Effect of Increased Protein Intake and Nutritional Status on Whole-Body Protein Metabolism of AIDS Patients With Weight Loss

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The aim of this study was to investigate nutritional status and protein metabolism during total parenteral nutrition (TPN) in AIDS patients with weight loss. Six patients on treatment for AIDS-associated complications were investigated and received TPN that supplied energy equivalent to 1.5 times the resting energy expenditure (REE). Amino acid (AA) supply increased from 0.6 g/kg body weight (BW)/d on days 1 to 3 and 1.2 on days 4 to 6 to 1.8 on days 7 to 9. Nonprotein energy was given as equicaloric amounts of glucose and fat emulsion. There were repeated measurements of nitrogen balance and whole-body protein turnover (WBPT) using a bolus ^{15}N-glycine method on the morning of days 3, 6, and 9. Principal findings were as follows: (1) increasing the supply of AAs significantly improves nitrogen balance in AIDS patients; (2) there is no simple linear effect of increasing amounts of AAs on WBPT in AIDS patients; (3) WBPT is high and variable in these patients; and (4) mean WBPT of each patient is significantly correlated with body cell mass (BCM) as a proportion of BW ($P < .001$, $r = .92$). We conclude that poor nutritional status in AIDS patients with weight loss is associated with high WBPT. However, these patients can attain at least transiently positive nitrogen balance with sufficient protein intake, predominantly through an increase in whole-body protein synthesis (WBPS).

PATIENTS WITH AIDS are frequently malnourished, and a proportion have severe wasting. The degree of weight loss in AIDS patients does not appear to be simply due to reduced food intake, malabsorption, or diarrhea.[1-4] Furthermore, patients who will develop weight loss are not easily identified by an increased resting energy expenditure (REE).[5] However, it would appear that weight loss in human immunodeficiency virus (HIV)-infected patients is characterized by a predominant loss of body cell mass (BCM).[3,4] A primary aim in such patients is to replenish or maintain this vital component of body weight (BW). Since BCM is essentially protein, it may be that changes in protein metabolism underlie this loss. To examine protein metabolism in detail, both nitrogen balance and whole-body protein turnover (WBPT) have to be measured, which in turn requires the use of labeled amino acids (AAs) as tracers. Data on protein metabolism in AIDS patients are scarce. In a single reported study, Stein et al,[6] using ^{15}N-glycine as a tracer for protein metabolism, reported that asymptomatic AIDS patients had a starvation-type response with decreased whole-body protein kinetics, decreased fractional synthetic rate for fibrinogen, and reduced total plasma AA levels. However, the patients had no documented weight (and presumably BCM) loss. Therefore, the effect of feeding on protein metabolism of weight-losing AIDS patients is unknown.

The aim of the present study was to examine the response of whole-body protein metabolism of AIDS patients with weight loss to increasing protein intake. For this purpose, we applied the ^{15}N-glycine bolus technique, which allows repeated measurements within short time intervals.[7] Energy intake was controlled by total parenteral nutrition (TPN) of constant energy content. Our results indicate that AIDS patients have increased WBPT in association with poor nutritional status. However, controlled AA-rich hyperalimentation is capable of reversing net protein catabolism.

SUBJECTS AND METHODS

Patients

Five men and one woman with AIDS (Walter-Reed classification 6) were investigated. All had been hospitalized due to progressive HIV disease and were being treated for related complications at the time of study, but none had an increased body core temperature (> 38°C) immediately before study. They all had documented weight loss of at least 3.8 kg in the previous 3 months.

The study protocol was approved by the Ethics Committee of the Medizinische Hochschule Hannover (Hannover, Germany). All patients were informed of the nature, purpose, and possible risks of the study and provided written informed consent before the start of the study.

Study Design

The study protocol is given in Fig 1. After an overnight fast of 10 to 12 hours' duration, baseline measurements of body composition, respiratory gas exchange using indirect calorimetry, and circulating proteins and AAs were performed.

