

Elimination diet in cow's milk allergy: Risk for impaired growth in young children

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Objective: The objective of this study was to evaluate the nutritional impact of therapeutic elimination diets and to identify risk factors predisposing infants with food allergy to poor growth.

Study design: We studied 100 children (mean age 7 months) with atopic dermatitis and challenge-proven cow's milk allergy and evaluated their growth during the symptomatic period before diagnosis and during the therapeutic elimination diet.

Results: Clinical control of symptoms was achieved in all patients. The mean length SD score and weight-for-length index of patients decreased compared with those in healthy age-matched children, $p < 0.0001$ and $p = 0.03$, respectively. Low serum albumin was present in 6% of the patients, 24% had an abnormal urea concentration, and 8% had a low serum phospholipid docosahexaenoic acid. The delay in growth was more pronounced in a subgroup of patients with early onset than in those with later onset of symptoms ($F = 6.65$, $p < 0.0001$). The duration of breast-feeding correlated positively with the sum of n-3 polyunsaturated fatty acids ($r = 0.39$, $p = 0.001$) and with the relative amount of docosahexaenoic acid ($r = 0.36$, $p = 0.002$).

Conclusion: A delicate balance exists between the benefits and the risks of elimination diets. (J Pediatr 1998;132:1004-9.)

According to several population studies, the incidence of allergic disorders is rising.^{1,2} Atopic dermatitis and food allergy are the first manifestations of such disorders.^{3,4} Therapeutic elimination diets in atopic patients with challenge-proven

food allergy have been shown to result in remission of symptoms, a decrease in allergen-specific IgE concentrations, and a decrease in proliferative response of peripheral blood mononuclear cells to food antigens.^{5,6} In contrast, patients with atopic dermatitis but no proven food allergy do not benefit clinically from extreme empirical elimination diets.⁷ The advantage of elimination diets therefore appears to be afforded by silencing the specific allergic inflammation induced by the responsible food.^{5,8}

See related article, p. 999.

Allergies to foods of vital importance including cow's milk predominate in early childhood, and the treatment con-

sists of highly restricted dietary regimens.^{6,9,10} During this vulnerable period of rapid growth, nutrition has long-term effects on later development and health.^{11,12} As our understanding of infant nutrition is evolving, it appears likely that a delicate balance exists between the benefits and the risks of elimination diets.

To assist in identifying risks, if any, of elimination diets, we evaluated the growth and nutrition of 100 consecutive atopic patients with challenge-proven cow's milk allergy during elimination diets. Specifically, we examined factors that can affect growth and nutrition at early age including the duration of breast-feeding, the onset of symptoms, the extent of sensitization, the management of cow's milk allergy, and dietary intake.

CI	Confidence interval
RAST	Radioallergosorbent assay
SDS	Length standard deviation score

METHODS

Subjects and Study Design

The study involved 100 consecutive children aged 1 to 17 months (mean 7 months) who had been referred to the Tampere University Hospital Pediatric Department on the basis of suspected cow milk allergy. They fulfilled the Hanifin criteria¹³ of atopic dermatitis in children and the additional criteria of positive open or double-blind, placebo-controlled cow's milk challenge and no breastfeeding at the time of the study. Cow milk elimination diet was started in infants <12 months with either an extensively hydrolyzed casein or whey formula ($n = 44$) or a soy formula ($n = 45$) or in

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older patients with calcium supplementation ($n = 11$). Of those originally receiving soy formula, 25 (56%) of 45 reacted clinically to the formula and were transferred to an extensively hydrolyzed formula. Of those assigned or transferred to one of the extensively hydrolyzed formulas, 10 (14%) of 69 required a change to an amino acid formula because of clinical reactions. On the basis of clinical history, skin tests, radioallergosorbent assay, and clinical challenges, additional dietary restrictions included egg in all and cereals (wheat, barley, rye, oats), citrus fruits, and vegetables in 70% of the patients. The restrictions of cereals, fruits, and vegetables were replaced by foods of the same group. After 1 month of the challenge, when the patients were receiving their assigned elimination diet, the symptoms had remitted.

