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Effect of energy intake on nitrogen metabolism in nondialyzed patients with chronic renal failure

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Effect of energy intake on nitrogen metabolism in nondialyzed patients with chronic renal failure. Dietary energy requirements were evaluated during 16 studies that were carried out in six clinically stable nondialyzed chronically uremic patients who lived in a clinical research center and were fed diets providing 45, 35, 25 or 15 kcal/kg/day. Each diet was fed for 23.7 ± 5.7 SD days and provided about 0.55 to 0.60 g protein/kg/day. Nitrogen balance after equilibration and adjusted for changes in body urea nitrogen, and change in body weight each correlated directly with energy intake. Correcting for estimated unmeasured nitrogen losses of about 0.58 g/day, nitrogen balance was negative in one of four patients fed 45 kcal/kg/day, one of five patients receiving 35 kcal/kg/day, three of five patients ingesting 25 kcal/kg/day and both patients fed 15 kcal/kg/day. The urea nitrogen appearance (UNA), the UNA divided by nitrogen intake, and several plasma amino acids, determined after an overnight fast, each correlated inversely with dietary energy intake. Resting energy expenditure measured by indirect calorimetry did not differ from normal and averaged 0.012 ± 0.0033 kcal/kg/min with the different diets. These observations suggest that although some clinically stable nondialyzed chronically uremic patients ingesting 0.55 to 0.60 g protein/kg/day may maintain nitrogen balance with energy intakes below 30 kcal/kg/day, a dietary intake providing approximately 35 kcal/kg/day may be more likely to maintain neutral or positive nitrogen balance, maintain or increase body mass, and reduce net urea generation.

Virtually all studies of the nutritional status of patients undergoing maintenance dialysis therapy that have been published in the last several years indicate that they are, on average, wasted or malnourished [1–11]. The wasting is usually mild or moderate although a small proportion of such patients are severely wasted. Some studies indicate that wasting is present at the time patients commence dialysis therapy, which suggests that this disorder begins in the nondialyzed, chronically uremic patient [5, 8, 12]. There are probably many causes for wasting and malnutrition in patients with chronic renal failure [12], and low energy intake may be one factor. Several reports indicate that the mean dietary energy intake of chronically uremic and maintenance dialysis patients is below normal [1, 3, 5]. However, the energy requirement for chronically uremic patients has never been defined, and it is possible that their energy needs may be less than normal.

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This study was undertaken to examine the energy requirements of chronically uremic patients who are not undergoing maintenance dialysis therapy. Studies were carried out in six patients who were fed a constant protein intake with varying energy intakes in a clinical research center. The effects of varying energy intakes on nitrogen balance, urea nitrogen appearance and anthropometric and biochemical parameters of nutritional status were investigated.

Methods

Sixteen metabolic balance studies were carried out in four men and two women with chronic renal failure who had not received dialysis therapy. Studies were carried out in the Special Diagnostic and Treatment Unit at VA Wadsworth Medical Center and in the Clinical Research Center at Harbor-UCLA Medical Center. The clinical and nutritional characteristics of the patients prior to the initial metabolic balance studies are shown in Table 1. Causes of renal insufficiency were nephrosclerosis (4 patients), interstitial nephritis (1) and unknown (1). At the onset of the study, the estimated glomerular filtration rate, calculated from the mean of the creatinine and urea clearances, was 7.8 ± 4.3 SD ml/min.

During the metabolic studies, patients ingested diets providing 45, 35 or 25 kcal/kg/day. In each patient, the order of administration of these diets was determined randomly. In addition, since some patients appeared to maintain or gain weight with 25 kcal/kg/day, two patients were also given diets providing 15 kcal/kg/day. At each level of energy intake, patients were prescribed 0.55 to 0.60 g protein/kg/day. In each patient, special effort was made to maintain the protein intake constant as the energy intake was varied. 29 ± 3 g/day of the dietary protein was of high biological value. The duration of 15 of the dietary studies varied from 19 to 30 days (mean, 24.8 days). During the sixteenth metabolic balance study, Patient 5 left the Clinical Research Center after he had received his fourth diet, which provided 45 kcal/kg/day, for seven days. Since his nitrogen output appeared to have stabilized during the last three days of study with this diet, his nitrogen balance and urea nitrogen appearance (UNA) data are presented in this paper. However, because anthropometric values, serum proteins and plasma amino acids may take longer to respond maximally to a change in dietary intake, these latter data are not presented for his 45 kcal/kg/day diet.

Table 1. Characteristics of chronically uremic patients undergoing nitrogen balance studies[a]

Patient	Age *yrs*	Sex	Race	Weight *kg*	Body surface area M^2	Serum creatinine *mg/dl*	Serum urea nitrogen *mg/dl*	Creatinine clearance *ml/min*	Urea clearance *ml/min*	Hematocrit *%*
1	61	Male	Black	69.5	1.75	11.3	84	9.3	5.1	28.5
2	60	Male	White	72.9	1.75	10.1	102	10.9	3.9	37.5
3	61	Female	Black	70.2	1.81	6.7	41	5.7	2.6	35.7
4	50	Male	Asian	43.6	1.44	6.1	63	9.6	2.9	25.4
5	55	Male	Black	78.5	1.90	5.0	43	13.9	5.4	28.5
6	49	Female	Black	80.0	1.90	5.8	55	15.6	8.6	31.6
Mean	56			69.1	1.76	7.5	65	10.8	4.7	31.2
SD	6			13.2	0.20	2.6	24	3.5	2.2	4.6

[a] Data obtained at beginning of the first diet administered.

