplained, although evidence is accumulating to suggest that different immunopathogenic mechanisms are involved.

Despite the wide spectrum of clinical manifestations, there are at least two prerequisites in common for the development of food allergy. First, intraluminal antigens must penetrate the intestine's mucosal barrier. Second, the absorbed antigens must cause harmful immune responses. Increased intestinal permeability and enhanced antigen transfer has been reported in children with cow's milk allergy caused by the hypersensitivity reaction. Particularly in infants with atopic eczema and cow's milk allergy, more extensive barrier dysfunction can ensue, refractory to an elimination diet [9].

On the basis of these data, a working hypothesis for the management of cow's milk allergy has been presented [10]. Cow's milk antigens evoke a local hypersensitivity reaction that may or may not induce local symptoms. The immunoinflammatory reaction impairs the intestine's barrier function. Although the intestinal inflammatory response may be specific to the triggering antigen(s), the resulting enhancement of antigen transport is not necessarily antigen specific. The enhanced absorption of antigens at the time of reduced mucosal barrier function could further increase intestinal permeability. Increased intestinal permeability may consequently underlie the development of multiple food allergies. Taken together, it would appear that impaired barrier function and defective handling of cow's milk antigens in the gut mucosa may be an important pathogenic mechanism in cow's milk allergy. Hypersensitivity reactions to cow's milk antigens disturb the gut defence

barrier and cause mucosal dysfunction, which consistently occurs in children with cow's milk allergy, irrespective of the focus of clinical reaction.

The targets of treatment in food allergy may be identified as elimination of the antigen responsible, alleviation of the immune inflammatory reaction, and stabilization of the gut mucosal barrier. Processing the major dietary allergens by gut microbiota-derived enzymes, alleviation of the inflammatory responses and strengthening the intestine's defence mechanisms may introduce a new approach in the management of food allergy.

Nutrients beyond nutrition?

Elimination diets form the basis for the management of documented food allergies [11]; their advantage is afforded in silencing the specific allergic inflammation induced by the food responsible [12]. Elimination diets may, however, be associated with an increased risk of nutritional inadequacies, particularly when the elimination from the diet of key foods such as milk or cereals is indispensable [12,13]. Even though the causes of growth decline are indefinite, impaired growth has been observed in patients with cow's milk allergy [13,14] and other food allergies [15], thus necessitating careful dietary planning and follow-up. This is, however, compromised by the development of food aversions, voluntary attempts to regulate the symptoms of the disease by the elimination of foods [16], and resultant inadequate dietary intake. Importantly, although nutritional consequences reflected in growth and dietary intake may be transient [17], the health consequences of an unbalanced diet may be of a long-lasting nature [18].

Recent studies on the immunomodulatory properties of fatty acids and probiotics, together with the antioxidant properties of certain nutrients, have shown that food is not only a source of dietary antigens causing sensitization, but may also contain protective factors. The realization of this may be particularly important in food allergies in balancing the restricted diet that results from the management of the disease, i.e. elimination.

Fatty acids

Dietary long-chain polyunsaturated fatty acids (PUFA) and mediators synthesized from PUFA have the capacity to regulate immune function, and therefore contribute to the development and severity of the symptoms of allergic disease. In particular, the increased intake of n-6 fatty acids results in the production of arachidonic acid-derived eicosanoid prostaglandin E_2 and thereby in elevated immunoglobulin E synthesis, as a result of the induction of B-cell differentiation in the presence of IL-4 [19] and proinflammatory cytokine responses. n-3 series fatty acids derived from dietary alpha-linolenic acid or directly from marine food sources appear to have less potent biological functions, even anti-inflammatory properties, which arise from their capacity to inhibit the release of arachidonic acid from membrane phospholipids, thereby reducing the production of proinflammatory eicosanoids [20]. The most frequently reported abnormality in the cell fatty acid composition of atopic patients has been an imbalance between series n-6 and n-3 fatty acids [21–23] predisposing patients to the adverse effects of prostaglandin E_2.

The concept of the potential benefits of n-3 fatty acids has resulted in intensive research on the effects of fish and fish oil in the management of allergic disease. One of the classic studies is by Hodge and co-workers [24], who found that children who ate oily fish had a reduced risk of asthma. In a more recent Norwegian study [25], fish consumption during the first year of life was associated with a reduced risk of allergic rhinitis at 4 years of age. Convincing evidence on the effects of n-3 fatty acids was provided by daily infusions of fish oil-based lipid emulsion for patients with atopic eczema and the consequent improvement of the disease severity score [26]. A recent systematic review attempted to resolve the associations between fish consumption or fish oil supplementation and asthma [27], but the number of trials was insufficient to examine dietary manipulation alone, and there were no consistent effects on n-3 fatty acid supplementation in asthma. Nevertheless, no adverse events were associated with fish oil supplements. A meta-analysis exploring the effects of oral fatty acid supplementation in atopic eczema found similar results; supplementation with fish oil did not improve the severity of atopic eczema, but only three fish oil supplementation studies fulfilled the criteria for the analysis [28].

