Allergic Infants: Growth and Implications while on Exclusion Diets

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Abstract

The complex nature of allergic disease exposes infants to an increased risk of nutritional inadequacies. Allergic inflammation requiring extensive dietary regimens may underlie the poor growth frequently reported. Nutritional management is directed towards the prevention of explicitly diet-related deficiencies, the mainstay of treatment of food allergy being strict avoidance of offending antigens in the diet. The advantage of elimination diets lies in silencing the specific allergic inflammation induced by the food responsible, the effect thus being antigen-specific. Concomitantly, food may also contain immunomodulatory factors, and indeed research into the management of allergic disease is evolving from passive allergen avoidance to the invention of novel dietary compounds with specific effects in alleviating the immunoinflammatory reaction and stabilizing the gut mucosal barrier. Active schemes include supplementation of nutrients, particularly fatty acids and antioxidant vitamins, and probiotics with properties influencing immunoregulatory pathways. However, the conceivable joint effects of a range of nutrients and other potentially active components in the subject's habitual diet cannot be ruled out. Prior to implementation of these concepts in management regimes or products for infants, further exploration of their effects and mechanisms, including both short- and long-term safety evaluation, is called for.

Introduction

Food allergy frequently constitutes the first manifestation of allergic disorders. Moreover, food allergy regularly accompanies atopic diseases at an early age, particularly atopic eczema. Concomitantly, however, food may contain a variety of immunomodulatory factors providing protection against allergic disease.
Food is linked to current theories explaining the increasing prevalence of atopic diseases, atopic eczema, allergic rhinoconjunctivitis and asthma over recent decades throughout the industrialized world. First, the hygiene hypothesis stating that the increase is related to reduced exposure to microbes at an early age also holds true for human nutrition. The shift in food preservation from drying and natural fermentation to industrial pasteurization and sterilization has reduced the microbial exposure associated with food intake [1]. More recently, the increase in the incidence of allergic diseases has been explained by western dietary habits. There are data suggesting that dietary lipids, especially long-chain polyunsaturated fatty acids, regulate immune function and may contribute to the development and severity of the symptoms of allergic diseases [2]. An inflammatory process results in endogenously generated oxidative stress and tissue injury, and exogenous oxidants may further exacerbate existing allergic manifestations, which underlines the importance of diet-derived antioxidant defense [3].

The basic foundation here lies in a healthy, balanced diet which follows dietary recommendations and guides healthy development and normal growth [2]. Nutritional management aims to prevent direct diet-related deficiencies, acknowledging the fact that the disease state, food allergy, may make specific requirements for energy and nutrients necessary, a deficiency in which may contribute to the deterioration of nutritional status and growth failure in children. The mainstay in the treatment of food allergy is indeed strict avoidance of offending antigens in the diet [4]. The advantage of elimination diets appears to lie in silencing the specific allergic inflammation induced by the food responsible, the effect thus being antigen-specific. Elimination diets have, however, been applied in attempts both to prevent and treat the allergic condition in early childhood. Despite the persuasive rationale of thereby reducing exposure to the most important source of antigens early in life, results have been disappointing [5]. The fact that allergies to foods of vital importance, including cow’s milk, predominate in early childhood, together with the recent demonstration of nutritional repercussions of such dietary regimens, calls for an improved understanding of the nutritional needs of the allergic child. Consequently, the management of allergic disease evolves from passive allergen avoidance to the introduction of novel dietary compounds with specific effects in alleviating the immunoinflammatory reaction and stabilizing the gut mucosal barrier (fig. 1).

**Is Allergy Manifested by Poor Growth?**

A number of studies in children have indeed shown that food allergy and atopic eczema are related to poor growth [6–10]. In addition to direct effects on height and weight, body composition, mainly muscle mass [11] and bone growth [6, 8], may be adversely affected, which is also reflected in serum
nutritional markers [7, 9]. Even though poor growth is evinced in allergy, growth failure would not appear to be a feature of allergy (atopic eczema) per se and would not be irreversible considering the adult height attained [12]. Factors related to the severity of the disease, to inflammation and to the type of dietary management may be more relevant, which possibly explains the relatively high prevalence of short stature, ranging from 2 to 15%, in allergic patients [6, 8, 11, 12].