Diets were supplemented with calcium carbonate to bring total dietary calcium intake (food plus supplement) to 1236 ± 35 mg/day. Patients were given vitamin supplements which provided each day vitamin A 5000 IU, vitamin D 400 IU, vitamin E 15 IU, ascorbic acid 60 mg, thiamin 1.5 mg, riboflavin 1.7 mg, niacin 20 mg, pyridoxine hydrochloride 2 mg, vitamin B12 6 mcg and folic acid 0.4 mg. The intake of water and sodium chloride was varied as clinically indicated to maintain water and salt balance and to control blood pressure; all drinking water was deionized. All patients carried out a prescribed quantity of exercise several times each day on a treadmill or stationary bicycle.

Metabolic balance studies were carried out as previously described [13, 14]. All urine output was collected over 24 hr periods and refrigerated immediately after collection. Urine and feces were each collected in pools, usually of seven days duration. The reported urine nitrogen values are the mean of the daily urine nitrogen excretion measured in both the daily and pooled urine collections. Brilliant blue or carmine red was given to identify the beginning and end of each seven day fecal collection. Duplicate diets (prepared weekly), rejected food, emesis, urine collections and feces were each analyzed for nitrogen. The nitrogen content of ingested medicines was also measured, and the nitrogen received each day from medicine intake was added to the daily nitrogen intake from foods. The amount of blood drawn in the patients averaged 6.7 ml/day.

Daily nitrogen balances were calculated as the difference between the measured daily nitrogen intake (minus emesis or rejected food) and the sum of urine and fecal output. Nitrogen balances were adjusted for changes in body urea nitrogen [13–15] but not for unmeasured losses from skin and integumentary structures, respiration, flatus and blood sampling, UNA, a measure of net urea generation, was calculated according to the following equation (all in g/day) [15]:

$$\text{Urea nitrogen appearance} = \text{urine urea nitrogen} + \text{change in body urea nitrogen.}$$

The change in body urea nitrogen was calculated as previously described [15]. Patients underwent serial measurements of relative body weight, triceps, subscapular and mid-thoracic skinfold thickness, and arm muscle circumference as previously described [5]. In brief, relative body weight is the patient's weight multiplied by 100 and divided by the weight of normal individuals of the same age, height and sex. Skinfold thickness was measured with a Lange® calipers. Total body fat was estimated from the triceps, subscapular and supra-iliac mid-thoracic skinfold thicknesses by the equations of Durnin and Wormersley [16]. Lean body mass was estimated from the difference between body weight and total body fat. Bone-free arm muscle area, an indication of muscle mass, was calculated as described by Frisancho [17]. In each patient, all anthropometric measurements were carried out by the same dietitian.

Energy expenditure was measured by indirect calorimetry at the end of study with each energy intake. A Beckman Metabolic Cart and a mouthpiece were used; the methods have been described in detail elsewhere (manuscript in preparation). Briefly, the subject was fasted from 8:20 p.m. the night before the study until the energy expenditure test was terminated. The patient did not leave his bed and was instructed to lie quietly from midnight until the test was completed. Before and during the study, the lights in the room were turned off, and care was taken to keep the room quiet. Starting at 7:00 a.m. the patient breathed into the mouthpiece for 40 minutes. A clamp was placed on the nose to prevent nasal breathing, and the examiner observed the patient on a continuing basis to ensure that air did not pass out of the mouth around the mouthpiece. Data collected during the first several minutes of study before equilibration occurred, during or immediately following any movement by the patient, or which deviated significantly from the mean values from the patient were excluded from analysis. For comparison, resting energy expenditure was also measured in 11 normal free living men and women who were eating ad libitum diets.

Blood for laboratory analyses was drawn between 8:00 a.m. and 9:00 a.m. after an overnight fast. Serum total protein and albumin were analyzed by biuret and bromcresol green methods, respectively [14]. Plasma was measured for amino acids with a Beckman 121 MB Amino Acid Analyzer using a lithium buffer system as previously described [18]; the plasma was first deproteinized with sulfosalicylic acid, 45 mg for 1.0 ml of plasma. The fasting plasma amino acid concentrations were compared to plasma values obtained after an overnight fast from nine normal free living adult controls who were eating ad libitum diets. Urea and creatinine were measured with an Astra Analyzer System (Beckman Instruments, Fullerton, California, USA). Nitrogen was measured by a modified macro-kjeldahl technique [13].

Table 2. Nitrogen balance and urea nitrogen appearance in patients receiving different energy intakes[a]

