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REVIEW ARTICLE

Partially Hydrolyzed Formulas: Do They Play Any Role in the Prevention of Atopic Dermatitis?

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Atopic Dermatitis (AD) is a chronic, recurrent, inflammatory skin disease with an immune mechanism. It appears in genetically predisposed children in whom hypersensitivity reactions to varied antigens (food, neumoalergens, bacterial proteins), release inflammatory mediators that lead to the development of eczematous skin lesions. It diagnosis is eminently clinical being the criteria of Hanifin-Rajka of 1980 the most used [1,2].

It is considered one of the clinical entities linked to the so-called Allergic March and a disease of childhood that in 60% of patients starts in the first year of life, in 85% in the first 5 years and only in 10% after 7-years-old, although both their prevalence and severity tend to decrease with age [1]. Approximately 12% of the first visits to the Pediatric Allergy consultations in Spain correspond to cases of AD, accompanied by a 40% sensitization to neumoallergens or foods (most frequently the cow's milk protein) [3].

In recent decades, an increase in the number of cases of AD has been described, especially in Western countries. In the United States figures are cited of up to 10-20%, while in our country it is estimated that there is a prevalence of around 4.1-7.6% [4].

In order to try to contain this trend, several strategies have been designed in the field of nutrition that have gone from focusing on avoiding exposure to the allergens most commonly involved in allergic diseases through diets in the pregnant and nursing mother, the use of highly hydrolyzed formulas in the first months of life and the delay in the introduction of some foods to a more active form of prevention based on immunomodulation and in trying to promote the induction of tolerance through eating patterns in the first months of life, a key period in the development of tolerance phenomena. This is a strategy that is considered today more attractive than the exclusion diet because it is relatively simple, it is not expensive and the risk of adverse consequences from the nutritional point of view is low. It includes the use of partially hydrolyzed formulas, vitamins, omega-3 fatty acids, prebiotics and probiotics as the most studied measures [5-7].

This article focuses exclusively on the role of a Partially Hydrolyzed serum Formula (PHFs) in the first months of life, as a preventive measure for the subsequent development of a DA, without considering the possible effect that the other dietary measures proposed may have on the prophylaxis of allergic diseases in general.

Partially Hydrolyzed Formulas or Low Degree of Hydrolysis

The main characteristic of these type of formulas is that its protein content has been subjected to processes of heating and enzymatic hydrolysis with the aim of reducing its allergenicity. Unlike extended or high-grade hydrolysates, partial hydrolysates are contraindicated in children with a diagnosis of cow's milk proteins allergy since they contain peptides whose molecular weight ranges from 4,000-10,0000 daltons on average to a high likelihood may trigger an allergic reaction in sensitized children [8]. They are designed for the consumption of healthy infants, being less expensive and more palat-

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Table 1: Studies of high-moderate quality on the use of partially hydrolyzed formulas for the prevention of atopic dermatitis.

Reference	Design of study	Population study	Breastfeeding	Supplementary feeding
Vandenplas [18,19]	Randomized Double-blind	2 AF - PHWP n 28 - CF n 30	No	0-4 m: formula 4 m: grated apple > 6 m: diversification without limitations
Marini [21]	Randomized Double-blind	2 AF - PHWP n 41 - CF n 43	Yes	0-5 m: BF ± formula 5-12 m: hypoallergenic foods > 12 m: unrestricted diet
Chan [23]	Randomized	1 AF - PHWP n 53 - CF n 57	No	0-4 m: formula > 4 m: diversification without limitations
Von Berg [24]	Randomized Double-blind	1 AF - PHWP n 241 - CF n 256	Yes	0-4 m: formula > 4 m: diversification without limitations

AF: First-Degree Family History of Atopy; PHWP: Partially Hydrolyzed Whey Protein; CF: Conventional Formula; BF: BreastFeeding.

able in taste than extensive hydrolysates. Initially marketed for the prevention of food allergy, over time they appear to have focused more on the treatment of minor digestive problems such as infant colic, gastroesophageal constipation or reflux and for which, accompanying the partial hydrolysis (decrease in the amount of lactose, palmitic acid in beta position, addition of a thickener, prebiotics and/or probiotics), although there are no serious scientific studies demonstrating the efficacy of these modifications in these diseases [9].

In relation to the type of protein, the majority only contains serum proteins, of better flavor than the caseins and that favor a gastric emptying faster. There is a belief that, because they are partially hydrolyzed, they can be digested better, although in reality there is no scientific evidence to prove it or the absorption and use of the nitrogen component is greater.

