

Dietary Interventions for Primary Allergy Prevention – What Is the Evidence?

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Abstract

Allergen exposure in the early postnatal life of an infant with a genetic predisposition for allergy is regarded as at least one essential risk factor for later development of allergic diseases. The most important allergen exposure in early life derives from the early nutrition of the baby. Thus, intervention based on the concept of reducing the allergen load in the diet is one approach for primary allergy prevention in children at risk. This includes breastfeeding, allergen-reduced diet of the pregnant and lactating mother, cow milk protein hydrolysate infant formulas (= hypoallergenic infant formula or HA formulas) and time of introduction of complementary food. Data on breastfeeding regarding allergy prevention are inconsistent: preventive with regard to atopic eczema and cow milk allergy in the first 2 years, but contradictory regarding wheezing beyond the first years of life. Allergen-reduced diet of the pregnant mother is not recommended because there is no evidence for a preventive benefit, but instead for unwanted effects on the child's intrauterine development. Data on a restrictive diet during lactation are also inconsistent. If breastfeeding is insufficient in the first 4–6 months, both partially and extensively hydrolyzed formulas have been successfully used to reduce the risk for atopic eczema, but not for asthma or allergic rhinitis, until school age. However, from the available data it is suggested that the preventive potential of a formula is not only dependent on the degree of hydrolyzation and the protein source, but also from other factors like the process of manufacturing the formula. Recommendations for a certain formula should therefore be based on its proven efficacy in controlled clinical trials. For all healthy children with and without risk for allergy, more recent findings support complementary food introduction in the 5th and 6th months – independent of the kind of milk feeding – according to the nutritional needs and abilities of a baby. Delayed introduction of complementary food beyond the 6th month is no longer recommended.

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The increase of allergic diseases in the last decades to almost epidemic proportions, especially in the pediatric population, has become a paramount challenge for the research of pediatric allergologists. Several large epidemiological studies with a long-term follow-up have improved the understanding of the natural course of allergic

diseases and have helped to identify at least some risk or protecting factors which act as a player in the complex interaction between genetics and the environment. It also became obvious that an interventional approach may have a preventive effect on one allergic manifestation but not on another (asthma, eczema, allergic rhinoconjunctivitis, food allergy). There is not the one prevention measure to prevent allergic manifestation in general.

A genetic predisposition due to an allergic family history together with allergen exposure in the early postnatal period is regarded as an important combination of risk factors for later development of allergic diseases.

Genetic inheritance accounts for 20–40% dependent on the number of immediate family members affected with an allergic disease, and rises up to 80% if both parents suffer from the same allergic phenotype (asthma, allergic rhinoconjunctivitis, atopic eczema, food allergy/intolerance or allergic urticaria) [1].

In the first months of life, in which the immune system develops from a Th2-dominant situation during pregnancy to a balanced Th1/Th2 environment, the neonate and young infant may be at the highest risk for sensitization and development of allergic symptoms [2]. However, this early period of life constitutes not only a ‘window of risk’, but is at the same time a ‘window of opportunity’ for primary prevention with certain environmental measures which may have an impact on the establishment of a Th1/Th2 balance aiming at induction of immunotolerance.

Of these, dietary intervention is one approach for primary allergy prevention. It is based on the concept of feeding hypoallergenic (HA) nutrition in order to avoid exposure to intact proteins in the first 4–6 months of life.

The target population for primary prevention of allergic diseases are infants at high risk, defined as born to a family with at least one parent or biological sibling suffering from any allergic phenotype (asthma, allergic rhinoconjunctivitis, atopic eczema, food allergy, allergic urticaria), who are still free of any signs of sensitization or allergic symptoms [3].

Dietary intervention for primary prevention includes: breastfeeding, allergen-reduced diets for pregnant and lactating mothers, cow milk protein hydrolysate infant formulas, and time of introduction and diversity of complementary food.

Breastfeeding

Breastfeeding is the ideal nutritional and physiological nourishment for all infants independent of the presence of an allergy risk, and therefore recommended worldwide for the first 4–6 months of life. As the gold standard for infant nutrition it is per se not a ‘dietary intervention’ for primary allergy prevention, although compared to standard cow milk formula (CMF) breast milk is less allergenic. Its content of β -lactoglobulin is less by a factor of 10^6 [4]. However, data of breastfeeding on allergy prevention are inconsistent.

There is evidence that, compared with regular CMF, breastfeeding is preventive with regard to atopic eczema and cow milk allergy in the first 2 years, but contradictory regarding wheezing beyond the first years of life [5–8]. However, this does in general not contradict the current recommendation.