Patient	Energy intake *kcal/kg/day*	Order of administration of diet[b]	Duration of study *days*	Stable period[c] *days*	Nitrogen intake *g/day*	Adjusted nitrogen intake[d] *g/day*	Urine nitrogen *g/day*	Fecal nitrogen *g/day*	Nitrogen output[e] *g/day*	Adjusted nitrogen balance[f] *g/day*	Urea nitrogen appearance *g/day*
1	43.1	4	27	10	6.99	6.99	3.65	1.64	5.29	+1.37	2.72
2	45.7	1	30	10	6.77	6.77	5.14	1.64	6.78	+0.25	3.47
4	46.3	1	30	9	3.77	3.70	2.40	0.18	2.58	+1.12	1.96
5	45.0	4	7	3	7.62	7.59	4.82	1.53	6.35	+3.44	1.93
Mean	45.0		23	8	6.29	6.26	4.00	1.25	5.25	+1.54	2.52
SD	1.39		11	3	1.72	1.74	1.25	0.71	1.90	1.35	0.73
1	35.0	1	26	15	6.82	6.82	4.87	1.47	6.34	+0.81	3.08
2	34.4	2	28	15	7.42	7.42	4.49	1.55	6.04	+0.94	3.65
4	35.0	2	21	14	3.77	3.71	3.31	0.24	3.55	+0.23	2.62
5	35.0	2	23	7	8.05	8.05	4.36	0.88	5.24	+2.58	3.35
6	35.0	2	21	14	7.07	7.07	5.40	0.94	6.34	+0.68	3.96
Mean	34.9		24	13	6.63	6.61	4.49	1.02	5.50	+1.05	3.33
SD	0.27		3	3	1.66	1.69	0.77	0.53	1.18	0.90[g]	0.88
1	25.0	3	28	18	6.94	6.94	5.74	1.27	7.07	+0.21	4.00
3	25.8	1	28	7	6.32	6.09	2.92	1.51	4.43	+0.33	3.54
4	23.9	3	21	14	4.06	4.06	3.33	0.26	3.59	+0.44	2.70
5	24.9	1	27	13	8.00	8.00	5.58	0.96	6.54	+2.13	3.94
6	25.0	1	22	14	6.89	6.88	5.56	1.20	6.76	+0.66	4.09
Mean	24.9		25	13	6.44	6.39	4.63	1.04	5.68	+0.75	3.65
SD	0.70		3	4	1.46	1.47	1.38	0.48	1.56	0.79	0.57
4	15.5	4	19	11	3.64	3.60	4.00	0.25	4.25	−0.64	3.29
5	15.0	3	21	14	8.02	8.02	6.97	0.95	7.92	+0.06	5.30
Mean	15.2		20	12	5.83	5.81	5.48	0.60	6.08	−0.29	4.29
SD	0.35		1	2	3.10	3.12	2.10	0.49	2.60	0.49	1.42

[a] Balance and urea nitrogen appearance data were obtained during stable period which is the time after patients had stabilized or equilibrated on each diet.
[b] Numbers refer to the chronological order in which the diets were administered to a given patient.
[c] Refers to the period when nitrogen balance had equilibrated and was no longer changing.
[d] Refers to measured nitrogen intake minus the nitrogen content of rejected or vomited food.
[e] Sum of urine and fecal nitrogen.
[f] Indicates nitrogen balance adjusted for changes in body urea nitrogen [13, 15] but not for measured losses.
[g] Significantly different from zero, $P < 0.05$.

Statistical analyses were performed with the Student's t test, the paired t test, and linear regression analyses. Variance was expressed as standard deviation. This study was approved by the Human Subjects Protection Committee, and informed consent was obtained from each patient.

Results

The nitrogen balance data and UNA, obtained in the stable period during the last three to 18 days of study with each dietary energy intake, are shown in Table 2. There were no differences between the dietary nitrogen intake with any of the diets. Neither urine nitrogen nor fecal nitrogen correlated with the energy intake. Nitrogen balance, adjusted for changes in body urea nitrogen, tended to be more positive with the higher energy intakes. Unmeasured sources of nitrogen loss such as from skin, exfoliation, hair, sweat, respiration, and toothbrushing are estimated to be about 415 mg/day [19]. The average amount of blood drawn in this study was about 6.7 ml/day which is equivalent to about 160 mg N/day. Thus, total unmeasured nitrogen losses were about 575 mg/day. Subtracting these values from the adjusted nitrogen balances, we estimate that mean nitrogen balance was negative in one of four patients fed 45 kcal/kg/day, one of five patients fed 35 kcal/kg/day, three of five individuals fed 25 kcal/kg/day, and both patients ingesting 15 kcal/kg/day.

Patient 5, who had the lowest resting energy expenditure of any of the patients, 0.009 ± .0005 kcal/kg/min, had the most positive nitrogen balance with each of the energy intakes. His adjusted nitrogen balance with 45 kcal/kg/day was the most positive balance observed in this study (Table 2). Although he received this diet for only seven days, his daily urine excretion fell during the first five days, and nitrogen balance became more positive with time. The patient's balance for the entire seven day period of study was +1.67 g/day, while it was +3.44 g/day for the last three days. These data suggest that his nitrogen balance during the stable period was not an overestimate of true balance.

Nitrogen balance correlated significantly with energy intake (r = 0.505, $P < 0.05$, Fig. 1). If the data from Patient 5 are excluded from the analysis, the correlation between nitrogen balance and energy intake was stronger ($Y = 0.037x - 0.67$, r = 0.682, $P < 0.025$).

The UNA, measured during the stable period, tended to be lowest with the 45 kcal/kg/day diet and correlated inversely with the energy intake ($r = -0.671$, $P < 0.01$, Fig. 2). Since there was some variability in dietary protein among the patients, the relationship between the UNA, divided by daily nitrogen intake, and energy intake was also examined. There was, if anything, a stronger inverse correlation between this "fractional UNA" and energy intake ($r = -0.736$, $P < 0.005$,

