

PRO AND CON

The role of hydrolysates for allergy prevention – pro

DOI:10.1111/pai.12180

Allergen exposure in the first months of life is regarded as one main risk factor for the development of allergic diseases, in particular in infants with at least one first-degree relative – parent or sibling – with a history of allergy (high-risk infant).

The main early allergen contact for the infant derives from food allergens, mainly cow milk allergen. If for high-risk children breastfeeding is not sufficiently feasible in the first 4–6 months of life, a cow milk protein hydrolysate is the recommended supplement to avoid the early exposure to intact milk allergen (1–4).

Hydrolysates (synonyma: cow milk protein hydrolysate formula, hypoallergenic formula, HA formula) are formulas processed by different techniques to reduce the antigenicity of the intact milk protein. Dependent on the degree of hydrolysis and the protein source whey (W) or casein (C), they are classified in partial (pHF) or extensive (eHF) hydrolysates (5).

eHFs, primarily intended for treatment of cow milk allergy (CMA), have later been used also for primary allergy prevention. pHFs were *a priori* made for allergy prevention only.

eHFs are characterized by >90% of peptides with a molecular weight <1.5 kDa with almost no antigenicity, while pHFs have a higher residual antigenicity that is supposed to actively induce immune tolerance. From the available clinical data, however, there is nowadays reason to believe that the mechanism of action of eHF is similarly active induction of immune tolerance rather than simply avoidance of antigen contact.

Hydrolysates in primary prevention – clinical experience

After more than 25 yr of clinical experience with hydrolysates, there is evidence that eHF as well as pHF has the potential for primary prevention in high-risk children (6–10). Several meta-analyses and systematic reviews on the allergy preventive potential of hydrolysates have investigated the role of eHF and pHF separately (11–14). Due to methodologic differences and possible biases, a direct comparison between the studies and their outcome is difficult (12).

Evidence for eHF

Extensively hydrolysed formulas based on casein (eHF-C, Nutramigen) or whey (eHF-W, Profylac, Nutrilon Pepti, HIPP HA) have been used in several prospective controlled peer-reviewed trials (12).

Taking together, the results observed with eHF-C (Nutramigen) and the eHF-W Profylac fed exclusively or as supplement to breastfeeding clearly shows a reduced prevalence and cumulative incidence in the first 3 yr mainly on atopic eczema (15) and food allergy (7).

Evidence for pHF

Many more studies have been conducted with pHF than with eHF. As for the studies on eHFs, a direct comparison is difficult due to methodologic differences. For the most frequently used partially hydrolysed 100% whey hydrolysate Beba HA (=NAN-HA), two recent meta-analyses based on the qualitatively best 33 (13) and 44 (14), out of 18 studies in high-risk infants confirmed a significant, more than 50% reduction of atopic eczema at 12 months and 38% at 3 yr of age compared with regular cow milk formula (CMF).

Few studies used eHF and pHF simultaneously. Even though there are also differences between them, these studies nevertheless allow to directly compare the efficacy of the formulas. Three studies used dietary intervention programs with hydrolysates with or without additional dietary recommendations for the breastfeeding mother and the baby (8–10). Other trials combined nutritional and environmental prevention measures like reduction in house dust mite allergen exposure (16, 17).

The GINI study

The German Infant Nutritional Intervention program (GINI) is the largest prospective, double-blind randomized controlled trial with the longest follow-up to investigate the effect of three different hydrolysates compared with CMF for the prevention of allergic manifestations. GINI has not only provided an important part of data for the systematic reviews/meta-analyses and recommendations, but also more differentiated insight in the effectiveness of hydrolysates for allergy prevention (10, 15, 18, 19).

Shortly, between 1995 and 1998, 2252 infants with a heredity risk for atopy were allocated at birth by a computer-generated list to receive one of three hydrolysed formulas (*pHF-W, **eHF-W, ***eHF-C) or standard ****CMF as only milk substitute in the first 4 months of life in case breastfeeding was insufficient or discontinued (10).

Solid foods should not be introduced before the end of the fourth month, otherwise no dietary recommendations were given for the children or for the lactating mothers (10).

The children were followed for the first 3 yr by structured interviews at regular intervals at 1, 4, 8, 12, and 36 months of age, additionally by annual ISAAC-modified questionnaires to the parents at 1, 2, 3, 4, 6, and 10 yr, and by physical examinations with blood sampling at 4, 12, 36 months and at 6 and 10 yr (10, 15, 18, 19).