**Link to Poor Growth: Impaired Gut Barrier Function in Allergic Disease**

Food allergy can affect several organ systems. Symptoms commonly arise from the gut, skin and respiratory tract. Clinical manifestations include acute-onset skin reactions such as urticaria, pruritus and exanthema, bowel disorders such as vomiting and diarrhea, and in the respiratory tract wheezing and
sneezing. Delayed-onset eczematous or gastrointestinal reactions such as loose stools, chronic diarrhea, malabsorption and failure to thrive are also frequently seen [13].

Patients with early onset of symptoms, manifesting during the first few months of life, compared to later onset, 6–10 months of age [9], appear to be more seriously affected and the delay in growth may be more pronounced. Further, skin more widely or severely affected by atopic dermatitis [6, 8, 10], associated asthma [6] or multiple food allergies in comparison to single food allergies [14] appear to affect the growth of patients. This may reflect allergy-related inflammation, which if sustained may result in reduced bioavailability or loss of nutrients, while metabolic requirements may be increased.

Indeed, notwithstanding the wide variation in symptoms and immune responder types, food allergy consistently affects the gut barrier, which means that dietary antigens penetrate the mucosal barrier of the intestine, and that the antigens absorbed induce an immunoinflammatory response [4]. Dietary antigens induce a local hypersensitivity reaction which impairs the barrier function of the intestine. Mucosal dysfunction may lead to aberrant absorption of intraluminal antigens. Targets in the treatment of cow’s milk allergy include elimination of the antigen responsible, alleviation of the immunoinflammatory reaction and stabilization of the gut mucosal barrier.

Elimination

Apart from alleviation of symptoms, antigen elimination preserves the barrier function of the intestine and prevents aberrant antigen absorption [as reviewed in 4]. Antigen elimination reverses the disturbance of the humoral and cell-mediated immune response, seen in a fall in serum total and specific IgE concentrations and a reduction in the proliferative response of peripheral blood mononuclear cells to the antigen. Antigen elimination improves the capacity of T lymphocyte regulation and immune elimination of dietary antigens in the gut. Uncoordinated elimination, again, may carry a risk of general nutritional inadequacy or deficiency in essential single nutrients, which for its part may even amplify the risk of sensitization. Hence the advantage of elimination diets appears to lie in silencing the specific allergic inflammation induced by the food responsible, the response being antigen-specific. The completeness of antigen elimination remains, however, questionable, as immunoreactive components of dietary protein can be detected in all substitute formulas currently available and even in breast milk. In any case therapeutic elimination diets may be potentially hazardous; recent case reports document fatal allergy as a possible consequence of a long-term elimination diet [15] and acute allergic reactions in children with atopic eczema/dermatitis syndrome after prolonged cow’s milk elimination diets [16].
Alleviation of the Inflammatory Response

The growth of allergic breastfed infants has been shown to differ from that expected for age [17]. Restoration of nutritional parameters and normal growth is achieved concomitantly with alleviation of the symptoms of allergic disease, which would imply that sustained food allergy may cause poor growth. Indeed, the target organs of allergic inflammation, the skin and the gut, are tissues with a rapid turnover even in the normal state. Persistent unnoticed inflammation in the skin or in the gut may cause ongoing nutrient loss. In an experimental animal model, active inflammation, via release of proinflammatory cytokines, has recently been shown to directly impair linear bone growth, independent of nutritional intake [4, 18].