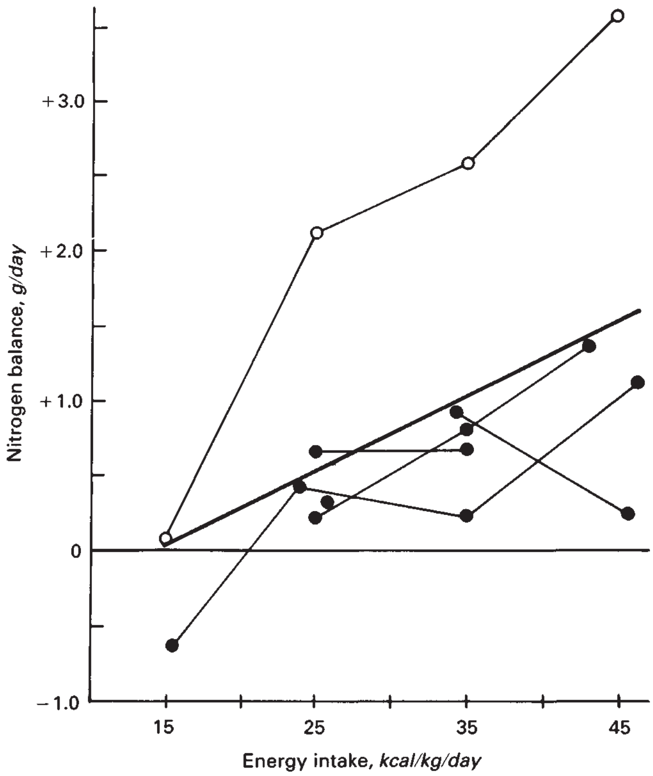

Fig. 1. *The direct correlation between nitrogen balance and energy intake in six clinically stable nondialyzed chronically uremic patients.* Nitrogen balance was obtained after metabolic equilibration and is adjusted for changes in body urea nitrogen but not for unmeasured losses. The open circles represent Patient 5 who had the lowest resting energy expenditure. The thin lines that connect the circles indicate the balance data from the same individual during different energy intakes. The heavy diagonal line represents the least squares regression equation. The heavy horizontal line represents zero balance not adjusted for unmeasured losses. $Y = 0.52x - 0.73$; $r = 0.505$; $P < 0.05$.

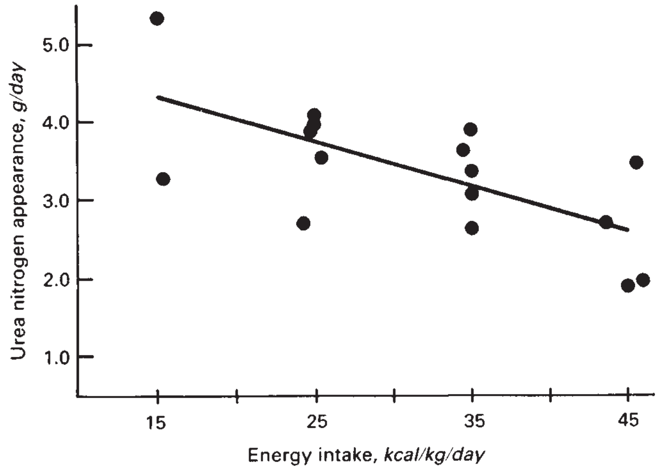

Fig. 2. *The negative correlation between the urea nitrogen appearance and energy intake in six chronically uremic patients.* Values shown were obtained after metabolic equilibration with each diet. The heavy diagonal line represents the least squares regression equation. $Y = 5.20 - 0.058x$; $r = -0.671$; $P < 0.01$.

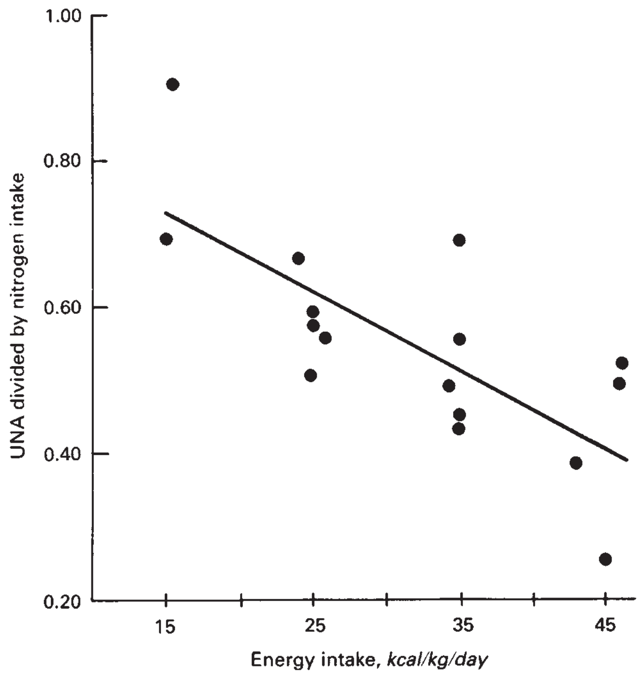

Fig. 3. *The negative correlation between the urea nitrogen appearance (UNA) divided by the dietary nitrogen intake ("fractional UNA") and energy intake in six clinically stable chronically uremic patients.* Symbols are described in the legend to Fig. 2. $Y = 0.89 - 0.011x$; $r = -0.736$; $P < 0.005$.

Fig. 3). The mean UNA was significantly lower with the 45 kcal/kg/day diet than with the 25 kcal/kg/day intake ($P < 0.05$) or the 25 and 15 kcal/kg/day intakes combined ($P < 0.05$). Moreover, the mean UNA with the 45 and 35 kcal/kg/day diets combined were significantly lower than with the 25 and 15 kcal/kg/day intakes taken together ($P < 0.05$). There were no other differences in the UNA between the various diet groups.

The anthropometric and serum total protein and albumin measurements are shown in Table 3. The mean anthropometric values for the six patients combined were not significantly different from normal although Patient 4 had markedly reduced relative body weight, bone-free arm muscle area, skinfold thicknesses and body fat. Despite these abnormalities, the response of this patient's nitrogen balance, UNA, and anthropometric and serum protein measurements to the different energy intakes was similar to the other patients.