The patients were then monitored from the diagnostic cow's milk challenge to the first rechallenge (mean follow-up 13 months), which was scheduled according to usual clinical practice to evaluate the need for continued elimination. Regular visits were scheduled at the outpatient department at 2- to 6-month intervals according to the patients's age for clinical examination and evaluation of growth. The clinical examination was made by the pediatrician or dermatologist in charge, not by the investigators. The diet of the patients was expanded with age-appropriate foods, and at each control visit a list of foods was given to the parents for this purpose. At the time of the rechallenge the growth and the nutritional balance of the patients were estimated.

Because an unselected patient population was enrolled in the study, we studied the growth and nutrition separately in a homogenous subgroup of 38 patients in whom cow's milk elimination diet was commenced at 6 months of age. Dietary intake was evaluated in these patients during the elimination diet at the age of 12 months in connection with a visit to a clinical nutritionist.

The control group comprised 60 healthy age-matched children chosen from one well-baby clinic in the city of Tampere; every fifth healthy child from the relevant age group was enrolled.

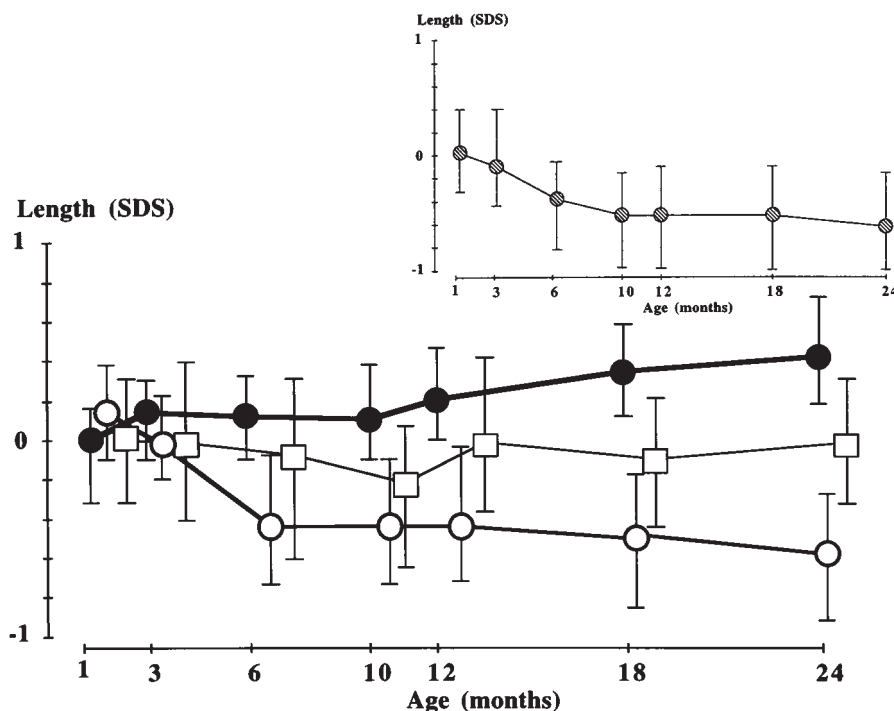


Fig. 1. Growth during first 24 months of infancy in patients with cow's milk allergy, during symptomatic period before diagnosis, and during therapeutic elimination diet, and in control group. Length-for-age in SDS is shown at 1, 3, 6, 10, 12, 18, and 24 months of age. *Open circles* represent mean of measurements in early onset group with mean (95% CI) age at onset of symptoms 2.7 months (2.3 to 3.1 months) and at start of elimination diet, 4.6 months (4.2 to 5.1 months). *Open squares* represent mean of measurements in older onset group with mean (95% CI) age at onset of symptoms 6.5 months (4.7 to 8.3 months) and at start of elimination diet, 12.5 months (11.5 to 13.5 months). *Solid circles* represent measurements in healthy control group. *Intersecting vertical lines* show 95% CI. **Inset:** SDS in subgroup of patients with early onset of symptoms in whom dietary intake was evaluated. *Barred circles* represent mean of measurements. *Intersecting vertical lines* show 95% CI.

