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Dietary protein and growth in infants with chronic renal insufficiency: a report from the Southwest Pediatric Nephrology Study Group* and the University of California, San Francisco

Ricardo D. Uauy, Ronald J. Hogg, Eileen D. Brewer, Joan S. Reisch, Cynthia Cunningham, and Malcolm A. Holliday

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Abstract. This report describes growth and nutrition data from the feasibility phase of a clinical trial that was designed to evaluate the effect of diet protein modification in infants with chronic renal insufficiency (CRI). The purpose of the proposed trial was to compare the safety (effect on growth in length) and efficacy [effect on glomerular filtration rate (GFR)] of a diet with a low protein: energy (P:E) ratio versus a control diet in such patients. Twenty-four infants with GFRs less than 55 ml/min per 1.73 m^2 were randomly assigned at 8 months of age to receive either a low-protein (P:E ratio 5.6%) or control protein (P:E ratio 10.4%) formula, which resulted in average protein intakes of 1.4 and 2.4 g/kg per day in the low and control groups, respectively. Overall energy intakes over a 10-month period of study averaged 92% ± 12% recommended dietary allowance (RDA) for length in the low-protein group and 92 ± 15% RDA in the control group. Weight for age standard deviation scores (SDS) were comparably low in both groups at the time of randomization (low-protein – 2.0 ± 1.3, control –1.9 ± 1.1) and at the end of the study (low –1.9 ± 1.2, control –1.7 ± 0.9). Length for age SDS at entry tended to be lower in the low-protein group but were not significantly different in the two groups (low –2.2 ± 1.4 vs. control –1.7 ± 1.4). However, at 18 months the low-protein group had a significantly lower SDS for length (–2.6 ± 1.2 vs. –1.7 ± 1.4). The length velocity SDS from 12 to 18 months were also different, with the low-protein group remaining strongly negative (–1.0 ± 0.9) while the control group improved (–0.1 ± 1.1). We conclude from this feasibility study that there is a need for caution in advising the use of low-protein intake in infants with CRI. However, our findings should be regarded as preliminary because of the small number of patients and the observation that the weight gains were the same in the two groups.

Key words: Growth – Nutrition – Infants – Renal failure – Dietary protein

* Southwest Pediatric Nephrology Study Group centers/participants

Baylor College of Medicine, Houston, Tex.
Phillip L. Berry, M. D., Andrea Forbes, R. N.
Baylor University Medical Center, Dallas, Tex.
Ronald J. Hogg, M. D., Tracy Shuck, R. N., Kaye Green
Tulane University Medical Center, New Orleans, La.
Frank Boineau, M. D., Karen Welling, R. N.
University of Arkansas, Little Rock, Ark.
Watson C. Arnold, M. D., Donna Floyd-Gimon, R.N.
University of Colorado, Denver, Colo.
Gary M. Lum, M. D., Jeff Paulsen, R. N., Gail D'Amico, R. N.
University of Tennessee, Memphis, Tenn.
F. Bruder Stapleton, M. D., Patti Lawson, R. N., Judy Vinson, R. N.
University of Texas Medical Branch, Galveston, Tex.
Ben H. Brouhard, M. D., Lisa Hollander, R. N., Susan Gemma, R. D.
University of Texas Medical School, Houston, Tex.
Susan B. Conley, M. D., Ann Ince
University of Texas Southwestern Medical Center, Dallas, Tex.
Ricardo Uauy, M. D., Ph. D., Joan Reisch, Ph. D., Steven Alexander, M. D., Nancy Simonds, R. N., Cynthia Cunningham, R. D.
University of Utah, Salt Lake City, Utah
Eileen Brewer, M. D., Miriam Turner, M. D., Jean Tealey, R. N., Greg Done, R. N., Patricia Reading, R. D., Cynthia Terrill, R. D.
University of California at San Francisco participants:
Malcolm Holliday, M. D., Jon Block, Ph. D., Martin Glasser, M. D., Jane Turner, Suzanne Young, R. N., Julie DuBois, R. N., Jon Hidayat, Jean Harrah
(Note that the location of the individual investigators reflects their institution during the time period of this study)

Correspondence to: R. J. Hogg, SPNSG Central Office, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, TX 75246, USA

Introduction

There is currently great interest in the possibility that a reduction in dietary protein intake may slow progression of renal insufficiency in patients with kidney disease. Previous animal studies have shown that very low-protein diets may slow the rate of progression in rats with renal insufficiency [1, 2], but this has often been associated with reduction in growth [3]. Unfortunately, results of comparable studies in humans have been ambiguous from the standpoint of both efficacy (does a low-protein diet *slow* progression?) and safety (is a low protein diet safe?) [4–7].

