Energy and Protein Metabolism in Malnutrition Due to Nonneoplastic Gastrointestinal Diseases

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Although a reduction in both energy expenditure and protein turnover has been demonstrated in starved volunteers, few metabolic data are available for patients in whom malnutrition is due to nonneoplastic gastrointestinal diseases. Chronically malnourished, unstressed adult patients with nonneoplastic gastrointestinal diseases (body mass index, 15.8 ± 2.5 kg/m², n = 13) and healthy control subjects (n = 10) were studied in the postabsorptive state using indirect calorimetry, as well as substrate fluxes of L[1-^{13}C]leucine, L-[2-^{15}N]glutamine (seven patients and six controls), and D[6,6-$^{2}H_2$]glucose (seven patients and eight controls). Resting energy expenditure (REE) expressed in kilocalories per 24 hours was significantly lower in patients than in controls; REE expressed per unit of fat-free mass (FFM) was not significantly different in both groups. Whole-body leucine turnover, oxidation, and nonoxidative disposal rates, based on either ^{13}C-leucine or ^{13}C-α-ketoisocaproic acid (KIC) enrichments, and glucose turnover rate were not significantly different between malnourished patients and controls. Moreover, glutamine turnover was increased by 28% in malnourished patients as compared with normal volunteers (429.8 ± 86.8 *v* 334.9 ± 15.9 μmol/kg/h, *P* = .02). These results suggest that hypometabolic adaptation, although previously documented in starved volunteers, is not operative during states of chronic malnutrition due to gastrointestinal disease. The increase in glutamine turnover rate might represent an adaptative mechanism to malnutrition for preservation of visceral mass or function.

IT HAS LONG BEEN recognized that prolonged starvation and very–low-calorie diets induce a reduction in both energy expenditure and protein turnover rates in healthy and obese volunteers.[1-4] This hypometabolic adaptation is not totally accounted for by a reduction in lean body mass and can be viewed as an adaptive mechanism allowing for prolonged survival through long periods of food shortage. However, malnutrition often occurs as a consequence of chronic diseases of the gastrointestinal tract that preclude adequate nutrient intake and/or absorption. Metabolic data are scarce with regard to unstressed, noncancer patients in this category, and it is not established whether hypometabolic adaptation occurs in that situation.[5,6] The aim of the present study was to assess the metabolic status of a group of patients presenting with chronic and overt malnutrition due to nonneoplastic gastrointestinal disease and devoid of sepsis, fever, or other conditions (eg, postoperative period) known to induce a hypermetabolic state. Indirect calorimetry and stable-isotope infusions were used to assess energy and protein metabolism in these patients before refeeding, and data were compared with those of healthy control subjects.

SUBJECTS AND METHODS

Subjects

Adult patients with progressive body weight loss of more than 10% of usual body weight (ie, pre-illness body weight) associated with noncancer gastrointestinal disease were eligible for the study. All patients were still losing weight. Patients were excluded if they presented with sepsis, renal, cardiac, or hepatic insufficiency, or a past history of diabetes mellitus or dyslipidemia, or underwent surgery in the 3 months before study. In patients with inflammatory bowel diseases, corticosteroid therapy had been interrupted 8 months, 1 year, and 2 years before study, respectively. All patients were admitted to the Nutrition Unit and were candidates for parenteral nutrition. After admission, dehydration and electrolyte imbalances present in eight patients were corrected in 3.0 ± 1.6 days (range, 1 to 6) before the start of study. As a vehicle for electrolytes, these patients (designated A to H) were therefore given intravenous dextrose 184.3 ± 29.3 g/d (range, 125 to 200), which was stopped 12 to 14 hours before study. Oral dietary intake was either nil or negligible in seven patients (B to H) and was preserved but counterbalanced by a marked malabsorption in six (A and I to M). No change was otherwise introduced in their usual oral caloric intake before study, and none of the patients had been intravenously refed before study. The study was approved by the ethics committee of the Lariboisière-Saint-Louis medical school; patients and healthy adult subjects who served as controls provided informed consent before enrollment onto the protocol.

Body Composition

Skinfold thicknesses were measured using a Harpenden caliper at four sites: biceps and triceps of the less-active arm, and subscapular and suprailiac areas. Body fat was calculated using the following equations established by Durnin and Womersley[7]: % body fat = ([4.95/density] − 4.50) × 100 and density = C − (M × log sum of four skinfold thicknesses), where C and M are constant values depending on age and sex. Fat-free mass (FFM) was calculated as the difference between measured total body weight and estimated fat mass.