After these measurements, continuous TPN was started and given for 9 consecutive days. Throughout this period, the patients were given the caloric equivalent of 1.5 times their measured REE, and the amount of protein, given over 3-day periods, was increased

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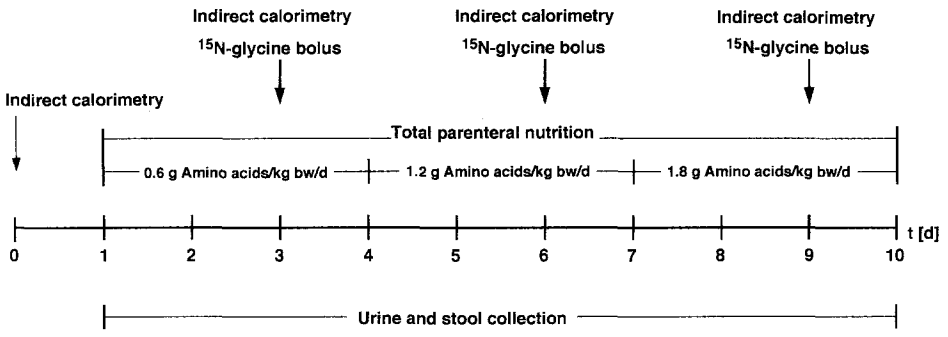

Fig 1. Study protocol.

from 0.6 g AA/kg BW/d (low-N diet, 457 ± 79 kcal/g N) to 1.2 (medium-N diet, 233) and then to 1.8 (high-N diet, 157). AAs were given as Aminoplasmal PO-10% with a nitrogen content of 15.5 g/100 g AAs (Braun, Melsungen, Germany). The AA content (grams per liter) of Aminoplasmal PO-10% is as follows: L-isoleucine 4.8, L-leucine 8.4, L-lysine 7.4, L-methionine 2.0, L-phenylalanine 4.2, L-threonine 4.8, L-tryptophan 2.0, L-valine 6.4, arginine 8.6, L-histidine 5.4, glycine 7.0, L-alanine 12.4, L-proline 7.0, L-asparagine 0.9, L-cysteine 0.6, glutamic acid 9.0, L-ornithine 1.8, L-serine 3.2, and L-tyrosine 2.0.

Nonprotein calories were given as 50% carbohydrate (40% glucose solution; Braun) and 50% fat (20% Lipofundin LCT/MCT emulsion; Braun). Trace elements and vitamins were also given by TPN (all-in-one solution). Oral intake of noncaloric fluid (water or tea) but not of solids was allowed during the study period.

Urine and feces were collected over the whole 9-day study period. At approximately 8 AM on days 3, 6, and 9, patients were given intravenous ^{15}N-glycine 50 mg over 10 minutes. Blood samples were taken for measurement of plasma protein and AA levels. Urine was collected for 9, 12, and 24 hours after ^{15}N-glycine. After this, respiratory gas-exchange measurements were performed to assess energy expenditure.

Nitrogen Balance and Whole-Body Protein Kinetics

Total urinary and fecal nitrogen samples were analyzed by chemiluminescence using an Antek Nitrogen System (Model 703C; Antek Instruments, Houston, TX).[8]

Nitrogen balance was calculated as the difference between nitrogen intake and nitrogen loss via urine, feces, and skin. Integumental nitrogen loss was estimated as 500 mg/d.[9] For nitrogen-balance measurements during days 3, 6, and 9, urea pool size was taken as constant, whereas correction for urea pool size was performed on the calculation of cumulative N balance of the 3-day periods as follows: N balance = $N_{intake} - (N_{urine+feces+skin} + [\Delta BU \times 0.06 \times BW \times C]/2.14)$, where ΔBU is the change of blood urea in millimolars, BW is body mass in kilograms, C is the correction factor (women = 0.55 and men = 0.60), N is nitrogen in grams, and 2.14 accounts for the molar nitrogen content of urea.

Whole-body protein kinetics were measured using a single dose of ^{15}N-glycine. Ammonia was extracted from urine collected before and over a 9-hour period after glycine by a sodium/potassium cation-exchange resin (AG50W-X8, 100 to 200 mesh; Bio-Rad Laboratories, Richmond, CA) and then displaced from the resin by potassium hydrogen sulfate.[10,11] ^{15}N enrichment in urinary ammonia was then analyzed by continuous flow-isotope ratio mass spectrometry.[11] Whole-body protein kinetics were calculated from baseline-corrected incorporation of ^{15}N into urinary ammonia over 9 hours using a simple two-pool model and the expression Q = d/E(c), where Q is WBPT (grams per kilogram per 9 hours), d is the dose of ^{15}N (grams per kilogram per 9 hours), and E(c) is the cumulative excretion of urinary ^{15}N-ammonia.