Promotion of the Barrier

It has been shown that a positive oral food challenge reaction results in albumin secretion in the gut, increased fecal α1-antitrypsin and tumor necrosis factor-α concentrations, as well as increased intestinal permeability [4]. Data on atopic patients with multiple food allergies indicate that altered macromolecular absorption in the gut may proceed even when the patient is on an elimination diet [19]. It is conceivable, however, that persistent unnoticed intestinal inflammation in these patients could have deranged the intestinal barrier. In a like manner, differences in the neonatal gut microbiota, in particular the balance between Bifidobacterium and Clostridium microbiota, may precede the manifestation of the atopic responder type with heightened production of antigen-specific IgE antibodies, suggesting a crucial role for the balance of the indigenous intestinal bacteria in the maturation of human immunity to a nonatopic mode. The establishment of an indigenous microbiota has a particularly strong impact on the immunophysiological regulation in the gut. The importance of the immunoregulatory potential of the gut microbiota is emphasized in a recent demonstration of cross-talk between the innate and the adaptive immune systems; the nature of the initial immune response governs the homeostasis of the adaptive immune response. The gut microbiota provides maturational signals for the gut-associated lymphoid tissue, particularly for the IgA plasma cells, conferring the first line of host immunological defense. Realization of this has led to the introduction of novel modes of therapeutic intervention based on the consumption of mono- and mixed cultures of beneficial live microorganisms as probiotics.

A number of probiotics have a long history of safe use and a demonstrated safety record in human consumption, and no health concerns have been observed [20]. The numerous immunological properties of probiotics have, however, raised concern over possible effects on the growth of infants. In our 4-year follow-up study the height of children was unaffected, but there was a tendency for their weight to be lower in the group perinatally receiving probiotics [11].
Diet-Related Causes for Poor Growth

The management of food allergy by elimination diet may not be without risks, particularly in cases where the avoidance of nutritionally significant foods such as milk or cereals is necessary. Undesirably, alongside the management of documented food allergies, elimination diets are also used in attempts to control the symptoms of a wider range of allergic conditions, most often in a self-determined manner [21]. The consequences of such dieting may be severe and even manifest themselves in a failure to thrive, as demonstrated in children whose parents chose to implement elimination diets [22]. In point of fact, inadequate or unbalanced intakes of energy and particular nutrients in food allergy [7, 14, 23] and to a lesser extent in atopic eczema [11] have been demonstrated in studies analyzing dietary intake from food records. On the other hand, dietary treatment, i.e. intakes of nutrients [7], number of foods eliminated from the diet and substituted by other foods of the same group [8, 9], or type of feeding, whether breastfed or formula-fed [10], has not explained poor growth or has only marginally influenced growth impairment. Feeding practices in infancy, including breast- or formula feeding, and the age at introduction of complementary foods have been related to the risk of allergy, but their relation to growth is more intricate, which most likely reflects the lack of randomized studies owing to ethical considerations and the difficult task of relating dietary intake to growth. Generally the intake over only a few days may be analyzed, whereas disturbances in growth may manifest with delay. Clearly long-term insufficiency of intake contributes to a deterioration in nutritional status and growth failure in children. Reduced energy availability originates from three main sources: reduced food intake due to poor appetite or symptoms of the disease such as gastrointestinal complaints or poor utilization of nutrients, increased losses, e.g. due to steatorrhea, or increased requirements, e.g. due to infections [2]. On the other hand, reduced physical activity due to ill health may compensate for the increased energy requirements. Appropriate guidance and monitoring of elimination diets and nutritional status are essential to the successful management of the disease, since the regulation of food intake may result in both quantitative and qualitative changes in dietary composition with effects which extend beyond growth. The current challenge lies in evaluation of the possible effects of dietary composition not only on growth but, in a wider perspective, on immune function.

Balanced Diet for the Allergic Infant

Diet may play a more significant role in the management of allergy than traditionally assumed. The natural interest in dietary factors in relation to allergic diseases has centered on proteins, the antigens, since their
exclusion from the diet forms the basis for management of documented food allergies.

With scientific knowledge accruing the significance of the diet for the maturing immune system in early infancy to ensure normal growth and development has received increasing attention. Specific nutrients and supplemental dietary compounds with immunomodulatory properties, including lipids, antioxidants and probiotics, have been exploited in therapeutic interventions. Food may not only be a source of dietary antigens causing sensitization, but may also contain protective factors. This may be particularly important in the case of food allergies in balancing the restricted diet ensuing upon the management of the disease, i.e. elimination.