Indirect Calorimetry

Minute ventilation, oxygen uptake ([$\dot{V}O_2$] milliliters per minute), and CO_2 production ([$\dot{V}CO_2$] milliliters per minute) were measured by open-circuit indirect calorimetry with a moveable device (MMC-Horizon; Beckman, Anaheim, CA) and a ventilated-hood system. Before each measurement period, atmospheric pressure and mixing-chamber temperature were entered into the system; calibration of gas flow was performed with a calibrated syringe, and measured

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Submitted December 22, 1993; accepted January 12, 1995.

Supported in part by a grant from La Fondation pour la Recherche Médicale.

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0026-0495/95/4409-0002$03.00/0

P_{CO_2} and P_{O_2} were compared with span gas (with known O_2 and CO_2 fractions) and pure N_2 (as zero-level gas). A gas check was performed after each measurement period by reading P_{O_2} and P_{CO_2} of the same span gas through the calorimeter; differences of greater than 5% from laboratory data would have invalidated measurements. The system was checked by burning methanol: the "respiratory quotient" ($\dot{V}CO_2/\dot{V}O_2$) of methanol was 0.668 ± 0.011 (n = 4). In addition, measurement of P_{O_2} in four different mixtures of oxygen (P_{O_2} range, 15% to 25%) and CO_2 (P_{CO_2} range, 0% to 4.8%) using the calorimeter indicated no significant differences between theoretic and measured values (0.3% ± 4% for P_{O_2} and 0.25% ± 2.6% for P_{CO_2}). Urinary nitrogen excretion was measured by chemiluminescence[8] or by the Kjeldahl method.[9] Resting energy expenditure (REE) was calculated from gas-exchange measurements and urinary nitrogen excretion, as described previously.[10] Estimated REE was given by the HarrisBenedict formulas for the subject's actual weight[11]: for men, REE = 66.4730 + (13.7516 × weight) + (5.0033 × height) − (6.755 × age), and for women, REE = 655.095 + (9.563 × weight) + (1.8496 × height) − (4.6756 × age), where weight is expressed in kilograms, height in centimeters, and age in years. The ideal body weight of each subject was established using the Metropolitan Life Insurance height and weight tables.[12]

Stable-Isotope Solutions

L-[1-^{13}C]leucine (99% ^{13}C), L-[2-^{15}N]glutamine, (99% ^{15}N), and D[6,6-$^{2}H_2$]glucose (98% $^{2}H_2$) were obtained from Tracer Technologies (Sommerville, MA) or from the Commissariat à l'Energie Atomique (Gif sur Yvette, France). Sterile, pyrogen-free solutions of each of the three labeled compounds were prepared for intravenous infusion using aseptic technique. An accurately weighed amount of each of the three compounds was dissolved in a known volume of sterile, pyrogen-free 0.9% sodium chloride solution and filtered through a 0.22-μm membrane filter (Millipore) into a sterile bottle that was then aseptically sealed. Solutions were prepared no earlier than 18 hours before use and were kept at 4°C until infused.

Analytic Procedures

Stable-isotope enrichments in plasma leucine, α-ketoisocaproic acid (KIC), glutamine, and glucose were measured by electron-impact ionization gas chromatography–mass spectrometry as previously described.[13-15] Expired-air CO_2 enrichment (atom percent excess) was measured with an isotope ratio mass spectrometer after separation of CO_2 by cryogenic distillation in vacuum as described previously.[16]

Calculation of leucine, glutamine, and glucose kinetics. Amino acid or glucose rate of appearance (R_a) into the plasma compartment in the steady state was calculated from the stochastic relationship,[15] $R_a = i[Ei/Ep - 1]$, where R_a is the rate of appearance of the considered substrate into plasma (micromoles per kilogram per hour or milligrams per kilogram per minute for amino acids and glucose, respectively), Ei and Ep are tracer enrichments (micromole percent excess) in the infusate and in plasma at steady state, respectively, and i is the tracer infusion rate (micromoles per kilogram per hour or milligrams per kilogram per minute). For leucine kinetics, steady-state ^{13}C enrichment of plasma KIC was used as an estimate of intracellular ^{13}C-leucine enrichment.[17,18] In the postabsorptive state, leucine R_a is entirely derived from unlabeled leucine released from protein breakdown, since protein breakdown is the only source of essential amino acid inflow. Leucine oxidation rate was calculated from $^{13}CO_2$ enrichment at plateau, $\dot{V}CO_2$, and plasma ^{13}C-KIC enrichment, $F^{13}CO_2 = (\dot{V}CO_2 \times ECO_2 \times 44.6 \times 60)/0.81 \times Ep)$ and Leu oxidation (Ox) = $[1/Ep - 1/Ei] \times 100 \times F^{13}CO_2$, where F is (fraction)(of)$^{13}CO_2$ or $\dot{V}^{13}CO_2$, ECO_2 is expired-air CO_2 enrichment, 44.6 converts milliliters of CO_2 at standard temperature and pressure—dry to micromoles CO_2, 60 converts minutes to hours, and 0.81 is a commonly used correction factor for incomplete recovery of $^{13}CO_2$.[16] Because the carboxyl group of leucine that carries the label (^{13}C) is either irreversibly lost to expired CO_2 or incorporated into protein, it is assumed that the nonoxidative portion of leucine disappearance rate represents leucine incorporation into protein. This portion is referred to as leucine outflow to protein (S):$S = R_a - Ox$.