The changes in anthropometric and serum protein measurements with the different diets are shown in Table 4. The data were calculated from the values obtained at the termination minus those measured at the onset of each level of energy intake. There was a tendency for the changes in anthropometric values, but not the serum protein concentrations, to be more positive with the 35 and 45 kcal/kg/day intakes than with the lower two energy diets. Mid-arm circumference decreased more with the 15 kcal/kg/day diet as compared to the 35 kcal/kg/day intake ($P < 0.05$), and bone-free arm muscle area fell more with 15 kcal/kg/day than with the 25 kcal/kg/day diet ($P < 0.05$). There was a significantly more positive increase in both edema free body weight and relative body weight with the 35 and 45 kcal/kg/day intakes combined as compared to the 15 and 25 kcal/kg/day diets taken together. The changes in body weight and relative body weight were each positively correlated with the energy intake (Fig. 4). On the other hand, serum

Table 3. Anthropometry and serum proteins at onset of study[a]

Patient	Relative body weight %	Mid-arm circumference *cm*	Arm muscle area cm^2	Skinfold thickness, *mm*			Body fat %	Serum total protein *g/dl*	Serum albumin *g/dl*
				Triceps	Subscapular	Mid-thoracic			
1	91	32.5 (31.7)[b]	73.0 (52)	11.0 (12)	13.5 (17)	22.5	23.8	7.5	4.1
2	96	32.1 (31.7)	63.4 (52)	5.5 (12)	8.0 (17)	8.0	18.7	7.6	4.2
3	90	33.2 (32.6)	48.5 (36)	22.0 (25)	19.7 (16)	18.5	37.3	6.8	3.6
4	64	24.0 (32.2)	27.8 (48)	7.0 (10)	7.0 (12)	7.0	15.4	6.7	4.2
5	102	34.5 (32.0)	46.2 (52)	25.2 (12)	14.8 (17)	18.3	37.1	7.0	4.0
6	114	40.9 (32.1)	62.3 (30)	36.6 (22)	24.8 (14)	21.1	40.2	8.2	4.2
Mean	93	32.9	53.5	17.9	14.6	15.9	28.7	7.3	4.1
SD	17	5.4	16.1	12.2	6.8	6.7	10.7	0.6	0.2
Normal values									
Mean		32.0	45.0	15.5	15.5				
SD		0.3	9.6	6.3	2.1				

[a] Data obtained at the onset of the first diet administered to the patient.
[b] Numbers in parentheses indicate normal values for the patients height, sex and frame size. Normal values were obtained from the median data for adults of similar height and frame size as reported by Frisancho [17].

Table 4. Change in nutritional status with each energy intake[a]

Energy intake *kcal/kg/day*	No. of subjects	Weight *kg*	Relative body weight %	Mid-arm circumference *cm*	Arm muscle area cm^2	Skinfold thickness, *mm*			Serum total protein *g/dl*	Serum albumin *g/dl*
						Triceps	Subscapular	Mid-thoracic		
45.0 ± 1.7[b]	3	+1.4 ±0.8	+1.9 ±0.9	0 (1)[c]	−0.3(1)	+1.0 (1)	+1.5 (1)	+1.0 (1)	+0.3 ±0.7	+0.5 ±0.4[e]
34.9 ± 0.3	5	+2.2 ±2.2	+2.6 ±2.7	+0.4 ±0.1 (3)[g]	−0.7 ±1.6 (3)	+1.9 ±1.9 (3)	−1.6 ±0.6 (3)	+2.0 ±1.4 (3)	0 ±0.3 (3)	−0.3 ±0.1 (3)
24.9 ± 0.7	5	+0.44 ±1.1	+0.5 ±1.4	−0.01 ±0.4 (4)	−0.3 ±0.2 (4)[g]	+1.0 ±0.6 (4)	+2.9 ±2.9 (4)	+0.3 ±1.3 (4)	+0.2 ±0.1 (2)	+0.4 ±0.2 (2)[f]
15.2 ± 0.3	2	−1.6 ±1.7	−2.0 ±2.1	−0.9 ±0.5	−0.9 ±0.2	−0.2 ±1.1	−1.6 ±1.2	+0.3 ±1.9	N/A[d]	N/A

[a] Calculated as the final minus the initial measurement of nutritional status in the individual patients during their study with a given energy intake.
[b] Mean ± standard deviation.
[c] Values in parentheses indicate the number of observations when it is less than the total number of subjects studied at this energy intake.
[d] N/A: data not available.
[e] Differs from 35 kcal/kg/day: [e]$P < 0.05$, [f]$P < 0.02$.
[g] Differs from 15 kcal/kg/day: $P < 0.05$.

albumin fell more with 35 kcal/kg/day than with either 25 or 45 kcal/kg/day.

The fasting plasma amino acid concentrations obtained at the end of study with each energy intake in the patients and in normal controls are shown in Table 5. The amino acid levels in the uremic patients, in general, were similar to those previously reported in renal failure [18, 20]. In the uremic patients as compared to the controls, there were often decreased plasma concentrations of histidine, isoleucine, leucine, lysine, phenylalanine, threonine, valine, total essential amino acids, tyrosine, ornithine, proline, serine, and the ratios of essential/nonessential amino acids and valine/glycine. The uremic patients also manifested elevated plasma levels of cystine, citrulline, N^{π}-methylhistidine (1-methylhistidine), N^{τ}-methylhistidine (3-methylhistidine), and the glycine/serine ratio.

For those plasma amino acids that tended to be reduced, the abnormalities were usually more pronounced in the patients ingesting the higher energy intakes than in those fed 15 kcal/kg/day. Indeed, there was an inverse correlation between postabsorptive plasma concentrations of several amino acids and the dietary energy intake (Table 5). This relationship was particularly apparent for essential amino acids, where a significant negative correlation was observed for leucine, phenylalanine, valine, and total essential amino acids (Fig. 5). An inverse relation was also observed between both tyrosine and ornithine and the dietary energy intake.