*Beba-HA, Nestlé, **HIPP-HA, HIPP (at that time identical with Nutrilon Pepti, Numico), ***Nutramigen, Mead Johnson, ****Nutrilon Premium, Numico.

GINIplus study

The GINI intervention study was from the beginning part of the population-based GINIplus study (German Infant Nutrition Intervention plus environmental and genetic influences on allergy development, N = 5991), which combined the intervention part in high-risk children (N = 2252) with an observational non-intervention part in children without allergy risk (N = 2,507) and children at high-risk whose parents did not agree to participate in the intervention trial (N = 1,232). The instruments to follow the non-intervention part included the annual ISAAC-modified questionnaires to the parents at 1, 2, 3, 4, 6, and 10 yr and physical examinations and blood sampling at 6 and 10 yr (20).

Hydrolysates in the GINI intervention study:

Short- and long-term effect on eczema

Only few studies were able to follow children who participated in an intervention program for allergy prevention into school age. The children of the GINI study could be followed until 10 yr, children from the Isle of Wight study are followed now until adolescence (21). Because in the latter a combined intervention program of dietary and environmental avoidance measures was implemented, it may not be possible to disentangle the respective effects. Therefore, data from the GINI study may be even more meaningful to assess the sole effect of the hydrolysates.

From an older Swedish study in high-risk infants, it was concluded that beginning with feeding hydrolysates after 6 months of age has no clear benefit against the control group at 18 months (22). More previous studies suggested that the 'window of opportunity' for hydrolysed formulas to exert their preventive efficacy is the first year of life (7) or probably even the first 4–6 months (6). This was confirmed in the GINI study. Atopic eczema (AD) was significantly reduced at 12 months in children who received eHF-C or pHF-W compared with the CMF group (10). This effect was carried on until 6 yr, when the prevalence and cumulative incidence of AD in the two groups were still significantly reduced in the intention-to-treat (ITT) and per-protocol analysis (PP) (15, 18). Significant effects on allergic manifestation (AM) (defined as the sum of AD, food allergy with manifestation at the gastrointestinal tract, allergic urticaria, and from 3 yr onwards also asthma and allergic rhinitis) in the eHF-C and pHF-W group until 6 yr were mainly driven by the effect on AD (15, 18).

The differentiation of AD in early onset (first 2 yr), late onset (3–6 yr), and persistent eczema (present in both periods) revealed that in particular the persistent type had benefited most from the preventive activity of the formulas eHF-C and pHF-W (20). Another important observation at 3 yr was the fact that not only mild and moderate eczema was prevented, as was often argued by critics of hydrolysate formulas (23). Severe

AD, defined as SCORAD score >21.5, was reduced by 52% and 39% in the eHF-C and pHF-W group, respectively (19). Given the high incidence of severe AD (3.7% in the first year, 7% until 3 yr), this finding is of great importance for the quality of life of the child and his family.

At 10 yr, the cumulative incidence from birth to 10 yr of AD was still significantly reduced in the formula groups eHF-C and pHF-W. Their effect was stronger if the family history is positive for AD. The period prevalence between 7 and 10 yr, however, was only significantly reduced in the eHF-C group in the PP analysis, but not in the pHF-W group. From these results, it is concluded that the significant effect on the cumulative incidence is mainly driven by the early preventive effect of the formulas in the first 6 yr, which, however, is not compensated by a rebound effect until 10 yr (19, 24).

Hydrolysates in the GINIplus study:

Of interest is the comparison between children from the GINI intervention study, who received the randomized study formula, and children from the non-intervention part with or without risk, who also needed supplementation in the first 4 months with any formula chosen by the mother herself. In the non-intervention part, it could be shown that the incidence for AD is twice as high in children with high-risk compared to those without (hazard ratio HR 2.1 (95% confidence interval CI 1.6–2.7)). However, if the incidence of AD in the three hydrolysate groups from the intervention study was compared against children from the non-intervention part without risk, then the difference was considerably reduced [eHF-C: HR 1.3 (95% CI 0.9–1.9), pHF-W: HR 1.6 (95% CI 1.2–2.3), eHF-W: HR 1.9 (95% CI 1.4–2.6)], but increased in those who were in the CMF group [HR 2.6 (95% CI 2.0–3.5)] (20). This observation is important for the clinical use, because it seems that the familial risk for the development of AD can be considerably compensated by early supplementation with certain hydrolysates, but worsened with CMF.