A large National Instituts of Health (NIH)-sponsored United States trial in adults is currently in progress and will hopefully resolve the issue for this age group [8].

In contrast to adults, infants and young children are more sensitive to the harmful effects of protein deficiency since normal growth is highly dependent upon protein intake. To date, the safety and efficacy of a low dietary protein intake in children with renal failure have only been addressed in two short-term, uncontrolled studies [9, 10]. Both studies reported improvement in growth in association with a slowing in the rate of renal failure when dietary protein was reduced. However, in these studies it is difficult to distinguish any specific benefit derived from the reduced protein intake from the general effects resulting from close patient management during the period of study. In addition, the method of assessing the rate of progression of renal failure in these studies was limited to following the reciprocal of the serum creatinine versus time, a method that is prone to substantial error. Furthermore, in one of the studies [9] adherence to the low-protein diet waned after 1 year so that growth problems related to a low-protein intake may not have been apparent.

In this report, we describe growth and nutrition data from the feasibility phase of a multicenter, randomized, controlled clinical trial that was designed to evaluate the effect of a low-protein intake in a group of infants with reduced renal function. The study incorporated serial measurements of nutritional intake, growth, renal function, and several other clinical indicators. The safety of the diet was tested by assessing nutritional intake and growth – as described in this report; the efficacy was tested by following serial measures of glomerular filtration rate (GFR), as reported elsewhere [11].

Patients and methods

Organization. The study involved 11 centers. The protocol was approved by the Committee on Human Research at each participating institution. The guardian of each patient signed a consent form after reading an illustrated brochure describing the study and discussing the protocol with their physician and research nurse. A manual of operations was prepared by the physician investigators with input from data management, nursing, dietary, and laboratory staff. The investigators and research nurses from each of the participating centers met prior to the start of the study for training in patient recruitment, diet preparation, clinical monitoring (including anthropometry and diet records), and in conducting the iothalamate clearance (C_{Io}) studies that were used to provide accurate measurements of GFR.

Data entry and monitoring of patient and center adherence to the study protocol were coordinated through the central office of the Southwest Pediatric Nephrology Study Group in Dallas. Diet records were obtained throughout the adjustment and study periods and the data were analyzed at the University of Texas Southwestern Medical Center (by J. R.). All laboratory studies used in data analysis, except serum electrolyte measurements, were performed in the core laboratory at the University of California, San Francisco (UCSF). Clinical monitoring was overseen by the three principal investigators (M. H., R. U., R. H.) and a nurse coordinator (at UCSF).

Patient population. Patients were eligible for the study if they met the following criteria: (1) "study age" 6 months or less, defined as chronological age adjusted for prematurity; (2) birth weight more than 1,500 g; (3) chronic renal insufficiency, defined as a serum creatinine of 0.5 mg/dl or greater, resulting from renal dysplasia, obstructive uropathy, polycystic disease, or perinatal cortical necrosis.

Table 1. Nutritional composition of study formulae

	Protein: energy ratios		
	5.6 (Low)	8.0 (Baseline)	10.4 (Control)
Macronutrients (/l)			
Protein (g)	9.5	13.6	17.7
Fat (g)	37.6	37.6	37.6
Carbohydrate (g)[a]	75.5	71.4	67.3
Ash (g)	3.0	3.0	3.0
Total solids (g)	125.6	125.6	125.6
Minerals and vitamins (/l) (concentration maintained constant in all three formulae)			
Calcium (mg)	400.0	Vitamin A (IU)	2,500.0
Phosphorus (mg)	225.0	Vitamin D (IU)	400.0
Sodium (mg)	160.0	Vitamin E (IU)	20.0
Potassium (mg)	580.0	Vitamin C (mg)	100.0
Chloride (mg)	400.0	Vitamin B_1 (mg)	0.65
Magnesium (mg)	42.0	Vitamin B_2 (mg)	1.0
Iron (mg)	12.0	Niacin (mg)	7.3
Zinc (mg)	5.0	Vitamin B_6 (mg)	1.0
Copper (mg)	1.5	Folic acid (μg)	100.0
Iodine (μg)	42.0	Vitamin B12 (μg)	1.5
Manganese (μg)	34.0	Vitamin K (μg)	55.0
Taurine (mg)	45.0	Pantothenic acid (g)	3.01
Carnitine (mg)	14.2	Biotin (μg)	30.0