The resting energy expenditure, measured at the end of study with each diet, was 0.016 ($N = 1$), 0.013 ± 0.003 ($N = 5$), 0.011 ± 0.002 ($N = 5$), and 0.012 ± 0.004 ($N = 2$) with the 45, 35, 25 and 15 kcal/kg/day diets, respectively. These values did not differ from each other or from levels obtained from 11 normal controls, 0.014 ± 0.004 kcal/kg/min. The measured resting energy expenditure in Patients 1 to 6, averaged from the values obtained at the end of each of their diet studies, was 0.014, 0.016, 0.0080, 0.015, 0.0087, and 0.012 kcal/kg/min, respectively (mean ± SD, 0.012 ± 0.0033), and did not differ significantly from the normal values.

Discussion

The results of this study indicate that clinically stable chronically uremic patients who ingest diets providing about 0.55 to 0.60 g protein/kg/day may need approximately 35 kcal/kg/day to

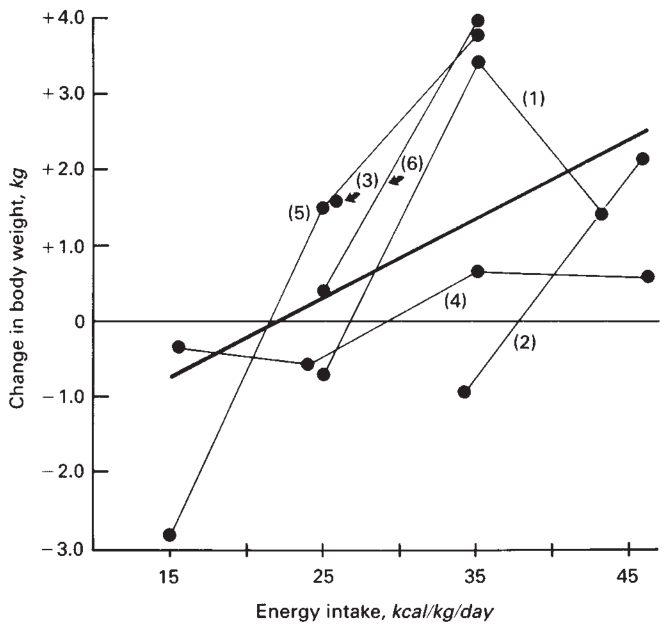

Fig. 4. *The direct correlation between change in edema free body weight and energy intake in six chronically uremic patients.* Change in body weight was measured as the difference between the weight at the termination and the onset of a given energy intake. The thin lines connect data obtained from the same patient. Numbers in parentheses indicate the patient from whom data was obtained. The heavy diagonal line represents the least squares regression equation. $Y = 0.10x - 2.31$; $r = 0.542$; $P < 0.05$.

ensure that they will be in neutral or positive nitrogen balance and maintain body weight and fat mass. This consideration is based on the observation that, when corrected for estimated unmeasured losses of about 0.58 g N/day, the mean nitrogen balance was slightly negative in three of the four patients fed the 25 kcal/kg/day diet but in only one of the patients fed the 35 or 45 kcal/kg/day intakes. Excluding Patient 5 whose nitrogen balances were outliers, the least squares regression equation for the relation between energy intake and nitrogen balance indicate that at a nitrogen balance of about +0.58 g/day (i.e., zero nitrogen balance if estimated unmeasured losses are subtracted), the energy intake is 34 kcal/kg/day.

The value that we selected to indicate neutral balance, +0.575 g N/day, is based upon our measured volume of blood removed and the studies of Calloway and coworkers in which nitrogen losses from the integument, expiration, toilet paper and other sources that are usually not analyzed were carefully measured [19]. The unmeasured nitrogen losses in chronically uremic patients have never been measured, but could be greater because of their azotemia; in normal individuals, the nitrogen losses through skin are directly correlated with the serum urea levels [19]. On the other hand, chronically uremic patients tend to sweat less than normal [21], and this might reduce dermal nitrogen losses. Uremic patients may also lose more nitrogen from the exhalation of volatile nitrogenous compounds [22].

It is pertinent that the changes in many of the anthropometric parameters tended to be less negative or more positive with the 35 or 45 kcal/kg/day intakes than with 25 or 15 kcal/kg/day. Thus body weight increased in four out of five patients fed 35 kcal/kg/day and in all three patients ingesting 45 kcal/kg/day (Table 4, Figure 4). In contrast, body weight decreased in two of five patients fed 25 kcal/kg/day and in both patients receiving 15 kcal/kg/day. Not all anthropometric changes tended to be more positive with 35 or 45 kcal/kg/day, and the change in serum albumin was significantly less positive with 35 kcal/kg/day as compared to 25 or 45 kcal/kg/day. In contrast, the anthropometric changes with 15 kcal/kg/day almost always were most negative.

The resting energy expenditure data are also consistent with the thesis that a daily energy intake of about 30 to 35 kcal/kg/day is necessary to maintain neutral balance in most chronically uremic patients. In healthy young men and women with mild to moderate activity, the energy requirement for maintenance is reported to be, respectively, about 1.7 and 1.6 times the basal energy expenditure [23]. If these relationships are also present in our chronically uremic patients who carried out a prescribed amount of exercise each day in the clinical research center, it would suggest that the mean total energy requirement is 29.1 ± 8.4 kcal/kg/day with individual mean values in Patients 1 to 6 of 33.0, 39.2, 18.4, 36.1, 21.2 and 26.5, respectively. Thus, three of the six patients had estimated dietary energy requirements of about 33 to 39 kcal/kg/day. The three lowest rates of energy expenditure were observed in the two women and in Patient 5.