REE

An indirect calorimeter (Deltatrac Metabolic Monitor; Datex Instruments, Helsinki, Finland) was used to estimate oxygen consumption and carbon dioxide production of patients. This calorimeter was calibrated before and after measurements. REE was calculated from gas-exchange measurements of the last 45 minutes of a 60-minute period using the following equation: $REE = 5.50 \cdot \dot{V}O_2$ [mL/min] $+ 1.76 \cdot \dot{V}CO_2$ [mL/min] $- 1.99U_N$ [g/d], where $\dot{V}O_2$ is oxygen consumption, $\dot{V}CO_2$ is carbon dioxide production, and U_N is urinary nitrogen excretion.

Gas-exchange measurements were also performed during TPN to assess diet-induced thermogenesis (DIT) on days 3, 6, and 9. DIT was calculated as the difference between basal energy expenditure and energy expenditure during TPN on days 5, 8, and 11 devided by the energy intake.

Body Composition Measurements

To assess body composition changes before and during feeding, a number of parameters were measured. Triceps skinfold thickness and midarm circumference (MAC) were measured using a skinfold caliper and a tape measure. Fat mass was derived using the calculated fat-free mass (FFM) and the measured BW (fat mass = BW − FFM). FFM was calculated from the measured total body water, that is, FFM = total body water/0.73. Total body water was measured using bioelectric impedance analysis (BIA) with a radiofrequency current of 800 μA at 50 kHz between a set of electrodes attached to the dorsum of the hand and foot (BIA/S RJL-Systems, Detroit, MI). BCM was calculated using software supplied with the BIA analyzer (program Bodycomp 2.55). As shown previously, anthropometric data (MAC and muscle mass) and BIA-derived BCM are in good agreement in patients with HIV infection.[12] Studies by our group and others further confirmed BIA as a valid method to assess malnutrition in HIV-infected patients.[4,13,14]

Twenty-four-hour urinary 3-methylhistidine excretion was measured to assess muscle catabolism. Muscle mass was calculated from 24-hour urinary creatinine excretion, assuming that 1 g creatinine equals 18.5 kg muscle mass.[15]

Plasma Protein and AA Analysis

The plasma proteins, albumin, fibrinogen, and prealbumin, and total iron-binding capacity were measured by standard in-house methods. C-reactive protein (CRP) level was quantitatively measured by particle-enhanced nephelometry with a typical detection limit of 2 mg/L (Behringwerke, Marburg, Germany). Quantitative measurement of plasma AA concentrations was performed by liquid chromatography using an automated Amino-Acid-Analyser (model LC 5001; Biotronik, Munich, Germany).

Table 1. Clinical Characteristics of Patients at Study Entry

Patient No.	Sex/Age (yr)	Albumin (g/L)	Temperature (°C)*	CRP (mg/L)	Status	Medication†
1	M/34	30	37.6	40	KS, FGL	PEN, FAN
2	M/34	29	37.0	6	Colitis, eczema	Flucloxacillin, erythromycin
3	M/27	14	36.4	29	KS, PCP, TSH	PEN, CLA, SEC, COT
4	M/47	24	37.8	114	TSH, FGL, PCP, ATMYC	PEN, CLA, SEC, IZ, PYR, RIFA, MY
5	F/32	22	37.4	47	Nonspecific colitis	Sulfasalazine, prednisolone
6	M/51	28	37.8	19	CMV-retinitis, STA	Foscarnet-Na, ciprofloxacin-HCl
Mean ± SD	5M:1F/38 ± 9	25 ± 6	37.3 ± 0.6	43 ± 38		

NOTE. Normal range: CRP, <5 mg/L; albumin, 37-51 g/L.

Abbreviations: KS, Kaposi's sarcoma; FGL, fungal esophagitis; PCP, pneumocystis carinii pneumonia; TSH, thrush; ATMYC, atypical mycobacteriosis; CMV, cytomegalovirus; STA, staphylococcus aureus sepsis; PEN, pentamidine; FAN, pyrimethamine + sulfadoxine; CLA, Cefotaxime; COT, sulfamethoxazole + trimethoprim; SEC, Azlocillin; IZ, isoniazid; PYR, pyrazinamide; RIFA, rifampin; MY, ethambutol.

*Rectal body temperature.

†Without antimycotic drugs.

Statistical Analysis

The correlation between two variables was calculated with Spearman's rank correlation test. Multiple comparisons were performed by ANOVA for repeated measures and subsequent Scheffé F test. A two-tailed P value less than .05 was considered significant.