Informed consent was obtained from the children's parents. The study was approved by the Committee on Ethical Practice of Tampere University Hospital and the Health Care Centre of the City of Tampere.

Skin Tests

Skin prick testing was done during the elimination period on the volar aspect of the forearm with a long list of dietary antigens of ALK (Allergologisk Laboratorium A/S, Horsholm, Denmark).⁴ A 1 mm, one-peak lancet with shoulder to prevent deeper penetration was used. Histamine dihydrochloride 10 mg/ml (ALK) was the positive and pricking by the vehicle (physiologic saline) the negative control. Reactions were read at 15 minutes, and a wheal size of at least 3 mm was recorded as positive, when negative control was 0.

Cow's Milk Challenge Protocols

For 2 to 4 weeks before the challenge the patients received no cow's milk but instead a tolerated formula or calcium supplementation. On the first day of the challenge, increasing amounts (1, 5, 10, 50, and 100 ml) of the allocated challenge formula were given at 15- to 30-minute intervals until intake appropriate for age was reached. The placebo formula was the amino acid-derived Neocate (SHS Int., Liverpool, U.K.), and the test formula consisted of Neocate and 100 gm cow's milk powder/L. As previously described,^{4,6} a computerized randomization schedule was used to fix the sequence of the challenges. The nursing staff, pediatricians, parents, and investigators were unaware of the administered formula's nature. For open challenge an adapted infant formula was used.⁴ The challenge period was 1 week for both

Table I. Clinical characteristics of patients with cow milk allergy diagnosed before 9 months of age (early onset group) and after 9 months of age (later onset group)

	Early onset group (n = 70)	Later onset group (n = 30)	Statistics
Total breast-feeding (mo) ^o	5.8 (4.9-6.8)	9.9 (8.6-11.1)	$F = 24.02$ $p < 0.0001$
Exclusive breast-feeding (mo) ^o	2.6 (2.3-3.0)	3.7 (3.2-4.2)	$F = 11.46$ $p = 0.001$
First intake of infant formula (mo) ^o	3.0 (2.5-3.6)	6.1 (4.9-7.3)	$F = 29.96$ $p < 0.0001$
Family history of allergy (%)	88	67	$\chi^2 = 5.80$ $p = 0.01$
Total IgE in serum (kU/L)	24 (11-55)	21 (6-71)	$F = 0.05$ $p = 0.83$
Elimination of cereals (%)	76	67	$\chi^2 = 0.87$ $p = 0.35$
Elimination of citrus fruits and vegetables (%)	69	73	$\chi^2 = 0.23$ $p = 0.63$

^oMean (95% CI).

placebo and test formula and for open challenge. Cow's milk allergy was defined as an unequivocal adverse reaction to challenge. To judge long-term tolerance and reveal any false-negative result of challenge, all patients negative to challenge continued to consume cow's milk. All patients were seen 1 month after the challenge was commenced, when the diagnosis was confirmed, as previously described.⁴

Evaluation of the Growth

To characterize the effects on growth of clinical factors, the length and weight of the patients were analyzed during the first 24 months of age. The idea was to depict growth in length and weight during the first 24 months of life in infants with cow's milk allergy, during the symptomatic period before diagnosis, and during the therapeutic elimination diet. The schedule for the follow-up mimicked that used in the well-baby clinics in Finland, with more frequent measures in the youngest infants (Fig. 1). The growth of infants in the healthy control group is shown for comparison. The length and weight of the patients were measured with a recumbent infant length board and an electronic scale. As described previously,⁶ the most recent Finnish standards were used for recording length-

for-age in SD score and weight-for-length by expressing weight as percentage of the mean weight-for-length in the normal Finnish population with same sex.¹⁴ SDS was calculated by a formula: $SDS = (\text{Measured length} - \text{Mean length for age}) / \text{SD of normal Finnish population of the same age and sex}$.