Realization of a link between dietary lipids and health dates from studies with Eskimos showing an association between the consumption of fatty fish and a low prevalence of cardiovascular diseases and asthma. Since then, the mechanisms whereby long-chain polyunsaturated fatty acids may modulate health have been extensively studied and evidence has accrued for their immunomodulatory properties [24], amenable to application in both the regulation of symptoms and reduction of the risk of allergic disease. Equally, antioxidants, including ascorbic acid, β-carotene, α-tocopherol, selenium and zinc, may counteract endogenously generated oxidative stress resulting from inflammatory processes in allergic disease [3]. In sequence, probiotics, added dietary compounds or compounds resulting from traditional food preparation methods, i.e. fermentation, exhibit a range of properties influencing health, among them their ability to avert deviant microbiota development, strengthen the immature or impaired gut barrier function and alleviate abnormal immune responsiveness [1]. Current practice focuses on active prevention schemes, including supplementation of nutrients and probiotics with properties influencing immunoregulatory pathways and thus with potential health effects. However, the diversity of nutrients and other potentially active components in the subject’s habitual diet and their conceivable joint effects may not be ruled out. A combination of dietary compounds would indeed appear to exert effects on the child’s health outcome [11]. The route for the first allergic responses arises from the gastrointestinal tract, and early modification of the diet towards a balanced intake of nutrients, with account taken of interactions amongst nutrients and microbes, may thus offer a tool for either prevention or management in addressing the increasing problem of allergic disease.

**Fatty Acids, Vitamins and Probiotics to Balance the Diet**

The most frequently reported abnormality in cell fatty acid composition in allergy, an imbalance between series n-6 and n-3 fatty acids, has been addressed in an attempt to modify the dietary lipid composition, mainly by an increase in intake of n-3 fatty acids; the expected effect was reduced production of the n-6 fatty acid-derived mediator, prostaglandin E_2 (PGE_2),
which has been linked to elevated IgE synthesis due to the induction of B cell differentiation in the presence of IL-4 [25]. A recent systematic review failed, however, to show consistent associations between consumption of n-3 polyunsaturated fatty acids, their sources being fish or fish oil supplements, and asthma [26]. Likewise, according to a meta-analysis, the severity of atopic eczema was not improved by fish oil supplementation [27]. In more controlled settings, infusion of n-3 fatty acid-based lipid emulsion for adult patients with atopic dermatitis has resulted in an improvement in symptoms [28]. The conflicting results may be explained by the different roles of fatty acids depending on the end-organ manifestations, skin or respiratory, or the types of allergy, namely atopic and nonatopic eczema [29]. Further, despite their apparent proinflammatory role, n-6 fatty acids may also contribute to an anti-inflammatory intestinal environment, as antigen stimulation up-regulates PGE$_2$ production from the n-6 fatty acid arachidonic acid, with ensuing suppression of antigen-specific T cell proliferation in gut-associated lymphoid tissue [30]. Polyunsaturated fatty acids may also exert their effects at the site of antigen introduction, since they are known to influence the integrity of the intestinal epithelium by regulating tight junction permeability [31].

Evidence for the joint action of dietary compounds comes from studies showing that polyunsaturated fatty acids affect the growth and adhesion of probiotics to the mucus and epithelial cells, thus modifying the fatty acid milieu within the intestine, the inflammatory mediators derived from them being thus readjusted by the intestinal microbiota [32]. With respect to mucosal function other nutrients, particularly glutamine, important for replication and functioning of the gastrointestinal cells, and vitamin A, may also have protective effects. In allergic disease, vitamin A has been found to inhibit IgE production in mouse peripheral blood mononuclear cells [33]. Additionally, supplementation with vitamin A in mice has resulted in depression of interferon-$\gamma$ and IL-4, the potential cytokines in allergic disease, and in an increase in mucosal IgA, with the capacity to protect mucosal surfaces [34]. Further, vitamin A may play a role in strengthening the host microbe interaction known to control intestinal epithelial homeostasis. The link between vitamins and fatty acid metabolism arises from the capacity of vitamin A to alter the activation of the arachidonic acid cascade and hence suppress PGE$_2$ production in vitro [35].