[a] Carbohydrate source 50% sucrose, 50% lactose

Study protocol. After informed consent was obtained, each patient entered an *adjustment period* from 6 to 8 months study age, during which time they were managed in accordance with a protocol directed to monitoring and correcting electrolyte, acid-base and/or mineral imbalances. All patients during this period were fed a formula with an intermediate protein: energy (P:E) ratio of 8% (described below), and the parents maintained diet records in order to assess the protein and energy intake of each patient.

At 8 months study age, if a patient's serum creatinine remained greater than 0.5 mg/dl, an C_{Io} study was performed. If the C_{Io} was less than 55 ml/min per 1.73 m^2, the patients entered the *study period* during which they were randomly assigned to receive a low P:E (5.6%) or control P:E (10.4%) formula. These were given from 8 to 18 months study age. Precise anthropometric, clinical, and laboratory data were collected on a bimonthly basis during the study period; C_{Io} studies were repeated at 14 and 18 months of age. Further details of the C_{Io} protocol are described elsewhere [11].

Diet formulae. Three isocaloric formulae patterned after Similac PM 60/40 were developed to give three levels of protein intake[1]. Each formula contained 37.6 g/l of fat (corn oil 50%, coconut oil 50%, mono- and diglycerides), as found in Similac PM 60/40. The formulae provided all the vitamins, minerals, and trace minerals recommended by the Committee on Nutrition of the American Academy of Pediatrics and, if consumed at a rate of 80% of the recommended calorie intake, met the recommended dietary allowance (RDA) for these nutrients. The formulae were at the lower end of recommended levels for phosphorus and potassium; the calcium: phosphorus ratio was 2:1. The carbohydrate source was half lactose and half sucrose to minimize the risk for lactose intolerance and to improve palatability.

The protein content of the formula given during the adjustment period (6–8 months) was intermediate (P:E 8%), whereas the P:E ratio

[1] Kindly provided by Ross Laboratories.

of the low- and control protein formulae were 5.6% and 10.4%, respectively. The low-protein formula P : E ratio is similar to that seen in human milk and conforms with the protein intake recommendations by the FAO/WHO/UNU expert committee for healthy infants [12]. The control formula P : E ratio reflects that contained in commercial infant formulae and is half that of whole cow's milk. The proteins used were casein and whey milk proteins in a proportion of 60 : 40. Comparable levels of caloric density were maintained between the formulae by making changes in carbohydrate to compensate for changes in protein (Table 1). The three formulae were coded and were indistinguishable from each other. Investigators, nurses, and parents were blinded to diet group assignments.

A list of low-protein, low-phosphorus infant foods was also developed and given to each parent to provide solid foods to the infants of both groups as they grew. The list expressed solids as exchanges. These were prescribed to provide no more than 20 kcal/kg per day and no more than 0.1 g of protein/kg per day.

Energy intake. The prescribed energy intake for patients in the study was 100% – 120% of the RDA for normal infants of comparable length (RDA for length). Length rather than weight was used because many infants with reduced renal function tend to have a low weight for length; under these circumstances the RDA for length is a better index of energy needs. The energy intake was considered to be adequate if dietary records indicated intakes greater than 90% RDA for length and if the patient's weight gain was satisfactory. However, we recognized early in this study that the accuracy of individual diet records tended to vary. Therefore, the weight gains and the other objective criteria of energy sufficiency were considered to be the most important criteria and diet records were questioned if the rate of weight gain in individual infants was less than would be expected from the energy intake derived from the diet histories. Throughout the study, one of the most important roles of the research nurses was to encourage the parents to provide accurate diet records. If the energy intake was deficient, the caloric density of the formula was increased from 0.67 to 0.8 or 1 kcal/ml. If this was not successful in providing adequate calories, intermittent or continuous nasogastric tube feeding was recommended. At some time during the study, 8 infants required an increase in the caloric density of the formula; 4 received tube feeding. An additional 4 infants met criteria for tube feeding, but this was not instituted. Home visits by the research nurse were recommended for patients with feeding difficulties.