Calculation of Dietary Intake

The parents completed home records of nutrient intake for 3 consecutive days, the quantities of solid and liquid ingested being estimated with household measures. The records were reviewed by a clinical nutritionist (R. I.). Calculations of nutrient intake were made with the AIVO computer program and were compiled from Finnish nutrient databases¹⁵ and manufacturers' data. Daily intake of nutrients was expressed as mean with 95% confidence interval. The nutrient intake of the patients was compared with that of healthy infants of this age group in Finland.¹⁶⁻¹⁹

Samples

At the initial challenge the serum total IgE (Phadebas IgE Prist, Pharmacia, Uppsala, Sweden) and cow's milk-specific IgE (RAST, Pharmacia) were measured; at the time of rechallenge the serum total IgE, cow's milk-specific IgE, and

concentrations of albumin, prealbumin, transferrin, urea, alkaline phosphatase, zinc, and vitamin A in serum were measured. Serum samples from members of a healthy age-matched control group were determined for comparison. Fatty acid composition in serum phospholipids was determined, and the results were compared with normal values obtained from 87 healthy 14-month-old infants (Salo MK, unpublished results).

Determination of Serum Fatty Acid Composition

Plasma lipids were extracted with chloroform methanol (2:1) and fractionated into phospholipids and nonpolar lipids by thin-layer chromatography.²⁰ Phospholipid fatty acids were transesterified in 2% H₂SO₄ in dry methanol. Fatty acid methyl esters were extracted into petroleum spirit and analyzed with a Hewlett-Packard 5890A gas chromatograph equipped with a 25 m 0.32 mm inside diameter NB-351 (HNU-Nordion Ltd Oy, Helsinki, Finland) fused silica capillary column and flame ionization detector. The results are expressed as percentages of the total area of 24 major fatty acids with 14 to 24 carbon atoms.

Statistics

Means are presented with ranges or with 95% CI in parentheses. Because of the skewed distribution of serum total IgE concentration, logarithmic (ln) transformation was used. Analysis of variance, ANOVA for repeated measurements, and the chi-squared test were used in statistical comparisons. The correlation coefficient was calculated to determine the association between the clinical factors and growth.

RESULTS

Clinical Characteristics at Diagnosis

The diagnosis of cow's milk allergy was made at 7 months (6 to 8 months) of age (mean 95% CI). The reactions involved pruritus, urticaria, morbilliform exanthema, or reactions of eczematous type. The reactions were confined to the skin in 80% of the patients. Vomiting, loose stools, and diarrhea occurred in 20% of the patients.

Cow's milk-specific RAST was positive (≥ 0.4 kU/L) in 41%, and skin prick test for cow's milk was positive in 36%. Skin prick tests for egg, cereals (wheat, barley, rye, oats), and various fruits and vegetables were positive in 51%, 51%, and 53% of cases, respectively. Polysensitization (more than two positive skin test results for these food groups) was detected in 41% of the patients.

Seventy patients who were younger than 9 months of age when the diagnosis of cow's milk allergy was made and treatment started, and 30 were older than 9 months (Table I). There were more family members with atopic disorders in the early onset group, 41%, than in the later onset group, 33%. When only one member was affected, it was more frequently the mother in the early onset group, 34%, than in the later onset group, 10%; chi square = 11.76, $p = 0.01$.

Growth During Elimination Diets

The relative length of patients decreased compared with the healthy control group ($F = 11.63$, $p < 0.0001$). The fall in relative length coincided with the onset of the symptoms suggestive of cow's milk allergy and the start of the elimination diet: between 3 and 6 months of age in the early onset group ($F = 9.78$, $p = 0.003$) and between 6 and 10 months of age in the later onset group ($F = 8.07$, $p = 0.009$). No catch-up was seen by 24 months of age. The relative weight in patients (Fig. 2) continued to fall compared with that in the control group ($F = 2.42$, $p = 0.03$). In the subgroup of patients in whom the symptoms of cow's milk allergy appeared at the age of 2.7 months (2.2 to 3.1 months) (mean 95% CI), the rate and the pattern of growth was consistent with the total study population (Figs. 1 and 2).