Frequently Asked Questions Regarding the Use of Partially Hydrolyzed Formulas

It should not be forgotten that the best option in infant feeding is BreastFeeding (BF). Only when it is not possible to carry it out exclusively, the question arises as to which formula has the best short-term and long-term effects in the area of allergic disease prevention and AD in particular.

To what extent are the results we have reliable?

The role of partial hydrolyzed formulas in the prevention of allergic diseases and AD has been studied by different authors although the analysis of the data obtained in these studies is not easy because many of them lack a good methodology. Several of them establish the diagnosis of AD without the need for the physical examination of the researcher and only with the description of the symptoms by the family through the form or the diagnosis by another non-doctor belonging to the study [10-14]. Others do not specify in detail the composition of the formula used, do not refer to adherence and tolerance data or do not take into account exposure to other factors that may influence the development of AD such as exposure tobacco smoke or diversification of the rest of the diet [15,16]. One of them initially compares the use of a Conventional Formula (CF), soy formula and later when it already includes 97 patients, adds as third formula to study the PHFs [14] and even three studies carried out by the same group, and whose results were initially based some revisions and recommendations, have finally been rejected because their results cannot be validated in a later revision [17].

That is why most reviews and meta-analyzes highlight the difficulty in obtaining clear conclusions and are based especially on the data obtained from 4 studies considered of higher quality and that have a study population and/or a similar design (Table 1).

The first is a Belgian study [18,19] which shows a lower incidence of AD at 3 years in PHFs-fed at-risk infants compared to those with CF, although it does not statistically compare both groups. Szajewska and Horvath subsequently performed it without finding significant differences in terms of Relative Risk (RR) with a 95% confidence interval (CI) of 95% per year (RR 0.46, CI 0.13-1.60) or 36 months (RR 1.07, CI 0.43-2.67) [20].

- Marini performs an intervention study in Italy with a follow-up up to 3 years of 279 at-risk infants who cannot maintain exclusive BF in the first 5 months [21]. Childs: 48 received PHFs, 47 received CF, 32 mixed with PHFs and 28 mixed with FC. Subsequently, all receive a hypoallergenic diet until the year of age along with environmental preventive measures. Although the number of cases of AD up to 3 years is lower in those who receive PHFs compared to those who receive hydrolyzed formula, the cumulative incidence of AD among the different groups, calculated in a subsequent analysis, does not show significant differences (per year: RR 0.48, CI 0.13-1.78 and at 3 years RR 0.42, CI 0.14-1.26) [22].
- Chan published in 2002 a study carried out in Singapore with 110 children, all fed from the outset with

artificial feeding, of whom 53 received PHFs and 57 exclusively CF during the first 4 months [23]. The type of feeding that they carry out in this period of intervention is known by the parents but not by the physicians who follow up, passing from the 4 months to the introduction of the complementary feeding without restrictions except by the type of formula received. The follow-up period lasts up to 30 months and the results obtained are evaluated taking into account several factors that can potentially cause confusion (socioeconomic level, family environment, presence of pets, use of air conditioning). However other factors that may also influence the development and evolution of AD such as the introduction of foods are not specified or valued.

The data reflect a significant reduction in the risk of AD throughout the first two years in the group receiving PHFs and a lower incidence accumulated in the follow-up period (odds ratio 0.20, p 0.011 at 3 months' odds Ratio 0.37, p 0.019 at 2 years) without observing differences in the incidence of other atopic manifestations (rhinitis and urticarial).

- Lastly, the GINI (German Infant Nutritional Intervention) study is a project designed and carried out in Germany to test the relative efficacy of three hydrolyzed formulas against CF in the field of prevention of allergic manifestations in children with risk [24].

It is a very important study, not only for its design but also for the large study population of 2,252 infants who, in the case of not being able to maintain exclusive LM, are assigned by randomization to take during the first 4 months of life: PHFs, CF, Extensive Casein Hydrolysate (ECH) or an Extensive Hydrolysate of serum proteins (EHsp).

As in Marini's study, it is not exclusion criteria to be with breastfeeding. In fact, around 42% of the infants received it exclusively in the first 4 months, with the rest (1249) actually forming the population to be studied. However, the quantity and duration of BF are not specified before starting artificial formula in the different groups, although complementary feeding takes place in a controlled way, starting at 4-6 months and avoiding the introduction of cow's milk, egg, fish, soy, tomato and citrus in the first year.