Supplementation with n-3 fatty acids may not be without risk, because eicosapentaenoic acid (EPA) has been seen to correlate with immunoglobulin E concentration [29]. Also, recent clinical observations have provided evidence for the possible deleterious effects of n-3 fatty acids in allergic disease, as total n-3 fatty acids, docosapentaenoic acid and docosahexaenoic acid were higher in the colostrum received by infants sensitized to foods at 6 months [30], and the risk of asthma was increased in relation to the increased dietary intake of EPA and docosahexaenoic acid and alternatively was reduced in relation to erythrocyte membrane linoleic acid levels [31]. Also, in a Japanese study [32] the prevalence of asthma was higher in subjects who ate fish one to two times per week compared with those who ate fish one to two times per month, even when adjusted for a parental history of asthma and the intake of vegetables and fruits. The possible adverse effects of n-3 fatty acids may be explained by their direct effect on T helper type 1 cell activation because of the suppression of IL-2 and by the indirect suppression of T helper type 1 cells by the enhanced cross-regulatory function of T helper type 2

cells observed in mice [33]. Alternatively, the effects of EPA may ensue via its regulatory role on n-6 fatty acids by means of inhibiting n-6 PUFA-derived eicosanoid production [34]. This effect of EPA would be particularly unfavourable in allergic disease, as n-6 PUFA arachidonic acid induces the activity of T regulatory cells [35]. This also calls into question the use of the artificial supplementation of high doses of fatty acids with possible deleterious or ineffective influences in allergic disease, also as a result of inclined interactions between the nutrients [36]. Although an impression is given that fatty acids may benefit both the management and the risk of developing allergic disease, the data thus far are fragmentary and inconclusive. Further research is needed on the potential effects of the overall fatty acid composition and the proportions of n-3 to n-6 fatty acids within the diet and with respect to other nutrients.

Antioxidants

In allergic disease, inflammatory processes result in endogenously generated oxidative stress, which both cellular enzyme-based antioxidants and diet-derived antioxidants, including ascorbic acid, β-carotene, α-tocopherol, selenium and zinc, may counteract [37]. Dietary antioxidants may thus be important in implementing the ability of the individual to restrain the inflammatory response and in avoiding injury to tissues. For example, the dietary intake of vitamin E has been shown to associate with a lower serum IgE concentration [38], suggesting that antioxidant deficiencies may be associated with symptoms of the allergic disease. Previous studies have, however, yielded contradicting results on the associations between dietary intake or the serum concentrations of antioxidant vitamins and minerals and allergic disease, and most studies involve patients with airway allergies [39–46].

In food allergy, vitamin A may play an important role as it is an imperative constituent for cell differentiation and thus for the mucosal function. Deficiency impairs innate immunity by diminishing the function of neutrophils, macrophages and natural killer cells as well as antibody-mediated responses by T helper cells [47]. The vitamin A deficiency compromises mucosal epithelial barriers in the gastrointestinal tract, particularly when complicated by infection, and it has been shown in children that recovering from diarrhoea may be faster when vitamin A supplement is received compared with placebo [48]. With regard to allergic disease, vitamin A has been found to inhibit IgE production in mouse peripheral blood mononuclear cells [49]. In addition, supplementation with vitamin A in mice has resulted in the depression of IFN-γ and IL-4, the potential cytokines in allergic disease, and in an increase in mucosal immunoglobulin A, with the capacity to protect mucosal surfaces [50]. However, data accumulated thus far on the specific antioxidant agents and their dose and mechanisms are insufficient to provide any recommendation on their use in either the prevention or the management of allergic disease.

Probiotics

A probiotic is currently defined as a live microbial food supplement with an established beneficial effect on human health [6]. Probiotics are selected from members of the normal healthy intestinal microbiota, most of them belonging to *Lactobacillus* or *Bifidobacterium*. The aims of intervention are to avert deviant microbiota development, strengthen the immature or impaired gut barrier function, and alleviate abnormal immune responsiveness.

Specific strains of the gut microbiota contribute to a T regulatory cell population amenable to oral tolerance induction [51], and to counter allergy by the generation of IL-10 and TGF-β [52,53]. These activities are associated with the suppression of the proliferation of T helper cells and the reduced secretion of proinflammatory cytokines, with the control of IgE responses [54] and reduced allergic inflammation in the gut [55]. These demonstrations suggest that intestinal microbial stimulation has effects on mucosal immune responses beyond the gut. The oral introduction of specific microbiota bacteria can also increase systemic and mucosal IgA responses [56–58].