RESULTS

Patient characteristics are listed in Tables 1 and 2. Plasma total aminograms of the AIDS patients did not change significantly over the 9-day study period (Table 3). Similarly, there were no significant changes over the course of the study in serum triglyceride concentrations (basal, 1.85 ± 0.63 mmol/L; day 3, 2.68 ± 1.4; day 6, 1.98 ± 0.83; and day 9, 2.60 ± 1.11) or serum glucose concentrations (basal, 4.5 ± 1.0 mmol/L; day 3, 5.5 ± 1.0; day 6, 5.0 ± 0.8; and day 9, 5.1 ± 0.6). Furthermore, there were no statistically significant differences in the measured body composition parameters BW (+1.2 ± 1.9 kg), fat mass (−0.02 ± 1.72 kg), BCM (−0.12 ± 1.16 kg), MAC (−0.08 ± 0.93 cm), and triceps skinfold thickness (+0.68 ± 0.89 mm), as well as circulating protein concentrations (Table 4), over the 9-day study period.

Mean REE on day 0 was 29.6 ± 7.2 kcal/kg/d (1,572 ± 205 kcal/d), or 108% ± 11% of the predicted energy expenditure (Harris and Benedict). The basal respiratory quotient was 0.80 ± 0.04 and increased to 0.90 ± 0.02 on day 3, 0.88 ± 0.04 on day 6, and 0.86 ± 0.03 on day 9 ($P < .05$, day 3 *v* basal and day 6 *v* basal). Energy expenditure was 30.3 ± 5.5 kcal/kg/d on day 3, 31.7 ± 4.7 on day 6, and 32.6 ± 6.3 on day 9 (NS). At the same time, energy balance decreased from +12.5 ± 3.6 kcal/kg/d on day 3 to +8.4 ± 3.6 on day 6 and +5.6 ± 4.6 on day 9 ($P < .05$, day 3 *v* day 9). Mean DIT was 4.3% ± 4.8% on day 3, 7.1% ± 5.1% on day 6, and 9.0% ± 4.7% on day 9 (NS). N intake correlated with DIT ($r = .75$, $P < .003$). In addition, a significant correlation between protein intake and nitrogen balance was observed ($P < .01$, $r = .73$). Positive nitrogen balance was achieved at an average AA supply of 0.83 g/kg BW/d (Fig 2). Mean basal nitrogen loss was 211 ± 108 mg/kg/d at study entry, corresponding to approximately 10.7 g per individual per day (range, 5.8 to 14.4), indicating a moderately catabolic state in these patients. The increase in AA intake of 0.6 g/kg/d between the low- and medium-N and between the medium- and high-N diets resulted in nitrogen retention rates of 64% ± 3.8% and 48% ± 8.1% over the 3-day periods, respectively.

With reference to whole-body protein kinetics, there was a significant increase in WBPT ($P < .05$) for 1.2 g AA/kg BW/d as compared with WBPT for 0.6 g AA/kg BW/d (Table 5). Blood urea concentrations were 4.0 ± 1.6 mmol/L on day 1, 2.2 ± 1.1 on day 3, 3.8 ± 1.4 on day 6, and 5.7 ± 2.6 on day 9 ($P < .05$, day 3 *v* day 9).

N intake did correlate with urinary N excretion ($r = .62$, $P < .01$) but not with WBPT, whole-body protein synthesis (WBPS), or whole-body protein breakdown (WBPB). Urinary nitrogen excretion increased significantly over the course of the study, but fecal nitrogen excretion did not (Fig

Table 2. Nutritional Status of Patients at Study Entry

Patient No.	BW (kg)	BMI (kg/m²)	IBW (%)	TSF (mm)	Fat Mass (kg)	BCM (kg)	MAC (cm)	Muscle Mass (kg)
1	58.0	17.1	79	3.5	10.5	18.9	24.0	18.6
2	71.0	19.8	91	4.3	14.7	25.6	27.5	26.8
3	42.7	13.9	61	2.7	2.7	10.8	18.5	7.3
4	45.5	14.5	62	3.0	7.1	15.7	23.0	18.0
5	41.0	14.5	66	5.0	9.9	14.5	21.0	12.8
6	73.5	21.9	98	6.0	8.2	29.0	30.0	27.2
Mean ± SD	55.2 ± 14.5	17.0 ± 3.3	76 ± 16	4.1 ± 1.2	8.9 ± 3.7	19.1 ± 6.3	24.0 ± 3.8	18.5 ± 7.8

Abbreviations: BMI, body mass index; IBW, ideal body weight; TSF, triceps skinfold thickness.