Nutrient Intake During Elimination Diets

A homogenous subgroup of patients with early onset of symptoms in whom the elimination diet was commenced at the age of 6 months was evaluated (Table II). The children were receiving an elimination diet containing 11% (95% CI, 10% to 12%) and 34% (95% CI, 31% to 37%) of energy as protein and fat, respectively.

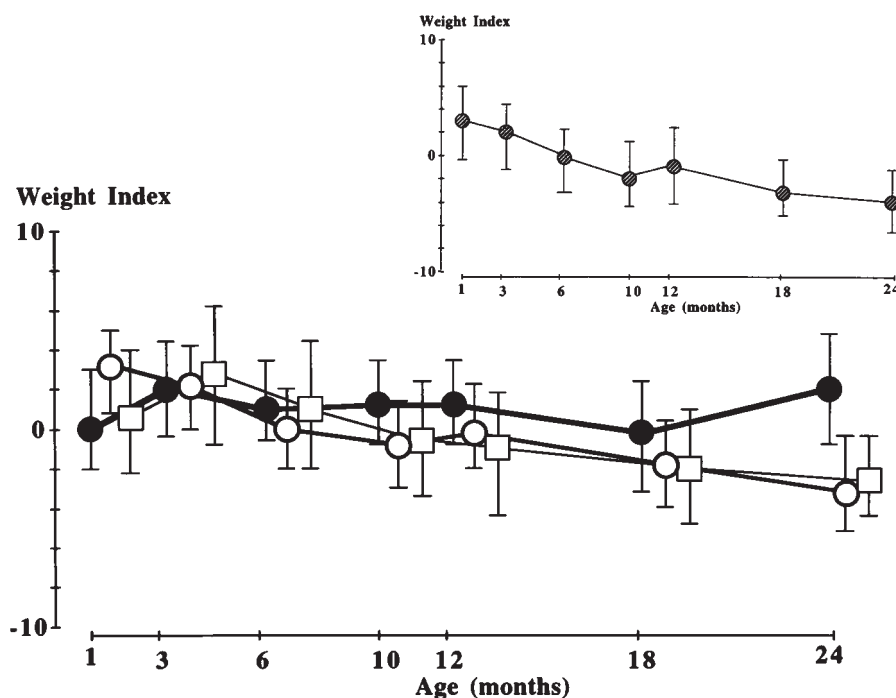


Fig. 2. Weight gain during first 24 months of infancy. Weight indexes are shown at 1, 3, 6, 10, 12, 18, and 24 months of age. Open circles represent mean of measurements in early onset group, open squares in later onset group, and solid circles those in healthy control group. Intersecting vertical lines show 95% CI. Inset: weight index in subgroup of patients with early onset of symptoms in whom dietary intake was evaluated. Barred circles represent mean of measurements. Intersecting vertical lines show 95% CI.

The amount of substitute formula consumed by the patients daily was 570 ml (95% CI, 490 to 650 ml). This was a major source of nutrient intake, particularly fat intake, at the age of 12 months.

Clinical Characteristics After Elimination Diet

A cow milk rechallenge was scheduled 13 months (12 to 14 months) (mean 95% CI) after the diagnostic challenge. The mean (95% CI) age of the patients was 21 months (20 to 23 months). At this time 15 of 100 of the patients, 11 (16%) of 70 of the early onset group and 4 (13%) of 30 of the later onset group, had attained clinical tolerance to cow's milk; chi square = 0.09, $p = 0.76$. The serum total IgE concentration was 38 kU/L (range 0 to 3598 kU/L), and cow's milk-specific RAST was positive (≥ 0.4 kU/L) in 33% of the patients.