The incidence of AD per year in the EHsp-consuming group is lower compared to CF when adjusted with factors also involved in the development of AD such as sex, exposure to tobacco, and the existence of AD in the background (odds ratio 0.56 CI 0.32-0.99). Both ECH and EHsp reduce the incidence of AD by more than 50% to one year, especially in those with no family history of AD, postulating the possibility that the preventive effect of nutritional intervention is more pronounced in children with no load important genetics. In the presence of a family history of AD, only HCF would reduce the risk of CF. This trend remains at 3 years, when the cumulative incidence of AD in the group receiving EHps continues to be lower than the one that receives FC, and also the significance persists when it is adjusted again with the aforementioned variables (odds ratio 0.60 CI 0.37-0.97) [25].

Subsequent publications show that the preventive effect of HF and EHsp on AD appears to be prolonged up to 10 years, with those concerning the 15 years of evolution still pending. These data should be analyzed more carefully because they refer to a high dropout rate (64.4%) and differ in some details from the initial design of the study up to 3 years, so that from this age onwards information is obtained through a survey of parents, with the possible bias that this may entail [26,27]. Although it does not provide data on the type of AD that is prevented in relation to intensity (mild, moderate or severe), it does provide information on the type in relation to the age of onset and its later duration, such that it reveals differences between groups in cases of persistent AD (onset of symptoms in the first 2 years, with persistence up to 5-6 years of age), being lower in those receiving ECH or EHsp. There are no variations in the other DA types, i.e. early-onset AD (below 2 years), late-onset AD (2-6 years), persistent AD up to 3-4 years and intermittent AD, in the evolution seems to be independent of the type of formula used [27].

The first reviews on the role of hydrolyzed formulas in the prevention of allergic diseases conclude that the use of hydrolysates (long and partial) up to 4-6 months are appropriate alternatives to BF for the prevention of allergic diseases in at-risk infants, emphasizing that this preventive effect is more noticeable in AD [20,22,28,29] One of them is a comparison between extensive and partial hydrolysates without appreciating benefits with the use of the former with respect to the latter except in the cumulative incidence of allergic diseases between 0-36 months [20].

Nonetheless, in spite of all the above, subsequent reviews with more rigorous criteria in the studies subject to analysis, offer a much more cautious and less categorical conclusion that highlights the limited evidence that exists on this subject that is almost exclusively limited to results of the 4 studies referred to above as being of higher methodological quality [30]. In 2010, Alexander encompasses data on the cumulative incidence of AD up to 36 months of age, based on the fact that they all have similar design, diagnostic criteria and follow-up (are randomized, in a population at risk, include as objective to evaluate the incidence of AD with rigorous diagnostic criteria and control the BF factor, either establishing it as an exclusion criterion or including it in the subsequent statistical analysis as a possible confounding factor). As a result of this joint assessment, there are statistically significant differences in the cumulative incidence of AD as early as 6 months of age (26 cases of

384 infants in the CF group versus 7 of 365 in the PHFs group) 12 months (72 of 384 vs. 35 of 365), 24 months (78 of 383 versus 41 of 364) and 36 months (96 of 370 versus 60 of 350) [31].

Following this line of caution, the US Food and Drug Administration (FDA) performs an excellent review focused exclusively on analyzing published scientific evidence on the use of PHFs in the prevention of AD up to 3 years of age in infants of risk. It concludes literally: "There is limited scientific evidence that for healthy infants who do not receive exclusive BF and who have a family history of atopy, feeding with PHFs up to 4 months of age instead of CF can reduce risk of development of AD throughout the first year of life and up to 3 years of age", reiterating the need to obtain more data through broad studies, high methodological quality that can contrast and validate those obtained in the GINI study [32].

Is the profit obtained from one hydrolysate to another from a different commercial brand, whose hydrolysis and composition are different, extrapolated?

Much had been discussed about what would be the main mechanism of action of the PHFs. Unlike extensive hydrolysates, they do not cause a decrease in sensitization, so avoiding antigen exposure is not a factor involved in its mechanism of action. As an alternative, it is speculated that partial hydrolysis may allow certain peptides with immunomodulatory properties, which favor immunological tolerance phenomena or antimicrobial properties to remain intact. In this case, the method used to obtain the hydrolysis would be of great importance since it would be determinant in the characteristics of the resulting peptides, beyond their molecular weight. In addition, other components of the formulas, oligosaccharides, omega-3 fatty acids and some probiotic strains may also have immunomodulatory properties and may enhance the preventive effect to a greater or lesser extent. This is why the EAACI in its recommendations emphasizes that the evaluation of the efficacy of the formulas should be based not so much on the type of protein they contain (caseins or serum proteins), so to trademarks [33].