*Calculated from 24-hour urinary creatinine excretion.

Table 3. Plasma AA Profile (μmol/L)

AA	Basal	Protein Intake Level I	II	III	Reference Interval
EAA					
Threonine	87 ± 36	103 ± 45	120 ± 33	117 ± 31	76-134
Valine	146 ± 25	106 ± 30	170 ± 44	221 ± 67*	119-215
Isoleucine	42 ± 10	31 ± 18	39 ± 13	57 ± 24	28-60
Leucine	81 ± 19	49 ± 14	69 ± 26	92 ± 33*	63-115
Phenylalanine	56 ± 22	47 ± 6	65 ± 8	70 ± 13	35-121
Tryptophan	19 ± 16	23 ± 13	34 ± 18	39 ± 13	27-75
Lysine	130 ± 36	132 ± 38	138 ± 28	155 ± 37	113-169
Methionine	13 ± 2	13 ± 7	14 ± 5	16 ± 6	12-28
NEAA					
Tyrosine	36 ± 11	29 ± 14	34 ± 9	34 ± 12	35-71
Serine	96 ± 24	101 ± 24	114 ± 21	114 ± 25	74-124
Asparagine	28 ± 8	24 ± 9	24 ± 8	26 ± 14	29-65
Glutamate	98 ± 85	86 ± 28	93 ± 69	88 ± 62	33-87
Glutamine	440 ± 147	542 ± 209	544 ± 157	536 ± 110	274-584
Glycine	155 ± 40	205 ± 84	181 ± 20	188 ± 53	142-284
Alanine	157 ± 26	236 ± 107	204 ± 50	233 ± 52	220-372
Ornithine	51 ± 12	46 ± 11	78 ± 15	95 ± 26†	55-117
Histidine	51 ± 9	55 ± 14	61 ± 14	70 ± 16	58-94
Cysteine	34 ± 12	30 ± 16	28 ± 14	31 ± 17	102-190
Arginine	54 ± 23	64 ± 30	58 ± 21	80 ± 26	53-97
Total	2,121 ± 338	2,246 ± 577	2,733 ± 548	2,647 ± 325	
EAA:NEAA (%)	56 ± 7	41 ± 6	48 ± 12	58 ± 7	

NOTE. Level I = 0.6 g protein/kg/d; II = 1.2; III = 1.8.
Abbreviations: EAA, essential AA; NEAA, nonessential AA.
*$P < .05$ *v* level I.
†$P < .05$ *v* basal.

3). No significant association was found between WBPT and serum CRP concentrations, serum fibrinogen concentrations, energy expenditure, DIT, and deviation of REE from predicted REE. At the same time, there was a strong association between the different parameters of nutritional status (BCM, muscle mass, MAC, body mass index, phase angle, and ideal body weight) and WBPT of study days 3, 6, and 9. However, multiple stepwise regression analysis showed that only BCM given as a percent of BW significantly and independently of all other parameters contributes to the prediction of WBPT ($P < .001$, $r = .60$). Similarly, mean WBPT of study days 3, 6, and 9 of each patient significantly correlates with mean BCM as %BW of each patient ($P < .001, r = .92$).

DISCUSSION

Hypercaloric, high-N TPN results in an anabolic response in AIDS patients. Similar to previously obtained data for oral diets in normal man,[16] we report nitrogen balance at an average AA supply of approximately 0.83 g/kg BW/d and an energy supply of 1.5 times measured REE. An intake of 1.8 g AA/kg BW/d further improves nitrogen balance without a significant accumulation in plasma AAs (Table 3). However, whereas two patients were already in positive nitrogen balance at a supply of 0.6 g AA/kg BW/d, one patient only reached positive balance at an intake of 1.8 g AA/kg BW/d (Fig 2). Thus, despite a similar response to TPN, the degree of catabolism is highly variable in AIDS patients.