Monitoring of growth. Body weight, length, head circumference, and triceps skinfold thickness were measured using standardized techniques by two trained staff members on even months throughout the study. Values of measurements between observers were required to agree within defined limits (20 g for weight, 0.5 cm for length, 0.2 cm for head circumference, and 1.0 mm for skinfold thickness) or a second round of measurements was made. The mean of all values was computed centrally and used for data entry. Growth data on weight, length, weight for length, and head circumference were computed as standard deviation scores (SDS) according to the age and gender using the NCHS norms [13 – 15]. Skinfold data were also computed as SDS [16]. Change over time was expressed as growth velocity SDS, weight velocity was computed for 2-month periods and length velocity for 6-month periods (6 – 12 and 12 – 18 months of age).

Clinical patient monitoring. Clinical monitoring during this study was performed by the research nurse and nephrologist at each of the study centers in accordance with the protocol described in the manual of operations. Monitoring was also carried out on a monthly basis by a central clinical monitoring committee that reviewed all relevant clinical and laboratory information on each patient. Particular attention was directed to the identification and treatment of: (1) electrolyte abnormalities such as salt wasting, free water deficiency, and abnormalities in potassium and acid-base homeostasis; (2) disorders of mineral metabolism – monitored closely by serial measurements of calcium, phosphorus, and alkaline phosphatase with specific guidelines for the use of dihydrotachysterol, calcium supplements, and phosphate binders (calcium carbonate); (3) deficiency of dietary energy intake.

Patient safety monitoring. Patient safety relative to the dietary protein intake was also monitored closely. This was performed by a member of the clinical monitoring committee who was not involved in direct patient care (R. U.) – in order to assure that blinding would be preserved among all investigators responsible for patient management. Protein deficiency was considered to be present if the serum albumin was less than 3g/dl or if weight gain was less than 50 g over a 2-month period (in the absence of an alternative explanation – such as morbidity or deficient calories). Protein excess was defined as a serum urea nitrogen (SUN) greater than 80 mg/dl or SUN/serum creatinine greater than 60. The response was the same in the case of either protein deficiency or excess; i.e., the study formula was combined (50 : 50) with the intermediate (8%) P : E formula. This resulted in patients in the "modified" low- and control protein groups receiving formulae with P : E ratios of 6.8% and 9.2%, respectively. Since the actions taken to treat signs of protein deficiency and protein excess were identical, neither the investigator nor parents were made aware of the protein content of the study formula for that patient. Two patients in each group were diagnosed as having possible protein deficiency (based on poor weight gain) or excess protein (high SUN/serum creatinine); combined diets were given for the remainder of the study in these patients. However, none of the patients had a serum albumin below 3 g/dl and no patient left the study as a result of safety concerns.

Data management and statistical analysis. All procedures involved in data collection, data entry, and data management were detailed in a data manual that was prepared prior to onset of the study (copy of the manual available from the Southwest Pediatric Nephrology Study Group office upon request). Data were entered using a double-entry verification system. Programs for data entry and data management were based on dBase III + software. Periodic data summary reports were provided for clinical and safety monitoring purposes using dBase programs.

Groups were compared at entry using standard parametric *t*-tests to verify that they were similar relative to the main dependent and intervening variables. Data were analyzed upon completion of the trial using repeated measures analysis of variance. Effect of time of study and diet groups and interactions were tested using F statistics. A P less than 0.05 was considered significant for the time and diet effects, a P less than 0.1 was considered significant for the interaction effect. Simple and multiple correlation analyses were performed to evaluate factors that might affect growth (i.e., diet protein, energy intake, and degree of renal insufficiency). Repeated measure analysis of covariance was used to test for the effect of baseline weight and length on the effect of dietary protein on growth over the 8 to 18 months period. In addition, length change from birth to 6 months and the recorded energy intakes were also used as covariates. SAS [17] and BMDP statistical packages were used for these purposes. All data are expressed in the text as mean ± 1 S. D.

Results

Relevant anthropometric and laboratory variables in the 11 low-protein and 13 control patients at the time of birth and at randomization are shown in Table 2. Both groups of patients were normal at birth but were growth retarded in weight and length at the time of randomization (8 months study age). The severity of the decreased length for age tended to be worse in the low-protein group, whereas the weight for length and triceps skinfold thickness tended to be lower in the control group at the time of randomization. However, these differences were not statistically significant in the small number of patients studied. Baseline SUN and serum creatinine levels were similar in the two groups. Serum albumin levels in the control group were statistically higher, although this was probably not of clinical significance (4.5 vs. 4.1 g/dl).