Comparison between formulas

Data of the GINI study have shown that different products classified as eHF are not necessarily equally effective. The eHF-W had a much weaker effect than eHF-C (10, 15). This is in contrast to the Danish study by Halcken, where the two eHFs, the eHF-C (Nutramigen), and the eHF-W (Profylac) demonstrated an allergy preventive potential of the same extent (9). The fact that the eHF-W in GINI performed even less than pHF-W suggests that neither the extent of hydrolysis nor the protein source alone is responsible for the preventive efficiency of a formula and that the effect of a formula cannot be predicted, unless the formula has demonstrated its potential to prevent allergy in a controlled clinical trial.

Biologic mechanism of hydrolysates

An argument against the use of hydrolysates for allergy prevention derives from the fact that the biologic mechanism is not understood (23). What we learned from the available data

and in particular from the GINI study is that, intervention by the oral route with certain hydrolysates has a strong effect on AD, but not on the respiratory allergic manifestations asthma and allergic rhinitis, nor on sensitization at 10 years (19). Whether it is a certain extend of avoidance or the effect of the modifying process itself which induces an immunologic response to prevent AD is not known. However, it seems unlikely, that the mechanism of action of hydrolysates for the prevention of AD is (only) avoidance of intact CM protein in order to prevent sensitization (24). Other unknown factors may also contribute to the effect. In contrast to national and international recommendations to use certain hydrolysates for the primary prevention of AD (2, 3), early exposure to intact proteins in order to induce oral tolerance have been recently promoted (25, 26). However, there is up to now no evidence to contradict the presented findings, nor change the current recommendations (27).

Nutritional adequacy

Nutritional adequacy is the precondition for the use of hydrolysate formulas. Rzehak in his paper on the development of BMI in the GINI participants from 0 to 10 yr could show that there is no difference until 10 yr between the three hydrolysate groups, CMF group and the exclusively breastfed group. The only exception pointed to a transient reduction in weight gain in the eHF-C group between week 4 and 48 (28). Whether this finding has any impact on later life remains a question for further analyses.

Health economy

The calculation of the number needed to treat (NNT) to prevent one case of AD was always in favor of eHF-C. At 10 yr, the NNT for the three formulas at 10 yr for pHF-W, eHF-W, and eHF-C was 11, 12, and 7, respectively, in the PP population, and 19, 18, and 9 in the ITT population (19). Considering health economy, the higher cost of hydrolysates, in particular of eHF-C, is an important issue. A cost-effectiveness evaluation based on data of the 6 yr follow-up of the GINI study came to the conclusion that the two formulas eHF-C and pHF-W can be cost-effective or even

cost-saving for the prevention of AD, while the effect of the eHF-W was dominated by the other two (29).

Conclusion

Data from previous and the GINI study have demonstrated strong evidence that hydrolysates play a role for the prevention of AD, but not of asthma, allergic rhinoconjunctivitis, nor of sensitization at school age. Consequently, national and international pediatric societies have implemented the use of hydrolysates for the prevention of AD in their recommendations for children at risk. In their Guidelines for Healthcare Professionals, the American Academy of Allergy Asthma & Immunology (AAAAI) recently stated: 'Partially hydrolysed whey formulas and extensively hydrolysed casein formulas have a preventive effect on atopic dermatitis and cow's milk protein allergy when used instead of intact cow's milk protein formula' (30).

The question remains, when and to whom to give which hydrolysate? First of all, the recommendation should be restricted to hydrolysates with proven efficacy. Until today, the use of hydrolysates for prevention is only recommended for high-risk children in the first 4 to 6 months of life. No studies exist which show a preventive effect in non-risk children.

Which hydrolysate? eHF-or pHF? Both types of formula have been shown efficacious on the cumulative incidence of AD until 10 yr. Their effect is stronger if the family history is positive for AD. The eHF-C showed generally a slightly more protective activity than pHF-W, but the taste and thus the acceptance by the baby and the price are in favor for pHF-W. The indication needs to be carefully chosen, because pHFs are not indicated for children with existing cow milk allergy.

Finally, on the basis of the presented data, there is a clear indication for primary prevention with certain cow milk protein hydrolysate formulas in children with a family history for allergic diseases, in particular AD, who cannot exclusive breastfeed in the first 4–6 months of life.

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