



ARTICLE REVIEW

Partially hydrolyzed whey protein: A review of current evidence, implementation, and further directions

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Abstract

Background: Human milk is known to be the best nutrition for infants as it provides many health benefits. For non-breastfed infants, cow's milk based infant formula is the most optimal option to provide the needed nutrition. However, approximately 2-5% of all formula-fed infants experience cow's milk allergy during their first year of life. Partially hydrolyzed whey formula (pHF-W) have been widely recommended to prevent the development of allergic disease in infants. However, according to epidemiological data, approximately half of the infants developing allergy are not part of the at-risk group.

Objectives and Methods: This article aims to review the effects of pHF-W in preventing allergy, especially atopic disease, in all non-breastfed infants, as well as the safety aspect of pHF-W if used as routine formula. The role of pHF-W in the management of functional gastro-intestinal (GI) disorders is also reviewed.

Results: Several clinical studies showed that pHF-W decrease the number of infants with eczema. The strongest evidence is provided by the 15-year follow up of the German Infant Nutritional Intervention study which showed reduction in the cumulative incidence of eczema and allergic rhinitis in pHF-W (OR 0.75, 95% CI 0.59-0.96 for eczema; OR 0.67, 95% CI 0.47-0.95 for allergic rhinitis) and casein extensively hydrolysed formula group (OR 0.60, 95% CI 0.46-0.77 for eczema; OR 0.59, 95% CI 0.41-0.84 for allergic rhinitis), compared to CMF as a control, after 15 years of follow-up. pHF-W was also found to be beneficial in the management of functional GI disorders such as regurgitation, constipation and colic.

Conclusions: The use of pHF-W in allergic infants has been recommended in various guidelines across the countries, as a primary prevention of allergic disease. One pHF-W has been approved by the US FDA and the European Commission's European Food Safety Authority (EFSA) for its safety and suitability as a routine infant formula for all healthy infants. According to the data obtained in the management of functional GI disorders, pHF-W is better tolerated than formula with intact protein. Further studies assessing the effect of routine use of pHF-W in a larger population of non-breastfed infants should also be conducted, in order to observe any potential harm and to determine the benefit and cost-effectiveness ratio.

Keywords allergy, breast feeding, formula, functional gastrointestinal disorder, infant, partial hydrolysate, whey

Introduction

Human breast milk is known to be the best nutrition for infants. Breast milk is found to provide protection for the children against infection and malocclusion, as well as improve the intelligence. Growing evidence also suggests that breastfeeding

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might protect against overweight and diabetes later in life.¹

Nevertheless, due to various circumstances, a large proportion of infants cannot receive human milk.^{1,2} Globally, only 38% of the infants are found to be exclusively breastfed.² For nonbreastfed infants, infant formula is the most optimal option to provide the needed nutrition. Infant formula is usually prepared from industrially modified cow's milk and processed to adjust the nutritional content according to the needs of infants. However, as cow's milk proteins constitute the most common food allergens in infants, cow's milk formula is one of the most frequent causes of food allergy in infants.^{3,4}

Approximately 2-5% of all formula-fed infants experience cow's milk allergy during their first year of life.^{5,6} Cow's milk allergy (CMA) is often associated with manifestations in various organ systems, such as gastrointestinal, respiratory tract, and skin. CMA may cause failure to thrive and even sometimes cause life-threatening anaphylactic reactions.^{5,7} In order to reduce the allergenic potential, cow's milk protein in the infant formulas can be modified by hydrolyzation processes to reduce the size of the peptides, and therefore could induce tolerance without sensitization.^{3,4}

Hydrolyzed formulas (HF), according to clinical studies, may give beneficial effects in reducing the risk of several allergic diseases, especially infants born in families with atopic disease (high-risk infants). Several reports have recommended the use of HF for the at-risk infants.⁸⁻¹⁰ Of all HFs available, the partially hydrolyzed whey formula (pHF-W) have been widely recommended to prevent the development of allergies in infants.¹³⁻¹⁶ However, according to epidemiological data, approximately half of the infants developing allergy are not part of the at-risk group. This is because the number of infants in the non-at-risk group is significantly larger than that in the at-risk group.¹¹ The infants in non-at-risk group have approximately 15% risk of developing allergies.¹²

Therefore, this article aims to evaluate and review the effects of pHF-W in preventing allergies, especially atopic diseases, in all non-breastfed infants, both the high-risk and non-at-risk infants, as well as the safety aspect of pHF-W to be used as a routine formula.