In summary, the nitrogen balance data, change in anthropometric measurements and measured energy expenditure each suggest that in clinically stable nondialyzed chronically uremic patients who are ingesting 0.55 to 0.60 g protein/kg/day and who are undergoing light physical activity, approximately 35 kcal/kg/day may be necessary to assure maintenance of neutral or positive nitrogen balance and body mass. It is to be emphasized that by the foregoing criteria, several patients had lower energy requirements. If it is possible to determine the energy requirements for individual patients, it may be appropriate to recommend lower intakes for those patients with lower energy needs. However, since measurement of energy requirements is not readily available in most clinical settings, it would seem reasonable to recommend an energy intake that allowed for individual variation and ensured neutral or positive balance in virtually all patients.

If patients ingest a greater nitrogen intake, it is possible that the dietary energy requirement for nitrogen balance may be lower. On the other hand, with greater physical activity, a nitrogen intake that is lower or of different composition, or superimposed catabolic illness, the energy requirement may be greater. Also, since protein conservation and nitrogen balance tend to be greater with 45 kcal/kg/day, this intake may be preferable for nutritionally depleted patients. It is also important to remember that this study was carried out only in four men and two women who were 49 to 61 years old. More studies are clearly needed to define energy requirements more precisely in both sexes of this age as well as in other age groups.

The nitrogen and energy intakes in this study were determined according to the patient's edema free body weight. This policy was chosen because the body composition of uremic patients can be abnormal, and total body water can be increased even in the absence of edema. It may be difficult to estimate a chronically uremic patient's desirable body weight or lean body mass when his body composition may be altered. Nonetheless, this policy may partly explain why the nitrogen balance data

Table 5. Postabsorptive plasma amino acid levels in chronically uremic patients fed different energy intakes and in normal controls

Energy intake *kcal/kg/day*	Chronically uremic patients				Normal adults	Correlation coefficient between energy intake and amino acid values	
	45	35	25	15		*r*	*P*
No. of studies	3	5	5	2	9	15	
Essential							
Histidine	65 ± 16[a,f]	66 ± 9[g]	63 ± 10[g]	72 ± 10[f]	93 ± 8		
Isoleucine	48 ± 32[e]	56 ± 15[e]	59 ± 18	67 ± 19	74 ± 10		
Leucine	65 ± 28[f]	84 ± 17[g]	89 ± 22[f]	115 ± 37	147 ± 27	−0.573	<0.05
Lysine	131 ± 46[f]	145 ± 41[f]	149 ± 29[f]	172 ± 18	215 ± 34		
Methionine	23 ± 9	29 ± 8	26 ± 4	26 ± 1	29 ± 4		
Phenylalanine	37 ± 10[f]	52 ± 13	51 ± 11[e]	62 ± 22	63 ± 9	−0.529	<0.05
Threonine	91 ± 12[f,h]	107 ± 44[e]	103 ± 32[f]	125 ± 8	163 ± 27		
Valine	108 ± 53[f]	139 ± 42[g]	153 ± 34[f]	198 ± 71	247 ± 44	−0.575	<0.05
Total Essential[b]	568 ± 199[g]	680 ± 125[g]	694 ± 133[g]	838 ± 183	1030 ± 121	−0.522	<0.05
Semi-Essential							
Cystine	74 ± 40	70 ± 16	90 ± 22[f]	99 ± 5[g]	59 ± 8		
Tyrosine	27 ± 11[e]	35 ± 9[e]	35 ± 8[e]	45 ± 13	60 ± 23	−0.511	<0.05
Non-Essential							
Alanine	321 ± 147	459 ± 143	412 ± 139	349 ± 99	452 ± 101		
Arginine	94 ± 35	118 ± 89	83 ± 28	68 ± 25	98 ± 20		
Asparagine	76 ± 62	60 ± 30	45 ± 12	42 ± 31	46 ± 9		
Aspartic Acid	16 ± 6[e]	19 ± 5	19 ± 4	16 ± 4[e]	21 ± 2		
Glutamic Acid	39 ± 31	51 ± 22	67 ± 33	40 ± 15	43 ± 11		
Glutamine	342 ± 47[f]	498 ± 127	495 ± 64	412 ± 97	564 ± 95		
Glycine	247 ± 69	367 ± 147	311 ± 134	279 ± 50	273 ± 71		
Ornithine	42 ± 14[e]	42 ± 7[f]	47 ± 5[e]	55 ± 5	67 ± 14	−0.533	<0.05
Proline	167 ± 53[e]	211 ± 36[e]	175 ± 35[f]	209 ± 18	272 ± 53		
Serine	72 ± 23[f]	86 ± 21[f]	74 ± 26[f]	86 ± 24[e]	120 ± 17		
Taurine	86 ± 55	90 ± 34	68 ± 21	53 ± 10	76 ± 15		
Citrulline	64 ± 24[g]	85 ± 10[g,h]	77 ± 13[g,h]	106 ± 8[g]	33 ± 9		
Total Nonessential[c]	1566 ± 379	2174 ± 471	1869 ± 358	1864 ± 150	2001 ± 406		
Total Amino Acids[d]	2246 ± 644[e]	2854 ± 595	2697 ± 421[e]	2702 ± 333	3260 ± 436		
N^{π}-Methylhistidine	25 ± 4[g]	39 ± 37[e]	16 ± 19	6 ± 2	5 ± 5		
N^{τ}-Methylhistidine	33 ± 24[f]	32 ± 11[g]	32 ± 14[g]	15 ± 18	4 ± 2		
Essential[b]/Nonessential[c]	0.38 ± 0.03[e,g]	0.36 ± 0.04[f]	0.39 ± 0.08[e]	0.51 ± 0.03	0.53 ± 0.10		
Valine/Glycine	0.42 ± 0.10[e]	0.43 ± 0.18[f]	0.55 ± 0.19[e]	0.75 ± 0.38	0.97 ± 0.33		
Glycine/Serine	3.52 ± 0.57[f]	4.46 ± 2.00[f]	4.40 ± 1.80[f]	3.30 ± 0.34[e]	2.28 ± 0.52		
Tyrosine/Phenylalanine	0.72 ± 0.09	0.70 ± 0.10	0.67 ± 0.05	0.73 ± 0.04	0.96 ± 0.38		