Nitrogen retention rates over 3-day periods after the increase of 0.6 g AA/kg BW/d between the low-, medium-, and high-N diets were 64% and 48%, respectively. These values are higher than those found by Shaw et al[17] for depleted patients, who reported retention rates over 7- to 8-day periods of 66% when changing from a glucose-based diet to 1.13 g protein/kg BW/d and a retention rate of 21% when changing from a low-N diet to 2.3 g protein/kg BW/d (energy equivalent to 1.31 × REE was given in all cases).

Table 4. Effect of Nitrogen Intake on Concentrations of Proteins (mean ± SD) for All Patients at Basal (day 0), Low-Nitrogen (day 3), Medium-Nitrogen (day 6), and High-Nitrogen Diets (day 9)

Compound	Basal	Day 3	Day 6	Day 9	Reference Interval
CRP (mg/L)	47 ± 36	36 ± 21	76 ± 73	39 ± 38	<5
Serum protein (g/L)	60 ± 6	58 ± 10	58 ± 8	62 ± 10	65-80
Serum albumin (g/L)	25 ± 6	24 ± 8	24 ± 7	26 ± 9	37-51
Serum prealbumin (g/L)	0.14 ± 0.06	0.15 ± 0.08	0.15 ± 0.07	0.19 ± 0.11	0.17-0.42
Serum TIBC (μmol/L)	41 ± 13	39 ± 15	37 ± 14	42 ± 17	45-73
Plasma fibrinogen (g/L)	6.1 ± 1.8	5.1 ± 1.4	5.2 ± 2.1	5.4 ± 2.3	1.8-3.5

Abbreviation: TIBC, total iron-binding capacity.

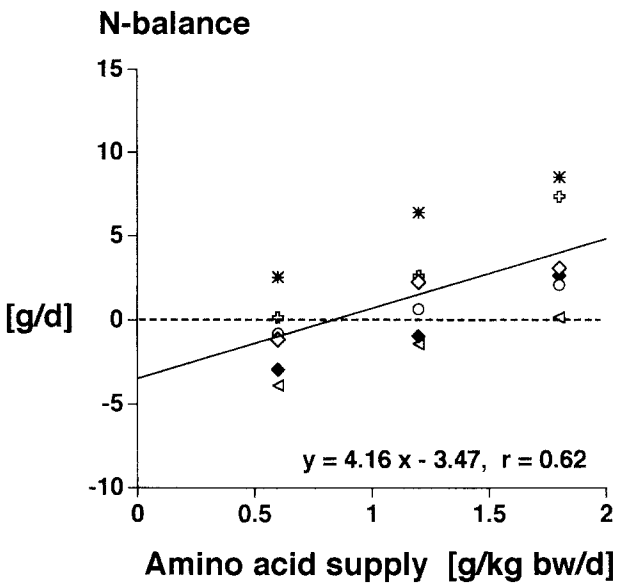

Fig 2. Correlation between AA supply and nitrogen balance per day. Nitrogen balance is achieved at an average AA level of 0.83 g/kg BW/d.

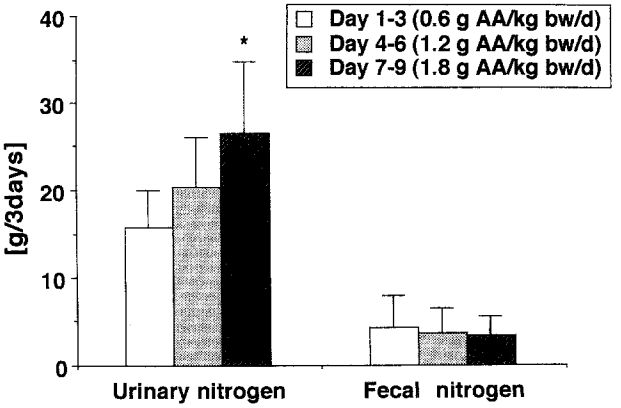

Fig 3. Cumulative urinary and fecal nitrogen excretion over the 3-day periods. *$P < .05$ v day 1-3.