Partially hydrolyzed whey formula (pHF-W)

Milk proteins consist of two fractions: casein and whey. Casein is the coagulum portion of milk, which becomes clots or curds inside the stomach. It contains the larger and more complex protein molecules, which are harder to digest. Casein protein also contains more allergenic proteins, which are responsible for the majority of milk allergies. On the other hand, whey is the liquid portion of milk, which makes it easier to digest. It also contains less allergenic proteins. From this standpoint, the casein protein is considered to be more likely to trigger allergies or general indigestion than the whey protein.^{2,17}

The composition of casein and whey in cow's milk is different from that in human breast milk. Cow's milk protein is 77% casein and 23% whey, meanwhile breast milk protein is approximately 30% casein and 70% whey, even though the casein/whey ratio in breast milk may fluctuate between 70/30 and 80/20 in early lactation and decrease to 50/50 in late lactation.² Other than that, the whey and casein proteins in cow's milk and breast milk might also differ in fraction number, amino acid composition, as well as the peptide mappings. Therefore, raw cow's milk must be processed and modified to resemble the human breast milk composition before it is considered safe for infant consumption.²

Hydrolyzed formulas (HFs) are typically derived from cow's milk proteins, either whey or casein, which have undergone several procedures to breakdown these natural proteins into lower molecular-weight peptides. These protein modification procedures may include heating, ultra-filtration, and enzymatic cleavage. Depending on the degree of hydrolysis and modification, the hydrolyzed cow's milk formulas can be differentiated into partially hydrolyzed formula (pHF), of which the molecular weight is 3-10 kDa, and extensively hydrolyzed formulas (eHF), of which the molecular weight is <3 kDa. Compared to the nonhydrolyzed (intact) formula with the molecular weight of 14-68 kDa, hydrolyzed formula have lower molecular weight peptides, which are thought to induce oral tolerance without causing sensitization. Thus, hydrolyzed formula is thought to reduce the risk of allergic disease

compared to the intact formula.^{3,4}

The allergy-preventing property of hydrolyzed formula, however, seems to not only depend on the degree of hydrolysis but also on the method of hydrolysis, as well as other factors. The qualitative changes of the peptides due to the hydrolysis process may also affect the potential benefit of the formula. There are at least three factors affecting the allergy-preventing effect of a hydrolyzed formula, which are the protein source (whey and casein), method of hydrolysis (temperature, pH, and the type of enzyme used), and the degree of hydrolysis.

Due to these reasons, it is safe to say that every HF is different and might even have contradictory characteristics from one to another, even with the same degree of hydrolysis. Nutten et al also confirms this statement. They studied the physicochemical profile of 76 commercially available whey- and casein-based eHF (eHF-W and eHF-C) products and found significant variability in the molecular weight profile of the peptides, amino acid components, as well as the allergenicity of the products, which would eventually affect the effectiveness of each product in preventing allergies.¹⁸ Researches studying the effect of HFs should, therefore, evaluate every HFs individually. Pooling together various hydrolysates (HFs) would be inappropriate, as it may cause bias and the results could not represent any of the individual HFs.^{3,4}

Partially hydrolyzed whey formula (pHF-W) is one of the partially hydrolyzed formulas composed of 100% whey protein. pHF-W has been demonstrated to result in positive effects on preventing the development of allergies, particularly atopic dermatitis, in infants.¹³⁻¹⁶ As yet, only one routine infant pHF-W has been granted a qualified health claim by the U.S. Food and Drug Administration for risk reduction of atopic dermatitis.^{4,19} The following sections discuss the current evidences found regarding the effect of pHF-W in preventing atopic disease, as well as the possibility of pHF-W to be used as a routine formula.