Allergen-Reduced Diet of the Pregnant and Lactating Mother

Until today there is insufficient evidence for a substantial allergy-preventive effect of maternal dietary restrictions during pregnancy. According to a Cochrane Review of four trials in 334 children, there was in contrast a risk for unwanted effects like significant lower intrauterine weight gain, a higher risk for preterm birth and lower median birth weight [9]. Similarly, this applies for maternal diet during lactation, at least in families without allergy risk. For children at risk, data are inconsistent [10]. Whether a regular diet of the mother including consumption of rather potent food allergens like egg, cow's milk, fish or nuts helps to induce oral tolerance in the baby by exposing the infant to small amounts of these allergens through transfer via the breast milk, or whether avoidance of such food reduces the risk for sensitization and the development of atopic eczema, remains speculative.

Cow Milk Protein Hydrolysate Infant Formulas

Cow milk protein hydrolysate infant formulas, also known as HA infant formulas, are recommended as a substitute or supplement to breastfeeding if necessary, in the first 4–6 months of life in children at risk for allergy. Based on the protein source they are differentiated into whey (W) or casein (C) hydrolysates and – dependent on the degree of hydrolyzation by different physicochemical processes – in partially and extensively hydrolyzed infant formulas (pHF and eHF, respectively). The molecular weight of peptides in eHF formulas is in more than 90% <3 kDa, and in a partially hydrolyzed whey formula 3–10 kDa. HA formulas are characterized by a reduced antigenicity of the protein targeting to prevent an immunological mediated allergic reaction and to induce oral tolerance to foods, a criterion that is fulfilled by both eHF and pHF. While eHFs were primarily intended for treatment of existing cow milk protein allergy, they are today also successfully used for primary prevention. In contrast, due to their comparatively higher antigenicity, pHFs are only intended to be used for primary prevention, but not for treatment of food allergy. In 2000 the 'Committee of Nutrition' of the American Academy of Pediatrics developed criteria for the definition of a HA formula to be labeled a formula for treatment or prevention [11].

Evidence for a Primary Allergy-Preventive Effect of Hypoallergenic Infant Formulas

In a systematic review of the role of hydrolyzed infant formulas on allergy prevention, the studies are divided into those including eHF and those including pHF [12]. Both types of formula have been studied in comparison to breast milk and/or regular CMF, and almost all are performed in infants at risk [12]. eHF and pHF have been directly compared in only three studies [13–15].

Problems for Comparison of Studies

One of the problems with all intervention studies using either type of formula is that they are difficult to compare due to several methodological differences. Most of the intervention studies have included only children at risk, however the definition of risk varies between mono- and biparental family history which influences the risk calculation for the children. There are several variations between the studies in design, including randomization and blinding of the formulas and investigators. There are studies without blinding of the formulas at all, and only two studies are double-blinded [13, 15]. In case of a comparison of a formula and breast milk, neither blinding nor randomization is possible and justifiable for ethical reasons. Further differences include size, time of first exposure to and duration of feeding with the study formula, recommendations for time of introduction and kind of solid foods, definition of end-points and kind of diagnostic tools (e.g. double-blind placebo-controlled food challenge, lung function, etc.). It is also important to consider whether and how a study was funded.

Most of the studies were designed as only dietary intervention studies, however some are multifaceted studies using also environmental prevention measures [16–18]. These studies are not included because it may not be possible to disentangle the single effects.

Primary Allergy Prevention – Evidence for eHF

The short- and long-term allergy-preventive potential of intervention with eHF has been evaluated in nine prospective controlled peer-reviewed trials compared to breast milk, regular CMF, soy formula and/or pHF [12]. The most frequently studied eHF is Nutramigen, an extensively hydrolyzed casein infant formula. Extensively hydrolyzed whey formulas were in addition to Nutramigen used in two studies, namely Prophylac in a Danish study [14] and Nutrilon Pepti as HIPP HA in the German Infant Nutritional Intervention (GINI) study [15]. Summarizing the results with eHF-C (Nutramigen) and the eHF-W Prophylac fed exclusively or as supplement to breastfeeding shows that there is a preventive effect on the prevalence and cumulative incidence on allergic manifestation in the first 3 years that is mainly driven by the effect on atopic eczema [14, 19] and food allergy [20]. In the GINI study with the longest follow-up until the age of 10 years, a significant reduction of the prevalence at age 7–10 in the per-protocol analysis and on the cumulative incidence of atopic eczema until 10 years

in per-protocol and intention-to treat analysis could be observed [21]. In contrast, the effect of the eHF-W in the GINI study was at all time points of measurement (1, 3, 6, and 10 years) weaker, reaching a transient significance only once at 6 years in the per-protocol analysis [15, 19, 21, 22]. Until 10 years, no significant effect on asthma or allergic rhinoconjunctivitis could be observed with either formula [19, 21, 22].

In the Danish study, a similar significant preventive effect of eHF-C and eHF-W was found [14]. Taking this and the finding in the GINI study together (with quite unequal effects of eHF-C and eHF-W) it becomes clear that the potential of a formula for reducing the risk of allergy is not only dependent on the extensive hydrolysis or the protein source, but also on other factors like the procedure of hydrolysis.

