

Selected Summary

A Follow-up Study of Nutrient Intake, Nutritional Status, and Growth in Infants with Cow Milk Allergy Fed Either a Soy Formula or an Extensively Hydrolysed Whey Formula. Leena Sappo, Riitta Korpela, Bo Lonnerdal, Leena Metsaniitty, Kaisu Juntunen-Backman, Timo Klemola, Aila Paganus, and Timo Vanto. *Am J Clin Nutr* 2005;82:140–5.

Summary: Because infants with cow's milk allergy (CMA) are reported to have reduced growth and special nutritional needs, the authors have investigated 168 infants with CMA randomized to either a soy formula or an extensively hydrolyzed whey formula. At inclusion in the study, the symptoms that occurred most often in the infants because of CMA were atopic eczema (59%) and gastrointestinal symptoms (22%). Biochemical and hematologic indices included serum alkaline phosphatase activity, serum ferritin and transferrin receptor concentrations, serum calcium, zinc and copper concentrations, hemoglobin and leukocyte concentrations, as well as red blood cell indices. There were no differences between the groups in the percentage of abnormal laboratory values. An adverse reaction to the study formula was confirmed in 8 of 84 infants (9%) in the soy group and 2 of 84 (2%) in the hydrolysed formula. The authors conclude that nutritional status and growth did not differ between the groups, and the selection of a formula can be made based on tolerability and, to some extent, on cost (1).

Comment: The specific purpose of the study was to compare nutritional status and growth in infants with CMA fed either a soy formula or an extensively hydrolysed whey formula. For the first time, adequate samples of infants with CMA have been included (an adequate sample should consist of at least 64 subjects for feeding group to check the null hypothesis of a between-group difference of 0.5 SD, $\alpha = 0.05$ and power of the test = 80%) and followed for a prolonged period of time. On the other hand, we should critically reconsider their conclusions concerning both the biochemical indices of nutritional adequacy and implications for the treatment of allergic infants.

While considering the most subtle biochemical indices of nutritional adequacy, the authors did not consider protein metabolism indices such as serum total protein concentrations, albumin, prealbumin and urea nitrogen concentrations. High serum urea nitrogen concentrations have been previously observed in infants fed either a casein hydrolysate (2,3) or a whey-hydrolysate formula (4). High concentrations of serum urea nitrogen, resulting from liver catabolism of excess amino acids in plasma, may originate from the high amino acid content of these formulas. Vandenplas et al. found higher serum urea nitrogen concentrations in infants fed a whey-hydrolysate formula compared to controls fed a whey-predominant formula, although the protein content of the formulas was similar (4). These observations have raised the hypothesis that amino acid utilization, the so-called "protein efficiency index," (ie, the net amino acid utilization for the building up of body proteins), may be lower from hydrolysate than from whole proteins, as

shown also in adults fed an elemental diet (5). A different protein utilization in infants fed hydrolysate formulas was also suggested by Decsi et al. (6), who found lower serum total protein concentrations in infants fed hydrolysate formulas compared to those fed a conventional infant formula. Another limit of all these studies is the use of formulas with different protein content between samples and controls.

Information on protein metabolism indices should reasonably be required to clarify the steps of the intermediate metabolism of the nitrogen fractions, in order to check the hypothesis of excessive amino acids, even if less efficiently used, supplied by hydrolysed formulas. In both cases (excessive supply, lower metabolic utilization), higher blood urea nitrogen levels should be expected. The authors of the present study have positively stressed that "protein intake at age 1 y in the 2 groups was twice the lowest amount of safe protein intake according to international dietary recommendations." (7) Nevertheless, negative effects of high protein intake in the first year of life on weight and fat development have been shown (8), whereas differences in height gain seem less marked (9). Therefore, besides the evaluation of growth, studies having as primary outcome the nutritional adequacy of special formulas should also primarily consider indices of protein metabolism. In this regard, the conclusions of the present study are partially incomplete because the infants' nutritional status has not been fully investigated.

As a second part of their conclusions, the authors state that the "selection of a formula can be made on the basis of tolerability and, to some extent, on cost." Infants began to receive the study formula at a mean age of 7.8 months in the soy formula and 7.5 months in the hydrolysate group, ranging from 2 to 11 months. Adverse reactions to the study formulas were found in 8 out of 84 infants (9%) for the soy group and 2 out of 84 (2%) for the hydrolysed formula group. No information is given on the percentage of adverse soy reactions in patients under 6 months of age and in patients suffering from gastrointestinal symptoms at enrolment, compared to those with other symptoms.

Adverse reactions to soy protein are more commonly detected in infants under 6 months of age (10). Moreover, adverse soy reactions have been more frequently reported in infants with nonimmunoglobulin E-associated CMA (such as enterocolitis-enteropathy syndrome) (11,12), even if this last issue has been challenged by Klemola et al. (10). Therefore, in the light of current evidence, it may be convenient to select a formula not only based on individual tolerability or cost, as suggested by the authors, but *also* based on infants' age, and soy formulas should not be used in infants younger than 6 months of age until further data will be available.

Enza D'Auria

Department of Pediatrics, San Paolo Hospital
University of Milan

Milan, Italy

dauria.e@email.it

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