pHF-W and prevention of atopic disease

Atopic diseases are a group of diseases caused by an exaggerated IgE immune response to otherwise

harmless allergens.²⁰ Pediatric atopic disease may include atopic dermatitis (eczema), asthma, allergic rhinitis, as well as food allergy. International Study of Asthma and Allergies in Childhood (ISAAC) reported a significant increase in the worldwide prevalence of pediatric atopic diseases in both developed and developing countries. Approximately 8% of children aged less than 3 years are affected by food allergy, meanwhile the prevalence of children with eczema is estimated to be as high as 30%.^{21,22} In general, the development of allergy is influenced by several factors, which are the genetic predisposition, allergen exposure (including time, dose, frequency of exposure, processing and consumption of food proteins such as hydrolysate, gastro-intestinal microbiome, LCPUFAs), and other contributing factors (such as cesarean section at birth, early exposure to antibiotics, seasonal variations, pollution, passive smoking, industrialization, pets at home, infections, lifestyle, and vitamin D). In order to prevent the development of allergic disease, current guidelines recommend several preventive measures, which include no maternal food restriction during pregnancy and lactation, exclusive breastfeeding for the first 4-6 months of life of the infants, timing of introduction of the complementary foods, and also the use of HFs with demonstrated efficacy when breastfeeding is not possible.⁹

The partially hydrolyzed whey formula (pHF-W) has been observed clinically to decrease the number of infants with eczema. Several studies have assessed the effectiveness of initial exposure to pHF-W to reduce the risk of eczema. Two different meta-analyses published in 2010 showed that healthy infants with a family history of allergies who are fed with pHF-W have a lower risk of atopic dermatitis compared to babies who are fed the intact cow's milk protein formula (CMF). Subanalysis conducted in the meta-analyses showed that the risk reduction of eczema was approximately 52 and 55%, respectively, at the age of 12 months, and approximately 38 and 36%, respectively, at that age of >30 months.^{3,23,24}

Baumgartner reported that the number of infants who developed atopic symptoms if fed a pHF-W was only 25% of those fed CMF (OR 0.25, 95% CI 0.18-0.36).²⁴ The analysis also showed that the effect of pHF-W in reducing the allergic

manifestations is equivalent to breast milk, especially for long-term prevention.²⁵ A literature review of 8 clinical trials also confirmed that pHF-W supports normal growth in infants, and showed that the risk of atopic dermatitis in infants who are not fully breastfed in the general population also decreases after administration of specific pHF-W, compared to CMF, in the first 4-6 months of life.²⁶

The strongest evidence is provided by the 15-year follow up of the German Infant Nutritional Intervention (GINI) study, which studied the effect of pHF-W, eHF-W, and eHF-C in 2,252 participants, compared to CMF as the control, in reducing the cumulative incidence and prevalence of pediatric allergic diseases. The result showed that there was reduction in the cumulative incidence of eczema and allergic rhinitis in pHF-W (OR 0.75, 95% CI 0.59-0.96 for eczema; OR 0.67, 95% CI 0.47-0.95 for allergic rhinitis) and eHF-C groups (OR 0.60, 95% CI 0.46-0.77 for eczema; OR 0.59, 95% CI 0.41-0.84 for allergic rhinitis), compared to CMF as a control, after 15 years of follow-up.²⁷

While the above studies showed positive effect of pHF-W for preventing allergies, several other studies showed contradictory results with other HFs. Several issues and weaknesses, however, are found in the methodology of each study that needs to be taken into account.^{13,28-30} The common issue is that these meta-analysis pool together different types of pHF from multiple manufacturers, which would give rise to different characteristics of the resulting peptides. Hence, the results of these studies might not be useful, as the collective results could not represent any of the protein hydrolysate.^{3,4}

Systematic review and meta-analysis by Boyle found no consistent evidence that both pHF, not only limited to pHF-W, and eHF can reduce the risk of allergies or autoimmune outcomes in babies with a high risk of allergies. This might be due to the inclusion criteria of this study, which included multiple interventions and retrospective cohort studies, excluded 7 pHF interventional studies, as well as the unusual segmentation of age (0-4 years, compared to other meta-analyses in which the segmentations were at 0-1 year).²⁸