Probiotics are live microbial food supplements or components of bacteria which have been demonstrated to have beneficial effects on human health [1]. Modification of the gut microbiota by probiotics and the immunomodulatory effects of specific probiotic strains may be taken as an alternative to attain a prophylactic or therapeutic effect in allergic disease in early childhood. The effects of probiotics in allergic disease have been attributed to restoration to normal of increased intestinal permeability and unbalanced gut microecology, improvement in the intestine's immunological barrier

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functions, alleviation of the intestinal inflammatory response, and reduced generation of proinflammatory cytokines characteristic of local and systemic allergic inflammation [1]. Moreover, the potential of specific strains of the gut microbiota to contribute to the generation of T helper 1- and T helper 3-type immune responses counterregulating the T helper 2-type immune responses in atopic disease may create optimal conditions to redirect the polarized immunological memory of the newborn to a healthy balance and thereby reduce the risk of atopic disease. The objective of probiotic intervention in allergy is to control the allergic inflammatory response, before the T helper 2-type immune responsiveness to environmental antigens is consolidated and before altered structure and function develop in the target organ.

Conclusions

Infants with allergic disease are at risk of nutritional inadequacies resulting from the complex nature of the disease. Careful dietary planning and monitoring allow the growth of infants to reach their genetic potential and population reference range. Failure to thrive may result from inadequate monitoring, as the reasons for growth failure are various, mainly related to elimination diets and disease-related inflammation. The challenge for the future lies in discovering an appropriate combination of active compounds and exploring their mechanisms of action for use as dietary supplements within a balanced diet or in modifying the infant’s diet to reinforce the development of innate immunity in the infant and management of allergic disease. A novel approach in the management is offered by joining the forces of nutrients and probiotics as dietary components, i.e. active prevention management as opposed to passive elimination diets. Particularly patients with extensive disease whose growth is most seriously affected may benefit from such an approach. Prior to applying these concepts in management regimes or products for infants, further exploration of their effects and their mechanisms, including both short- and long-term safety evaluation, is of the essence.

References

**Discussion**

*Dr. Haschke:* When talking about probiotics, I think we need to know more about the strains you were using in your studies. You have very good and interesting results with certain strains. This is very important, as for probiotics, there is wide variety in breast milk, and we have little idea of what they are really doing. We are just starting to understand this. As we learned yesterday for probiotics; one strain might have a specific function in terms of prevention of allergy, another prevents diarrhea, the third helps to treat diarrhea. Can you elaborate a little on the strains you are working with?

*Dr. Laitinen:* Thank you for raising this important point. The studies done in Turku by Dr. Isolauri’s team mainly used *Lactobacillus GG*, and indeed the intervention study for prevention of allergy and investigation of the joint effects of nutrients and probiotics used *Lactobacillus GG* [1].

*Dr. Haschke:* This is the first time that you refer to a ‘system’; it is not only the probiotic strain to be added which helps, you also mention other factors in the diet. How did you determine this? Is it shown by statistical methods that these components might also have an effect? Why do you mention this now as this is relatively new, this ‘system’.

*Dr. Laitinen:* Generally in research we tend to look at single nutrients, food items or probiotics and their health effects instead of the diet as a whole. Often it is thought that supplementing with something makes everything alright, but this is not the case. Certainly the diet as a whole, compared to, e.g., single nutrients, appears to have joint or even additive properties influencing health outcome, whether it is a question of the prevention or management of allergy. By performing multivariate analyses we have been able to generate new hypotheses and now it may be the time for intervention studies to explore the matter in more detail. Certainly some studies have been done in vitro, e.g. looking at how polyunsaturated fatty acids can influence probiotics [2], and this is a good start for studies of this kind.

*Dr. Fisberg:* There is a recent editorial in the *Pediatric Allergy and Immunology* by Wjst [3] in which he made a statement about the relationship of vitamin D and allergy, especially with regard to the relationship between decreased levels of rickets and the levels of vitamin D supplementation, and the increased levels of allergy, especially asthma, in many countries. Do you have any data on this?