Primary Allergy Prevention – Evidence for pHF

A pHF for prevention of allergy was first introduced in 1985. As the first one, most of the currently available pHFs are 100% whey hydrolysates (pHF-W). As eHFs they are characterized by a reduced antigenicity and are supposed to actively induce oral tolerance. They are intended for allergy prevention, but explicitly not for treatment of food allergy [11].

The short- and long-term effects on primary prevention of pHF-W have been studied in 12 prospective controlled birth cohort trials. In most of the studies the 100% pHF Beba-HA (= NAN-HA) was used. The limitations for comparison between the studies are the same as for eHF. Summarizing the effect of all available studies with pHF-W, they all show an effect of various degrees on atopic manifestation, even if not always significant. In a recent meta-analysis, Szajewska and Horvath [23] have chosen the three studies with the highest quality (out of 15 trials from 12 study populations) and found a 52% risk reduction of atopic eczema at 1 year and 38% at 3 years. The first result could be confirmed in another meta-analysis by Alexander and Cabana [24], who calculated a 55% reduction of eczema when they analyzed the 4 best out of 18 publications representing 12 populations.

Comparison of eHF and pHF

The direct comparison of eHF and pHF in the studies by Oldaeus et al. [13] and Halken et al. [14] revealed a marginally significant superior preventive effect on atopic eczema, food allergy and cow milk allergy in infancy for eHF (in both cases eHF-C) [25, 26]. However, in the GINI study no significant difference between the preventive effect on atopic eczema of eHF-C and pHF-W was observed. The meta-analysis by Szajewska and Horvath [23], which included the results of the three studies, did not see a significant difference between the two groups at any time until 3 years [23].

The German Infant Nutritional Intervention Study

The GINI study is the world's largest with the longest follow-up until 10 years in the field of primary allergy prevention with cow milk protein hydrolysate infant formula [21]. The study was funded for 3 years by grants from the Federal Ministry for Educa-

tion, Science, Research and Technology (Grant No. 01 EE 9401-4). Between 1995 and 1998, 2,252 neonates with a positive family history for allergy were recruited at birth and randomly assigned to receive one of four blinded formulas as supplement to breastfeeding in the first 4 months of life if necessary: partial (pHF-W, Beba-HA) or extensive whey hydrolysate (eHF-W, Nutrilon Pepti, at the time of intervention as HIPP HA on the German market), extensive casein hydrolysate (eHF-C, Nutramigen), or standard CMF [15]. The most important results of this study are summarized as follows:

Compared to standard CMF, the eHF-C and the partial 100% whey hydrolysate, but not the extensive hydrolyzed whey formula, have a long-lasting preventive effect on the cumulative incidence of atopic eczema. The significant risk reduction until 10 years is influenced by the effect that developed in the first year, and persisted into school age without a rebound phenomenon. None of the formulas demonstrated any significant effect on asthma or allergic rhinitis [15, 19, 21, 22]. At 10 years there was no difference in sensitization between the four study groups [21].

The long-term follow-up of the study also allowed to investigate the development of growth. Except for the period 4–48 weeks of life in which children from the eHF-C showed a transient lower development of BMI due to lower weight gain, there was no significant difference between the three hydrolysate groups, neither compared to the standard cow-milk formula group nor to the exclusively breast-fed children until 10 years [27].

Time of Introduction and Diversity of Complementary Food

Findings of several epidemiologic and clinical studies of the last years do not support the former recommendation, neither to delay complementary food introduction in children at risk to the second half of the first years of life, nor to delay introduction of foods with high allergenic potential (like eggs and fish) to after 12 months or later. Instead, based on the more recent observations it is now recommended to introduce solid foods in the 5th and 6th months according to the nutritional needs and abilities of a baby, independent of the kind of milk feeding (breast or formula). This applies to healthy children without but also with a hereditary risk of allergy, as long as they are free of allergic symptoms [28–30].

Conclusion

Dietary intervention is one approach for primary allergy prevention in children at risk for allergic diseases due to a positive family history for allergy. Data regarding allergy prevention are inconsistent for breastfeeding. An allergen-reduced diet of the preg-

nant mother has not shown beneficial effects, but instead unwanted effects on the intrauterine development. There is also no consistent beneficial evidence of allergen-reduced diet during lactation. If breastfeeding is insufficient in the first 4–6 months of life, cow milk protein hydrolysate infant formulas are an appropriate alternative to breastfeeding. In children at risk for allergy, both pHFs and eHFs are effective in reducing the risk for atopic eczema, but not for asthma and allergic rhinitis, until school age. However, it has been shown that the potential for allergy prevention is not only dependent on the degree of hydrolysis or the protein source. Therefore, the efficacy of each single hydrolyzed formula should be separately proven. For all healthy children more recent findings support complementary food introduction in the 5th and 6th months independent of the kind of milk feeding (breast or formula) according to the nutritional needs and abilities of a baby. A delay beyond the 6th month is no longer recommended.

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