Table 2. Variables at birth and at time of randomization (8 months study age)[a]

	Low protein ($n = 11$)	Control ($n = 13$)
At birth[b]		
Weight (g)	2,869±521	2,935±91
Length (cm)	48.4± 4.2	48.9± 3.8
Gestational age (weeks)	36.7± 2.2	38.2± 2.6
Length gain 0–6 months (cm)	14.5± 4.4	14.6± 3.7
At randomization (8 months)		
Weight for age (SDS)	–2.0± 1.3	–1.9± 1.0
Length for age (SDS)	–2.2± 1.4	–1.7± 1.4
Weight for length (SDS)	–0.4± 1.0	–0.8± 0.8
Head circumference (SDS)	–1.6± 0.9	–1.5± 1.9
Tricep skinfold (SDS)	–0.1± 0.8	–0.9± 0.9
Arm circumference (SDS)	–0.2± 1.9	–0.6± 1.0
SUN (mg/dl)	35.0± 18.6	28.2±12.4
Serum creatinine (mg/dl)	1.27± 0.4	1.19±0.6
Serum albumin (g/dl)	4.1± 0.3	4.5± 0.3*

SUN, Serum urea nitrogen; SDS, standard deviation score
[a] Data expressed as mean ± SD
[b] Data were derived from information obtained in the patient's birth histories
* $P < 0.05$

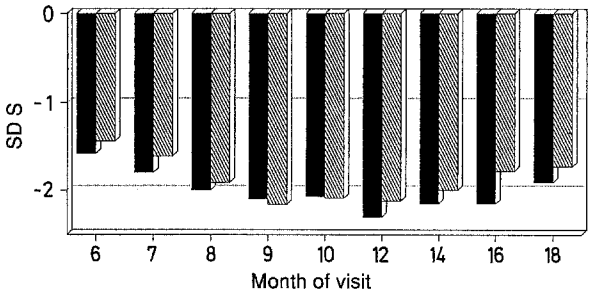

Fig. 1. Sequential weight for age standard deviation scores (*SDS*) from 6 to 18 months in 11 low- (■) and 13 control (▨) protein group patients

Sequential indices of the energy and protein status of the two groups of patients are shown in Table 3. Mean energy intakes are comparable in the low-protein and control groups and oscillated around 100 kcal/kg body weight per day, but when expressed as percentage RDA for length, the intakes were only 92% of that considered ideal for normal children of equivalent length. Not shown in this Table is the fact that one-third of the patients received less than the minimum energy intake considered acceptable (80% of RDA for length) on one or more occasions during the study, despite our intervention strategy for energy insufficiency. The patients in the low and control groups received an average of 1.4±0.3 and 2.4±0.4 g of protein/kg per day from 8 to 18 months of age. Differences were observed in SUN after 2 months that corresponded with these differences in protein intake, whereas serum albumin levels did not differ in the two groups at any time after the patients were randomized to their respective diet groups.

Sequential anthropometric data (Table 4) revealed some surprising differences between changes in individual indices (including weight and length) in the two groups. Absolute increases in weight (low-protein group, 2.28 kg; control, 2.41 kg) and head circumference (low-protein group, 3.3 cm; control, 2.7 cm) from 8 to 18 months were not different between the groups. However, the length gain from 8 to 18 months was 1.3 cm less in the low protein group (9.4 cm) than the controls (10.7 cm); this resulted in significant time/diet interaction [repeated measure analysis of variance (ANOVA) $P = 0.083$]. The other anthropometric measures (triceps skinfold thickness and midarm circumference) showed time-related increases which were not different between the two groups. Similar results were obtained when the growth data were analyzed in terms of

Table 3. Sequential indices of energy and protein status in 11 low-protein and 13 control patients[a]