*Dr. Laitinen:* In our research team we have no data on this, but there is at least one Finnish epidemiological study were the association was shown between vitamin D supplementation and an increased risk of allergies in later life [4].

*Dr. Morelli:* Congratulations on your presentation because it has introduced some new aspects on the work of Dr. Isolauri about atopic dermatitis and *Lactobacillus GG*. Your data now suggest that the protective action observed against atopic dermatitis in the very large work that was published in the *Lancet* and other papers, is to be attributed not only to the feeding of *Lactobacillus GG* but also to other supplemements. So we have to presume that what was observed is not only the result of the *Lactobacillus GG* action, it is also related to the presence of other supplements.

*Dr. Laitinen:* The study did not actually involve supplements; except probiotics, we were looking at the diets that infants were habitually consuming and we didn’t
have an intervention concerning nutrients. But yes, it appears that there may be synergistic effects of different nutrients and probiotics. If you look at these vitamins on their own, e.g. vitamin A is important for the gut and zinc for growth and so on, thus there appears to be a rationale behind the effects and the interactions as well.

Dr. Seidman: Your group has pioneered studies using probiotics to prevent atopic disease in high risk infants. One study in Switzerland [5, 6] suggested that it may be interesting to intervene even in children who are not at risk for atopy. This is based on the understanding that the 30% of all infants that are at risk would be in equal number to the 70% who don’t have a parental history. What is your opinion about the general use of probiotics in all infants, whether or not at risk, for preventing atopic disease?

Dr. Laitinen: Here it is best to approach the issue by considering whether there might be any concerns related to the use of probiotics. According to our data, there doesn’t appear to be any problem in terms of growth. If the child can eat normal food, there doesn’t appear to be any concern that would prevent eating probiotics. In the literature there are only a few cases where the use of probiotics may not be advisable, these are individuals compromised by immune defense. So from the point of view that there might be benefits, why not.

Dr. Brunser: You said that intestinal microorganisms and probiotics may work together. When you say intestinal microbes, do you mean the resident microbiota or those bacteria in transit along the gastrointestinal tract? I think these are two different situations, and probably from the functional point of view they operate on the gut in completely different ways.

Dr. Laitinen: I was mainly thinking of inflammatory responses that might occur due to microbiota and how the host–microbe interaction works, what might be the inflammatory responses there, and how could probiotics influence that process.

Dr. Brunser: Tomorrow I am going to show some experimental work by Menard et al. [7] showing that, if probiotics are given, the resident microbiota exert a depressing effect on the responses of blood mononuclear cells to lipopolysaccharide stimulation, and that it is possible to establish a clear distinction between the effects of the resident microbiota and that of the probiotics. The resident microbiota is a system that operates ‘in the background’. But individuals who live in an environment contaminated by bacteria produce another type of response, what we call chronic environmental enteropathy, that apparently protects the individuals against allergic reactions because it is probably the result of stimulation of the Th1 mechanisms by the passing organisms. In Chile, which has gone through a very rapid improvement in environmental sanitation, we no longer see intense histological manifestations of chronic environmental enteropathy, but instead we are experiencing a tremendous increase in asthma and eczema, and this in a span of less than 30 years.

Dr. Laitinen: Perhaps that goes back to the original hygiene hypothesis. We certainly don’t want back the diseases we used to have, so now probiotics may be the answer for modifying intestinal microbiota and thus health promotion. Coming back to the safety issue, as far as I understand probiotics do not colonize the intestine permanently, so if you stop consuming probiotics, you stop the effects.

Dr. Domellöf: I was very intrigued by your data from the multivariate analysis. If you were to design a supplementation trial with a combined probiotic and multinutrient supplement, which components would you include?

Dr. Laitinen: I don’t think I have an answer but I would probably take the diet as a whole and not any particular nutrient. Perhaps meeting the general dietary recommendations could be a good starting point, if we were even able to change the fat composition of the diet and meet the optimal intake of the nutrients. Perhaps for an intervention I would have a cocktail of nutrients, particularly those influencing gut
integrity, glutamine and vitamin A. But there is more work to be done before there is an answer to your question.

References