To evaluate the clinical effect of probiotic therapy in food allergy, infants with atopic eczema and challenge-confirmed cow's milk allergy were fed an extensively hydrolysed whey formula or a similar formula containing *Lactobacillus* GG [15]. There was a significant improvement in the clinical course of atopic dermatitis concomitant with a reduction in the concentrations of TNF-α during the one-month management with probiotics. Similar clinical results with probiotic intervention have been obtained in both young infants and older children with the condition [59–61], as well as in milk-hypersensitive adults [62].

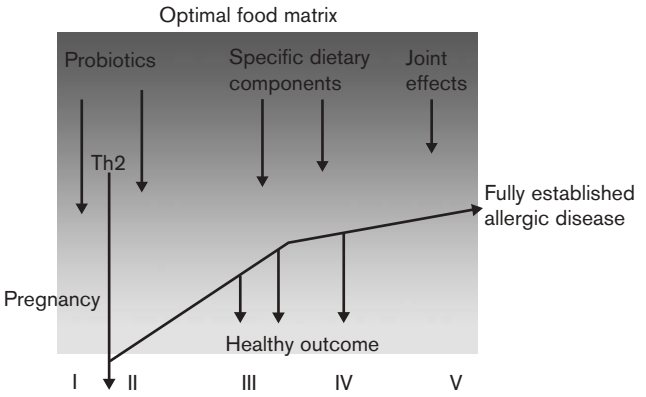
Single dietary components or joint forces?

Taken together, the possible role of fatty acids, antioxidant nutrients and probiotics in allergic disease individually appear to have beneficial effects. Current research is focusing more on active prevention schemes that identify the factors that possibly influence immunoregulatory pathways in early life. However, supplementation with single components overlooks the role of the dietary composition with a range of nutrients and other potentially active components (microbes) and also the plausible joint effects.

PUFA have been shown to affect the growth and adhesion of probiotics [63], and in our recent results, the protective effect of probiotics [64,65] appears to evolve

in joint action with the dietary intake of particular nutrients, reducing the risk of allergic disease [66]. With regard to antioxidants, the plausible protective role of vitamin A in allergic disease [66] may be that the efficacy of innate immunity requires an adequate intake of vitamin A, which strengthens the host microbe interaction previously shown to control intestinal epithelial homeostasis [67]. Furthermore, vitamin A may also alter the activation of the arachidonic acid cascade and hence suppress prostaglandin E_2 production *in vitro* [68], thus adjoining another joint effect of nutrients. The route for the first allergic responses arises from the gastrointestinal tract, and thus early modification of the diet towards a balanced intake of nutrients and taking account of interactions among nutrients and microbes may offer a tool for both prevention or management in addressing the increasing problem of allergic disease. However, one should be careful about the supplementation of nutrients as their use in high doses may not be without risks [69–71]. One explanation may arise from the compositional differences of natural and synthetic forms, as shown for vitamin E [72]. The challenge for the future lies in the identification of the components and mechanisms of action of dietary factors, and well-controlled intervention studies are required to address the potential effects of different dietary modifications and supplementation with regard to the joint effects.

Fig. 1



Induction of allergic disease. A schematic presentation of the potential targets of future research on preventive and therapeutic intervention at different stages: I Pregnancy: physiological T helper type 2 priming; intrauterine allergen exposure. II Neonatal period: neonatal T helper type 2 responses are lower in infants who develop atopic disease compared with those who remain healthy; mode of delivery, the establishment of gut microbiota and neonatal antigen exposure. III Critical window: healthy infants exhibit a decline in T helper type 2 responses during the early postnatal period, whereas a converse pattern is characteristic in infants developing atopic disease; counterregulatory mechanisms. IV Early symptoms of allergic disease: atopic eczema, food allergy; induction of tolerance, control of allergic inflammation. V Fully established allergic disease: consolidation of the immune responder type; control of allergic inflammation. Figure modified from Isolauri [73].

Conclusion

The intestinal barrier consists of physiological and immunological factors that restrict mucosal colonization by pathogens, prevent foreign antigens from penetrating the mucosa and regulate antigen-specific immune responses [51]. In food allergy, dietary antigens induce a local immunoinflammatory response that impairs the intestine's barrier function. Mucosal dysfunction leads to the aberrant absorption of intraluminal antigens and the generation of proinflammatory cytokines. Intestinal inflammation is accompanied by an imbalance of the intestinal microbiota. This leads to abrogation of the interaction maintained in health between the microbiota and the immune system, leading to perpetuation of the inflammation. The treatment of food allergy should therefore counteract the mechanisms that initiate and perpetuate intestinal inflammation and promote mechanisms that terminate immunoinflammatory responses (Fig. 1) [73]. All these aspects of the gut barrier function are potential targets for probiotic intervention. Bearing in mind the need for further evaluations, dietary modification towards a balanced dietary intake of nutrients and probiotics may offer a tool for both the management and risk reduction of allergic disease.

Conflict of interest
None declared.

Authors' contributions
The authors designed the review and are responsible for the final version of the article. Kirsi Laitinen was responsible specifically for the sections related to fatty acids and Erika Isolauri for issues on probiotics.

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