Nutritional Balance After Elimination Diet

The mean (95% CI) concentration of albumin in serum was lower in patients,

41 gm/L (40 to 43 gm/L) than in the control group, 46 gm/L (44 to 48 gm/L); $F = 11.24$, $p = 0.001$. A total of 6 (6%) of 96 patients had values below the normal reference values (36 to 50 gm/L). Likewise, the proportion of patients with an abnormal serum urea concentration was 24% (low levels in 18% and elevated levels in 6%), whereas none of the members of the control group had abnormal serum urea concentrations (reference value 2.7 to 6.0 gm/L). The mean (95% CI) serum urea concentration in patients, 3.81 mmol/L (3.47 to 4.14 mmol/L), was not different from that in the control group, 3.95 mmol/L (3.42 to 4.49 mmol/L). The remaining nutritional parameters tested, prealbumin, transferrin, alkaline phosphatase, zinc, and vitamin A, were within normal values.

The relative amount of linoleic acid in serum phospholipids was normal in all patients (normal range 16.7% to 26.7%), but 9% of the patients (11% of the early onset group and 6% of the later onset group) had a level of α -linolenic acid below the normal range (0.17% to

Table II. Intake of energy, protein, fat, and carbohydrates and respective percentages derived from substitute formula in infants with cow milk allergy

	Intake per day	Intake per kg body weight per day	Percentage derived from the formula
Total energy			
kcal	1002 (910-1094)	112 (101-122)	40 (34-45)
kJ	4197 (3811-4582)	467 (423-511)	
Protein (gm)	28 (24-31)	3 (2.7-3.4)	41 (35-47)
Fat (gm)	38 (33-45)	4 (3.6-5)	52 (44-60)
Carbohydrates (gm)	132 (120-144)	15 (13-16)	35 (29-41)
Mean (95% CI).			

0.53%). Five percent of the patients had an abnormally low and 13% an abnormally high percentage of arachidonic acid (normal range 6.6% to 12.0%); 8% of the patients had low docosahexaenoic acid (1.9% to 5.8%).

Clinical Factors Affecting the Growth and Nutrition in Patients With Cow's Milk Allergy

The factors independently contributing to the growth of patients with cow's milk allergy were the age at onset of symptoms and the diet. Lag in growth was more pronounced in the early onset group than in the later onset group; $F = 6.65$, $p < 0.0001$ (Fig. 1). In contrast, the extent of dietary restriction in terms of number of foods eliminated (cereals and vegetables) from the diet and substituted by other foods of the same group did not explain the lag in growth ($p = 0.20$ and $p = 0.70$, respectively), nor did polysensitization or the presence of gastrointestinal manifestations affect the growth of these patients ($p = 0.35$ and $p = 0.70$, respectively).

A disproportionate amount of nutrients deriving from the substitute formula at the expense of introduction of solid foods was one factor contributing to poor growth. During the follow-up an inverse correlation was found between the amount of protein intake derived from the substitute formula and the rate of growth in length ($r = -0.37$, $p = 0.05$) and in weight ($r = -0.43$, $p = 0.02$).

The proportion of energy derived from the substitute formula correlated negatively with the sum of n-3 polyunsaturated fatty acids ($r = -0.41$, $p = 0.04$). The

duration of breast-feeding correlated positively with the sum of n-3 polyunsaturated fatty acids ($r = 0.39$, $p = 0.001$) and with the relative amount of docosahexaenoic acid ($r = 0.36$, $p = 0.002$).

DISCUSSION

The use of elimination diets has become an accepted adjunct in attempts at both prevention and treatment of allergy in early childhood. Despite the persuasive rationale of decreasing exposure to the most important source of antigens early in life, the results have been conflicting. Moreover, knowledge of the nutritional repercussions of exceptional diets is fragmentary. Our results substantiate a delicate balance between the benefits and risks. Therapeutic elimination diets resulted in clinical control of symptoms in all patients and reduction in antigen-specific IgE and in acquisition of clinical tolerance in 15% of the patients during follow-up. At the same time a constant risk of nutritional inadequacy was demonstrated. Growth in allergic patients differed from that expected for the age group, and it was reduced compared with that in our healthy control group.