To what extent is it worth the possible preventive effect achieved on AD?

In all the studies there is a common constant and is that the use of PHFs has no preventive effects on asthma, allergic rhinitis and sensitization to allergens. Does the use of PHFs justify the potential preventive effect on AD? The answer must be considered taking into account that the benefits will be variable according to the region, the BF rate, the prevalence of AD and the severity of the same.

An estimate of the economic impact that the use of an PHFs compared to a CF would offer in 5 European countries (Denmark, Germany, Switzerland, France and Spain) had been published. It takes as a basis the prevention estimates published so far. It includes variables on loss of time and income for families, use of resources of the Health System and the costs associated with the treatment of AD. The results related to cost-benefit in our country have a positive effect in all of them [34].

Is the use of hydrolysates safe in a healthy population?

It is speculated by some authors that extensive hydrolysates could cause a lack of induction of tolerance and in the long term cause an increase in the risk of developing allergy. There is, however, no work to date that has reported negative effects with the use of hydrolysates in healthy population, neither from the nutritional point of view (parameter specially controlled in the GINI study) nor from the evolutionary point of view although there is no reduction in the prevalence of asthma, nor is there a statistically significant increase in the same in the groups that use PHFs compared to those who use CF [35].

Are the current recommendations on food in the first year of life for the prevention of allergic diseases appropriate?

Practically there are only two preventive measures that unanimously all the Scientific Societies recommend. One is to avoid exposure to tobacco smoke in both gestation and lactation and to maintain the exclusive BF in the first months of life [36]. Considered the most suitable form of feeding of any healthy infant, doubts arise when it is not possible to maintain it: what is the best alternative? what kind of formula? for how long? in what type of children? What other preventive measures?

Although the different Scientific Societies initially made quite different recommendations, today, after the last published reviews, they are very similar [33,37,38] (Table 2).

Focusing only on the use of PHFs, all Scientific Societies maintain that there is some evidence that their use in the first 4-6 months of life may have a medium- and long-term preventive effect on AD, but there is not enough data yet to recommend the use of partial hydrolysates in the prevention of it in a systematic way.

We must not forget, finally, that all these preventive measures are focused exclusively on the so-called risk population defined only on the basis of family history, despite the fact that there is a significant percentage of children who develop allergy and AD without having a history of atopy. Would the percentage of cases decrease even more if preventive measures were taken in the general population? Unfortunately, as has been a constant in this subject, there are no studies designed correctly that can answer this question and therefore we still do not know if different results will be obtained with the application of broader prevention strategies.

Table 2: Current recommendations for feeding during the first year of life for prevention of allergic diseases.

	ESPGHAN/EAACI [33,37]	AAP [38]
Definition of infant high risk	A first-degree relative with atopy	Two first-degree relative with atopy
Exclusion diet pregnancy foods	Not recommended There is no evidence nutritional risk benefit	2000: Not recommended, with the possible exception Peanut exclusion 2008: Not recommended There is no evidence to support the exclusion of Peanut diet
The exclusion diet mother during LM	Not recommended There is no evidence nutritional risk benefit	2000: Diet peanut exclusion nuts. Consider exclusion of egg, milk beef and fish. 2008: Not recommended
LM exclusive	Recommended for 4-6 months	2000: 6 months 2008: Suitable for 4-6 months
Use of hydrolysates	Reduced allergenicity formulas (extensive hydrolyzed) to 4-6 months as a substitute/supplement LM	Hydrolysed or otherwise extensive hydrolysates partial to 4-6 months substitute/supplement LM. There are only some evidence that the use of PHWP decreases/DA delays.
Using formulas soy	Not recommended	Not recommended
Beginning of diversification feed	Not before 4-6 months	2000: From 6 months 2008: not before 4-6 months
Delayed introduction food	Not recommended There is no evidence that modifications dietary beyond 6 months have preventive effect	2000: a year cow's milk, egg at 2 years, peanuts, nuts and fish at 3 years 2008: There is no evidence supporting the delay in the introduction of egg, fish and food containing peanut protein

ESPGHAN: European Society of Pediatric Gastroenterology and Nutrition; EAACI: European Academy of Allergology and Clinical Immunology; AAP: American Academy of Pediatrics.

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