When interpreting these data, one must consider that the order of administration of diets was not randomized in our study, and therefore, this may have affected the magnitude of nitrogen retention rates. Furthermore, it is likely that the equilibration period of 3 days was not sufficient to reach a steady-state nitrogen balance, and therefore, the magnitude of positive nitrogen balance may have been overestimated. Nevertheless, the response pattern of early N retention compares well with previous reports.[16] This finding suggests that prolonged periods of positive nitrogen balance are also achievable in this patient group. Indeed, in a recent study we have shown that long-term feeding by gastrostomy is capable of reversing malnutrition in AIDS patients, as indicated by increases in BCM, MAC, and other nutritional parameters.[12]

The DIT of the TPN diets is similar in magnitude to that seen with oral diets, because digestion and absorption play only a small part in DIT. The short-term thermic effect of infused AA has been shown to be on the order of 20%;[18] mean estimates for the thermic effect of carbohydrates and fat are on the order of 7% and 3%, respectively. Thus, when these substrates are given together, the estimated DIT would be 6.1%, 7.2%, and 8.4% for low-, medium-, and high-N diets in this study, respectively. The observed average values of 4.3%, 7.1%, and 9.0% observed at the end of the 3-day periods are similar and indicate that no major deviation of DIT in malnourished AIDS patients occurs.

A potential criticism of the present study is that we did not have a control group. However, given the duration of the study protocol, it was not considered ethical to examine normal subjects using TPN. We therefore compared WBPT of our patients with turnover values of normal subjects found in previous studies using similar methodology. Reported values for WBPT during feeding in healthy controls vary, but are typically between 2 and 5 g protein/kg BW/d.[19-22] In a study reported by Waterlow and Jackson,[19] feeding at hourly intervals resulted in a protein synthesis rate of 3.3 g/kg BW/d and a protein breakdown rate of 2.1 g/kg BW/d. On a diet supplying 0.8 g protein/kg BW/d and energy of 36 kcal/kg BW/d, nonpregnant women had a protein turnover rate of 4.9 ± 1.0 g/kg BW/d.[20] Vaisman et al[21] reported for females at a protein intake of 1.6 ± 0.3 g/kg BW/d (energy intake, 36.3 ± 11.0 kcal/kg BW/d) a protein turnover rate of 3.8 ± 1.6 g/kg BW/d and for males at a protein intake of 1.9 ± 0.4 g/kg BW/d (energy intake, 45.4 ± 13.9 kcal/kg BW/d) a protein turnover rate of 3.8 ±

Table 5. Protein Metabolism at Different Levels (I, II, and III) of Protein Intake

Patient No.	WBPT (g/kg BW/9 h)			WBPB (g/kg BW/9 h)			WBPS (g/kg BW/9 h)			N Balance (g/d)			3-Methylhistidine Excretion†		
	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
1	2.5	8.7	4.4	2.3	8.3	3.7	2.2	8.3	3.8	−1.15	2.26	3.09	0.015	0.012	0.014
2	2.4	4.3	5.9	2.2	3.9	5.2	2.0	3.9	5.4	−0.80	0.65	2.09	0.010	0.011	0.010
3	4.2	9.4	5.1	4.0	9.0	4.4	3.9	8.7	4.8	0.15	2.62	7.37	0.017	0.019	0.019
4	2.9	4.9	5.0	2.7	4.4	4.4	2.7	4.6	4.4	−2.94	−0.96	2.64	0.023	0.014	0.013
5	6.3	6.1	4.4	6.1	5.7	3.7	6.1	5.7	4.0	−3.87	−1.41	0.17	0.025	0.015	0.016
6	1.7	2.8	2.3	4.1	1.5	2.3	1.7	2.5	2.0	2.54	6.40	8.53	0.015	0.013	0.014
Mean	3.3	6.0*	4.5	3.6	5.5	4.0	3.1	5.6	4.1	−1.01	1.59	3.98*	0.018	0.014	0.014
SD	1.7	2.6	1.2	1.5	2.8	1.0	1.7	2.5	1.2	2.28	2.86	3.25	0.006	0.003	0.003

NOTE. Protein intake: I = 0.6 g protein/kg/d; II = 1.2 g; III = 1.8 g.

*$P < .05$ v I.

†Twenty-four-hour urinary 3-methylhistidine excretion in μmol divided by 24-hour urinary creatinine excretion in μmol.

1.0 g/kg BW/d using the ^{15}N-ammonia end-product method. Jeevanandam et al[16] systematically evaluated the influence of increasing dietary protein given as an oral formula diet on WBPT using the end-product model (arithmetic means of urea- and ammonia-derived values were used). They found that at a protein intake of 1.8 g/kg BW/d and an energy intake of 30 kcal/kg/d, protein turnover was 4.15 g/kg BW/d in healthy males. In patients with protein-calorie malnutrition, TPN of 10 to 14 days' duration resulted in a WBPT rate of 3.1 ± 0.6 g/kg BW/d.[23] In contrast, our patients all had consistently higher WBPT values, except patient no. 6 during the low-N diet (4.5 g/kg BW/d; Table 5, WBPT values expressed per 9 hours).