	Formula	Adjustment	Post-randomization periods					Mean values
Age (months)		6– 8	8–10	10–12	12–14	14–16	16–18	8–18
Energy intake (kcal/kd per day)	Low	102±18	98±16	106±17	102±19	96±23	95±25	101±17
	Control	100±13	98±15	111±27	106±31	100±17	103±19	103±18
Energy intake (% RDA for length)	Low	92±14	89±14	95±12	94±14	89±17	91±20	92±12
	Control	88± 9	85±12	98±21	96±27	92±14	95±17	92±15
Protein intake (g/kg per day)	Low	2.0±0.3	1.5±04	1.4±0.3	1.4±0.3	1.3±0.4	1.3±0.4	1.4±0.3
	Control	2.0±0.3	2.4±0.4	2.6±0.6	2.4±0.6	2.3±0.4	2.3±0.5	2.4±0.4*
Albumin (g/dl)	Low	4.1±0.3	4.4±0.2	4.3±0.4	4.3±0.4	4.4±0.4	4.2±0.4	4.3±0.3
	Control	4.5±0.2[b]	4.4±0.4	4.5±0.3	4.5±0.3	4.5±0.4	4.5±0.3	4.5±0.2
SUN (mg/dl)	Low	37±18	24± 9	26±10	27±12	25±12	23±13	25±10
	Control	29±13[b]	39±17	39±20	44±19	41±16	42±18	41±17*

RDA, Recommended dietary allowance
[a] Mean ± SD
[b] Mean of values obtained at 7 and 8 months of age
* $P = 0.0001$ by repeated measures analysis of variance (ANOVA)

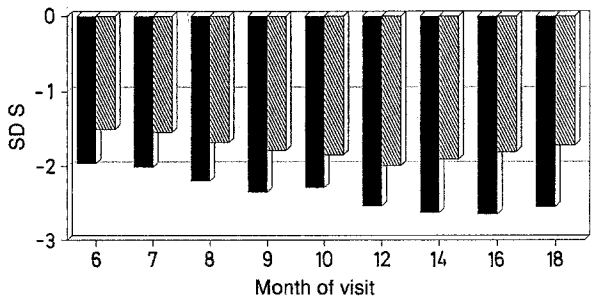

Fig. 2. Sequential length for age SDS from 6 to 18 months in 11 low- (■) and 13 control (▨) protein group patients

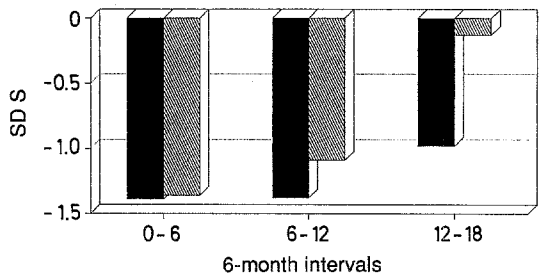

Fig. 3. Comparison of length gain velocity SDS in 11 low- (■) and 13 control (▨) protein group patients from 0–6, 6–12, and 12–18 months

SDS. Weight for age SDS remained comparable between the groups throughout the study period (Fig. 1), whereas length for age scores were worse in those in the low-protein group (Fig. 2) (repeated measures ANOVA $P = 0.083$).

A comparison of the length gain velocity SDS over three 6-month periods in the two groups is shown in Fig. 3. It is apparent that the scores were equally negative in the two groups from 0 to 6 and 6 to 12 months of study age, the latter period including the 2-month adjustment period during which both groups received the same formula (P:E 8%). However, the control group improved to a normal length velocity score during the 12 to 18 month period (–0.1 SD), whereas the low-protein group continued to have a negative score (–1.0 SD) (Fig. 3). The interaction of diet group and time was significant ($P = 0.069$). Further analysis of this relationship was performed using baseline weight (at 8 months), length, energy intake (expressed as kcal/kg per day and % RDA for length) and change in length from birth as covariates. Both baseline weight ($P = 0.015$) and length ($P = 0.032$) strengthened the effect of diet tested with this interaction model. Multiple regression models to evaluate the effect of energy intake on the anthropometric variables or their change over time failed to indicate an overall relationship. Overall regressions of energy effect on specific growth indices were not significant ($P > 0.2$).

No effect of diet on serum albumin, calcium, phosphorus, hematocrit, sodium, potassium, and chloride was detected. Although patients in the low-protein group had significantly higher serum bicarbonate levels at 18 months (24.9 ± 2.1 mEq/l vs. 21.3 ± 3.3 mEq/l in the control group, repeated measure ANOVA P value = 0.034), both groups maintained values within clinically acceptable ranges.

Discussion

The results of our feasibility study suggest that a low-protein diet may result in compromised linear growth in infants with chronic renal insufficiency (CRI). Hence, caution should be exercised when considering the use of a low-protein diet in infants and children with renal disease. Our study represents the first prospective randomized trial of the effect of protein restriction in rapidly growing infants with renal insufficiency. Our conclusions should be considered preliminary, however, because the small number of patients in this feasibility study, the apparent disparity between the effect of the low-protein diet on length gain compared with weight gain, and the trend towards different baseline lengths in the two groups of patients may have contributed to our findings.