It is unlikely that poor growth was associated with the allergic state per se; previous studies demonstrated that catch-up growth could be achieved in an identical patient population with rigorous elimination diets supplemented with an amino acid-derived formula.^{6,10} Because protein hydrolysates have been shown to support normal growth,⁶ the hypothesis that such formulas are nutri-

tionally inadequate can be rejected. Inadequate nutrient intake also does not explain the growth disturbance. The intake of the substitute formula was adequate, and the total energy and protein intakes achieved during elimination diets corresponded to the recommended dietary allowances. Nutrient intake and growth of healthy infants of this age group in Finland were evaluated during the study period.¹⁶⁻¹⁹ These studies constantly demonstrate normal growth in healthy infants receiving this level of energy and protein intake. Thus the hypothesis that dietary recommendations are inadequate can be rejected. However, we have shown that the younger the child is at the onset of symptoms and start of the diet, the more significant the risk of poor growth is, perhaps resulting in an inability to increase the amount of solid foods in the diet at the rate of healthy children.¹⁸ Certain families may be very timid in introducing new foods,²¹ and children with food allergies may have developed food aversions during the symptomatic period of the disease, increasing the risk for undernutrition.

The most plausible explanation for the demonstrated nutritional hazards could be poor use or loss of nutrients caused by sustained allergic inflammation. Persistent unnoticed inflammation in the target organs (skin or gut) may cause ongoing nutrient loss. A positive cow's milk challenge results in albumin secretion into the gut²² and increased fecal α -1 antitrypsin and tumor necrosis factor- α concentrations.⁸ Taken together with the demonstrated low serum albumin in some patients, the notion of low-degree loss of protein may be supported. The demonstrated low urea concentration may reflect malnutrition and elevated urea concentration or poor use of amino acids or peptides.^{23,24} It is important that active inflammation by release of proinflammatory cytokines directly impairs linear bone growth independent of nutritional intake.²⁵

What could be the cause of sustained allergic inflammation in atopic infants with food allergies during elimination diets? First, the substitute formulas render them hypoallergenic but not nonallergenic.^{6,9,10} The result may be continued low-grade antigen challenge, particularly

in patients with multiple food allergies.^{6,10} Indeed, the level of antigenicity distinguishes the amino acid-derived formulas with the ability to promote catch-up growth in patients with multiple food allergies from protein hydrolysates.^{6,10} Second, any degree of noncompliance with extensive dietary limitations would result in persistent antigen challenge in these patients.^{26,27} More rigorous adherence to the elimination diet may be achieved if in addition to clinical follow-up, markers of inflammation are also monitored.

Our results also emphasize the necessity for development of improved formulas for these patients, especially in the group of patients identifiable by maternal atopic predisposition, short duration of breast-feeding, and early onset of symptoms in whom the formula furnishes the major source of protein even beyond the "formula age."⁶ First, the quality of proteins has been manipulated in producing less allergenic formulas; however, knowledge of the nutritional repercussions is scanty. There are lower amino acid concentrations in the plasma of atopic patients with cow's milk allergy treated with extensively hydrolyzed formula than in age-matched healthy breast-fed infants.⁶ Second, the substitute formulas are significantly different in fatty acid composition compared with breast milk. Low serum α -linolenic acid, phospholipid arachidonic acid, and docosahexaenoic acid concentrations were observed. Low serum and tissue arachidonic acid content has been associated with poor growth.²⁸ Our result further implies that the use of special formulas involves a risk of abnormally low tissue levels of docosahexaenoic acid; this fatty acid is required during rapid brain growth.

As the understanding of the importance of early nutrition on later development and immunocompetence is extended,^{11,12,29} the necessity for coordinated dietetic and pediatric evaluation of allergic patients is underlined. Such evaluation should include meticulous diagnosis of food allergy to avoid unnecessary elimination diets and encourage compliance to the individually tailored elimination diets.

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