A randomized-controlled trial (RCT) by Boyle analyzed the use of pHF and prebiotic supplementation, compared to standard formulas, in preventing eczema in high-risk infants. The results

showed that there was no difference in incident of eczema between the intervention of pHF+prebiotic and standard formula in high-risk infants within 12 months of follow-up. This might be due to the methodology, such as the use of different pHF and the randomization process which was performed at the age of <1 month (not at birth), which could lead to biased results.²⁹

A Cochrane meta-analysis by Osborn also stated that there is no evidence that pHF provides positive effect in preventing allergies, compared to exclusive breastfeeding. However, the analysis of the studies performed in preterm and term infants were combined. Other than that, the study also analyzed different types of pHFs, which could cause the findings of this meta-analysis to be considered invalid, as different pHFs might exhibit different effect on preventing allergies.³⁰

The RCT by Lowe et al¹³ also revealed that pHF-W could not reduce the risk of allergic manifestations, compared to standard formulas. However, some weaknesses were also found in the methodology of the study as; the end point was conducted by telephone interview, only 50% of infants received formula at 4 months of age, 16.5% never received the allocated formula, and that the study was single blind.

pHF-W for all non-breastfed infants: safety aspects

The use of pHF, including pHF-W, in allergic infants has been recommended in various guidelines across the countries, as a primary prevention of allergic disease, mainly atopic dermatitis, in high-risk infants.⁸⁻¹⁰ However, the compliance rates for these guidelines are relatively low. The Pouessel et al³¹ study in 2006 revealed that there are still around 50% of children born with genetic risk not given hydrolyzed formulas, including pHF-W, as a form of prevention. The 2008 ASCIA annual meeting also concluded that in practice, guidelines were not followed, and in fact only 2.5% of children born with genetic risk were given a hydrolyzed formula.⁸

Although the use of pHF-W has been recommended for at-risk infants,¹³⁻¹⁶ The fact is that half of all infants who develop allergies are not part of the at-risk group, as mentioned above. This is because the number of infants in the non-risk group

is significantly larger than the number of infants in the risk group.¹¹ Therefore, it is under debate on whether pHF-W should be considered as a routine formula for all nonbreastfed infants, regardless of their risk of allergies.⁴

One pHF-W has been approved by the US FDA and the European Commission's European Food Safety Authority (EFSA) for its safety and suitability as a routine infant formula for all healthy infants, regardless of its relationship to its use in preventing allergies.^{20,33} In terms of nutritional content, pHF-W is very similar to CMF, except that the protein content in several pHF-Ws is slightly higher than in CMF. This makes pHF-W also meets all nutrient requirements as required for standard CMF.⁶ pHF-W typically contains 67 kcal/100 mL of energy, 11.2 g/100 kcal of carbohydrate, 5.1 g/100 kcal of fat, with the protein content varied in the range of 1.8-2.2 g/100 kcal. Meanwhile, CMF contains 67 kcal/100 mL of energy, 11 g/100 kcal of carbohydrate, 5.3 g/100 kcal of fat, and 1.8 g/100 kcal of protein.^{33,34}

Based on limited data of the long-term effect of pHF-W in healthy infants, it was found that there was no significant difference between the growth of pHF-W infants and CMF infants.²⁷ For the long-term use, Rzehak et al found no significant differences between the BMI trajectory in the pHF-W group, extensively hydrolyzed whey formula (eHF-W), CMF, and breast milk groups after 6 years of follow-up. In fact, it was found that pHF-W shows the closest growth rate to breast milk, among the other infant formula.³⁵ In another study, the Z-score trajectories showed that the weight gain in pHF infants is normative, despite the accelerated weight gain in CMF infants.³⁶ A systematic review and expert consensus also concluded that pHF-W was as safe as CMF in terms of supporting normal development. There was no difference found in the nutritional value and safety of pHF-W compared to CMF.³⁷