The limitations of whole-body protein measurements are well recognized. It is likely that absolute values for WBPT are in error, particularly when there are major changes in the mixture of proteins being synthesized as compared with the normal state.[24,25] In the present study, patients had evidence of an ongoing inflammatory response (CRP > 5 mg/L). This was associated with an increase in circulating fibrinogen concentrations and a decrease in albumin, and it is therefore likely that there was a significant alteration in the mixture of proteins synthesized.[24] Nevertheless, the ^{15}N-glycine used in the present study has yielded comparative data, which is consistent with findings using other approaches.[25] Therefore, although absolute values for WBPT and WBPS in the present study may be in doubt, there would appear to be no reason that the relative changes in these parameters are not correct.

In the present study, there was no simple relationship between WBPT and energy expenditure or nitrogen intake. However, it is of interest that there was a significant increase in WBPT when the diet was changed from 0.6 to 1.2 g AA/kg BW/d, but not when the diet was 1.8 g AA/kg BW/d. The basis of this variable alteration in WBPT is not clear; however, it may be that this was a reactive increase of WBPT on the 1.2-g AA/kg BW/d diet in response to a depleted labile protein pool, and therefore, it would not be further increased on the 1.8-g AA/kg BW/d intake. This hypothesis is supported by the 3-methylhistidine excretion data, which suggest that skeletal muscle breakdown is reduced on the 1.2-g AA/kg BW/d intake and remains at a similar level at 1.8 g AA/kg BW/d (Table 4). With reference to the measured changes in WBPS and WBPB, it would appear that the positive nitrogen balance was due to a greater increase of WBPS versus WBPB (Table 5).

No correlation of WBPT with nitrogen balance or protein intake was found, but several nutritional markers did show correlation. BCM expressed as percent BW was the best independent predictor of WBPT in this study. It is known that BCM is a reliable estimate of the degree of wasting in HIV-infected patients because body fat is relatively spared.[4] An association between nutritional status and protein turnover has been reported for malnourished children and men.[26,27] However, whereas malnourished children had a low rate of protein turnover, malnourished and undernourished men have been shown to have higher rates of protein turnover than normal-weight controls. A negative association between protein turnover and BCM could partly reflect compartmentalization of the body protein pool. At rest, visceral tissues have higher rates of metabolic activity than muscle. A relative decrease of muscle tissue can therefore result in an association between increased protein turnover and reduced nutritional status. However, it is unclear if malnourished HIV-infected patients have high viscera to muscle ratios. Body composition studies of patients with simple starvation show that changes of muscle mass are associated with similar changes of visceral tissues, indicating a largely constant viscera to muscle ratio.[28]

In contrast to WBPT rates, which are elevated in our patients in comparison to previously reported values for healthy subjects during feeding, REE is only 8% above predicted values according to the Harris-Benedict prediction in this study (shown earlier). Moreover, there is no correlation between individual rates of WBPT and REE. Thus, although AIDS patients have rates of WBPT approximately 100% greater than in healthy subjects, this does not result in a distinct increase in REE. However, from stoichiometry it can be estimated that the minimum energy required for synthesis of 1 g protein is approximately 0.9 kcal.[29] Assuming an increase of protein synthesis in our patients in the order of 2.0 g/kg BW/d[16,19-23] (Table 5) and a given mean BW of 55.2 kg (Table 2), the extra protein synthesis rate would require expenditure of 95 kcal, which represents approximately 6% of the patients' mean measured REE. A change of this magnitude is at the limit of detection of the method used to measure REE. Nevertheless, the observed increase in REE of 8% in our patients agrees well with the calculated value of 6%. The lack of a significant correlation between WBPT and REE has been previously reported for cancer patients, and was partly explained by the large variability of REE even in healthy subjects.[30]

We conclude that AIDS patients with weight loss have no major alteration of DIT and tolerate an AA supply of 1.8 g/kg BW/d without major increases in plasma total AA and urea concentrations. Hypercaloric, high-N nutrition results at least transiently in a positive nitrogen balance primarily due to WBPS being increased more than WBPB. The intraindividual level of WBPT is strongly associated with nutritional status and thus is not affected by nutritional measures in the short run.

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