[a] Mean ± standard deviation.
[b] Calculated as the sum of the concentrations of histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine and valine.
[c] Calculated as the sum of the concentrations of alanine, arginine, asparagine, aspartic acid, glutamic acid, glutamine, glycine, ornithine, proline, serine, taurine, and citrulline.
[d] Calculated as the sum of total essential amino acids, total nonessential amino acids, cystine and tyrosine.
Significantly different from normal values: [e]$P < 0.05$, [f]$P < 0.01$, [g]$P < 0.001$.
Significantly different from 15 kcal/kg/day: [h]$P < 0.05$, [i]$P < 0.01$.

were so positive in Patient 5; his estimated body fat was approximately twice normal for men [24]. Hence, his lean body mass was estimated to be about 60% rather than 80% of body weight. Since the energy requirement is probably related more to lean body mass than to total body weight, this patient may have received a relatively greater dietary energy and protein intake than most of the other patients. Thus, the 15 kcal/kg/day intake may be equivalent to 20 kcal/kg/day in other patients, and his 45 kcal/kg/day may be equivalent to 56 kcal/kg/day in less obese patients. His exceptionally positive nitrogen balance and low UNA may therefore reflect the fact that he received a relatively greater energy and nitrogen intake per kg lean body mass. Also, his energy expenditure would not be as low if it was normalized for lean body mass.

It is puzzling that the resting energy expenditure of our patients did not decrease when they were fed the lower energy intakes. In normal individuals in whom energy intake is varied widely, resting or basal energy expenditure tends to fall when energy intake is reduced [25]. The absence of this relationship in our chronically uremic patients may indicate that each energy intake was not fed for sufficient time or that the range over which the energy intake was varied in most patients was not great enough to demonstrate this effect. Alternatively, chronic renal failure patients may not be able to conserve energy expenditure normally when energy intake is restricted. This latter explanation, if correct, may be another cause of the wasting and malnutrition in renal failure.

It is of interest that other nutritional and metabolic parame-

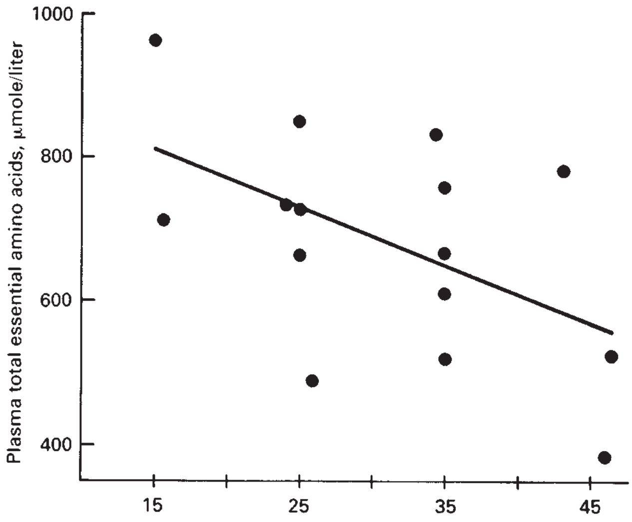

Fig. 5. *The negative correlation between the plasma total essential amino acid concentrations and energy intake in six chronically uremic patients.* The plasma was obtained for amino acid analysis after an overnight fast at the end of study with each energy intake. Total essential amino acids were calculated as the sum of the concentrations of histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine and valine. $Y = 937 - 8.20x$; $r = -0.522$; $P < 0.05$.

ters were affected by energy intake in this study. Thus, there was a strong inverse correlation between energy intake and the UNA and between energy intake and the UNA factored by nitrogen intake (Figures 2 and 3). These data provide evidence independent of the nitrogen balance data that increasing energy intake in chronically uremic patients improves protein utilization and reduces net protein catabolism.

The tendency for the postabsorptive plasma concentrations of many amino acids to rise as energy intake fell is intriguing (Table 5, Figure 5). The cause for this phenomenon, which was observed more frequently with the essential amino acids, is unclear. It may reflect the fact that at the lower energy intakes there was greater net catabolism of protein. This could lead to less incorporation of amino acids into synthesized protein and greater release of amino acids from catabolized protein. Either factor might serve to increase the extracellular amino acid pools.

The results of this study relate to whether the abnormally low energy intakes in clinically stable, nondialyzed chronically uremic patients are sufficient for their nutritional and metabolic needs. The present data suggest that the energy requirements of these patients are similar to that of normal individuals [23]. Their low energy intakes are not an adaptive response and, in fact, may represent anorexia. Hence, the abnormally low energy intakes may contribute to the wasting and malnutrition that is frequently present in such patients when they commence maintenance dialysis therapy [8].

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