Data regarding the effects of pHF-W in hormonal response and metabolism of healthy infants were also limited. Hoppe et al reported that whey protein increased fasting insulin by 21% ($p=0.006$) in young boys aged 8 years in 7 days, with no change in IGF-1 ($p=0.27$), suggesting an increase in insulin resistance. This would naturally arise concern that pHF-W may induce the development of diabetes

mellitus.³⁸ However, as to anticipate this concern, the FDA-approved pHF-W has undergone the process of removing the caseino-Glyco-MacroPeptide (cGMP), resulting in the formation of modified sweet whey (MSW) formula.³⁴ This formula is found to have lower plasma level of a number of amino acids, such as leucine, isoleucine, threonine, and valine, which are considered to be insulin secretagogues (insulinogenic amino acids). This formula would, therefore, lead to a reduced risk of developing diabetes, compared to the classical pHF-W.^{34,39} It was also found that the administration of pHF, including pHF-W, in infants with a genetic risk of developing type 1 diabetes mellitus did not increase incidence of type 1 diabetes.⁴⁰

pHF and functional gastro-intestinal disorders

Functional gastro-intestinal disorders (FGIDs) are a frequent cause of parental concern and consequent impaired infants and relatives' quality of life, and impose a financial burden to health care, insurance and families.⁴¹ Management of these FGIDs should focus on improving both infants symptoms and family quality of life. If more than parental reassurance is needed, available evidence suggests that nutritional advice is recommended as it is effective and most of the time devoid of adverse effects.

Troublesome regurgitation occurs in about 25 % of all infants and usually improves spontaneously within the first year after birth.⁴² A thickened pHF-W was reported to be more effective than a thickened formula with intact protein.⁴³

Infant colic is reported to occur in about 20 % of all infants.⁴² Frequent and extensive auto-medication by parents of infants with colic has been reported.^{44,45} Therefore, management should focus on sustaining parents to cope with their child's excessive crying and distressed behavior by informing the parents that in general crying peaks at about four to six weeks after birth, may last up to three hours per day in otherwise normal infants and steadily diminishes from 12 weeks onwards.⁴⁶ In formula fed infants, when CMPA is an unlikely diagnosis, a partial hydrolysate with prebiotics and beta-palmitate; or a synbiotic formula with reduced lactose and partially hydrolyzed protein may be beneficial.⁴⁷

Functional constipation occurs in about 10% of all infants.⁴² A pHF-W, (a mixture of) prebiotics, probiotics, synbiotics, and beta-palmitate and/or a formula with high magnesium content (but within normal ranges) may offer some benefit.⁴¹

pHF-W has also been shown to have some beneficial effect on functional GI manifestations, such as regurgitation and constipation.⁹ A review by Vandenplas et al. showed that there was a significant decrease in the number of regurgitation events per day with the use of pHF-W. In addition, stool in the infants group with pHF-W was also found to be softer compared to stool in the standard formula^{33,43} and soy-based formulas.⁴³ Other data also showed that the use of pHF-W in non-breastfed infants can accelerate gastric emptying, reduce the incidence of infantile colic, and other functional gastrointestinal symptoms, when compared to CMF.³⁷

Conclusion

Breast milk is still the best nutrition for babies. In nonbreastfed infants, CMF can provide adequate nutrition to support normal growth and development. However, CMF is known to often induce cow's milk allergic reaction. In a large-scale GINI study and several other studies, pHF-W has been proven as a formula which is superior in reducing atopic disease and has been recommended in several guidelines to prevent atopic disease in high-risk group infants. Even so, more large-scale clinical studies replicating these studies, particularly GINI study, might be needed to confirm the effectiveness of pHF-W.

As the number of infants developing allergy is greater in the non-at-risk group compared to the at-risk group, the use of pHF-W should not be limited to the at-risk group only. Despite some reported differences in studies, pHF-W has always shown superior benefits among all the available infant formulas, with minimal potential harm for healthy term infants. According to a comparative pharmacoeconomic analysis, pHF-W is also superior over the standard formula in the aspect of family and societal perspectives, as well as the attractive cost-effectiveness.⁴⁷ Further studies assessing the effect of routine use of pHF-W in a larger population of nonbreastfed infants should also be conducted, in order to observe any potential harm

and to determine the benefit and cost-effectiveness ratio.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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