The number of patients was small because the study constituted the feasibility phase of a proposed longer clinical study supported by the NIH. However, lack of progression of renal failure in the patients led to the conclusion that we would not be able to evaluate whether the low-protein diet would have any effect on the patients' GFR over that period of time. The results of this part of the study have been detailed in a separate manuscript [11]. In essence, there was no significant change in renal function from 8 to 18 months between the low- and control protein groups. In fact, both groups demonstrated an overall increase in abso-

Table 4. Sequential anthropometric values in the 11 low-protein and 13 control patients

	Formula	Adjustment	Post-randomization periods					
Age (months)		6	8	10	12	14	16	18
Weight (kg)	Low	6.39±1.2	6.88±1.4	7.46±1.3	7.75±1.3	8.34±1.2	8.61±1.3	9.16±1.4
	Control	6.34±0.9	6.88±1.0	7.57±1.3	7.88±1.0	8.41±1.0	8.92±1.0	9.29±1.0
Length (cm)	Low	62.9±3.9	65.2±3.9	67.5±3.6	69.0±3.5	70.9±3.5	72.6±3.7	74.6±3.7
	Control	63.5±3.1	66.3±3.4	68.5±3.9	70.5±3.7	72.8±4.0	74.8±4.2	77.0±4.3*
Head circumference (cm)	Low	42.3±1.2	43.4±1.3	44.6±1.2	45.3±1.2	45.7±1.1	46.3±1.3	46.7±1.3
	Control	42.4±1.8	43.6±1.6	44.2±1.8	44.9±1.7	45.5±1.8	46.2±1.8	46.3±1.7

Mean ± SD

* Two-way repeated measure ANOVA revealed statistically significant time-diet interaction ($P < 0.1$)

lute GFR during the period of study – even the patients whose GFR at 8 months was more severely reduced. Hence, the full clinical trial was never undertaken, and the data that are presented here have by necessity been confined to patients recruited and studied during the feasibility phase.

We encountered very few abnormalities from our clinical monitoring of safety issues – as assessed by biochemical indices of protein excess or deficiency. Only 2 patients in each diet group required action to either reduce or increase their protein intake by combining the study formula (5.6% or 10% P:E) with the baseline formula (8% P:E). The use of SUN/serum creatinine allowed us to verify adherence to the diets, thus confirming the value of this index of protein intake for the analysis of group data.

A number of concerns must be acknowledged in interpreting the results of this study, including the potential confounding influence of deficient energy intake that occurred in some patients, a problem that may have varied to some extent between individual centers, although we attempted to minimize such differences between centers by using a standardized approach and stressing the need for conformity with the research nurses in each center. However, the possibility of variability in energy intake may be important because protein utilization is lower when energy intake is deficient; under such circumstances, a 5% change in energy intake will affect nitrogen retention the same as a 10% change in protein intake [18]. However, since children with CRI often have deficient calorie intakes [19], the effects of limiting dietary protein under the circumstances existing in this study may well reflect the situation that exists when a clinician prescribes protein restriction for an infant with CRI. Whether the results would have been the same if both groups had maintained energy intakes of 100% – 120% of the RDA for length remains unanswered.

As stated earlier, our efforts to maintain a normal energy intake were clearly not successful in all patients. We often provided formulae with increased energy density (up to 1 calorie/ml) by concentrating the formula. However, the anorexia typical of children with CRI limited the success of this strategy. Our use of nasogastric tube feeding was also of limited success. We encountered resistance to the use of tube feeding from both parents and primary care physicians, whose reaction to a recommendation for tube feeding was often to wait longer before initiating such treatment. Eight of the patients met predefined criteria for tube feeding, yet only 4 received this treatment. Despite its documented efficacy, nasogastric tube feeding is seen as a major undertaking by both parents and health professionals. A more aggressive stance towards achieving an adequate energy intake using early tube feeding has been advocated by several investigators and appeared to be helpful in some of our patients.

In conclusion, the data from our studies in infants with CRI lead us to recommend that caution should be exercised when considering the use of protein restriction in such infants. Until data are available to document the efficacy and safety of such treatment, based on long-term, prospective, controlled studies, we believe that safety considerations should prevail and infants should continue to receive an intermediate level of protein intake (P:E ratio of approximately 8%) [19].

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