Calculation of protein turnover. Protein turnover (PT) was estimated from leucine turnover, obtained with either ^{13}C-KIC enrichments or ^{13}C-leucine enrichments, according to the following equation: PT = Leu R_a ($\mu mol \cdot kg^{-1} \cdot h^{-1}$) × 24 (h)/610.7 μmol leucine × g · protein^{-1}. This equation is based on accepted values of 8 g leucine/100 g for leucine content of whole-body protein and the weight of 0.000131 g/μmol leucine.

Protocol

At 7 AM on the day of study, indirect calorimetry measurement was started after an overnight fast and performed during at least 20 minutes of steady state. Overnight urinary output was recorded, and urine samples were analyzed for N content. At 8 AM, a short, smooth catheter was inserted into an antecubital vein using aseptic technique, and a 4-hour primed-continuous infusion of labeled amino acids and glucose was delivered from 8 AM to 12 noon via a calibrated syringe pump. A second catheter was inserted in a superficial vein of the contralateral hand for arterialized venous blood sampling[19] through a heated box (50° to 60°C air temperature). Blood and breath samples were obtained just before administration of isotopes and at regular intervals during the third and fourth hour of tracer infusion (at plateau) to determine isotopic enrichments in plasma amino acids and glucose and $^{13}CO_2$ enrichment in expired air.

Control Subjects

Ten healthy control subjects underwent anthropometric measurements and indirect calorimetry in the postabsorptive state. A second group of six healthy control subjects underwent measurement of whole-body L-[1-^{13}C]leucine and L-[2-^{15}N]glutamine kinetics in the postabsorptive state. A third group of eight control subjects received D-[6,6-$^{2}H_2$]glucose in the postabsorptive state.

Hormone Levels

Serum insulin and cortisol levels were determined in the postabsorptive state in nine patients, using radioimmunoassay as described previously.[20]

Statistical Analysis

Results are expressed as the mean ± SD. Data were compared by paired or unpaired Student's *t* test when appropriate. Linear regression by least-squares analysis was used to assess correlations between sets of data.

RESULTS

Patients' diagnoses and relevant nutritional characteristics (serum levels of albumin, retinol-binding protein, and C-reactive protein [CRP]) are listed in Table 1. The two patients with inflammatory bowel diseases had no residual overt lesions. Values for the sum of skinfold thicknesses and other anthropometric results of malnourished patients and controls are listed in Table 2. Mean body weight, FFM,

Table 1. Diagnosis and Selected Serum Protein Levels of Malnourished Patients

Patient	Diagnosis	Serum Albumin (g/L)	CRP (mg/L)	RBP (mg/L)
A	Crohn's disease with short bowel	29.9	<5	42
B	Chronic radiation enteritis	30.2	7.5	25
C	Chronic radiation enteritis	26.1	15	65
D	Chronic intestinal pseudo-obstruction	38.4	<5	17
E	Chronic intestinal pseudo-obstruction	28.6	<5	27
F	Toxic esophagitis	31.9	9.5	19
G	Chronic intestinal pseudo-obstruction	34.2	<5	42
H	Toxic esophagitis	31.6	<5	43
I	Ulcerative colitis with proctocolectomy and short bowel	38.5	<5	65
J	Mesenteric infarction and short bowel	29.1	<5	21
K	Mesenteric infarction and short bowel	25.8	<5	25
L	Crohn's disease with proctocolectomy	33.1	7.5	40
M	Mesenteric infarction and short bowel	29.7	<5	23
Mean ± SD		31.3 ± 4.0		34.9 ± 16.3
Normal control value (range)		35-45	<5	30-60

Abbreviation: RBP, retinol-binding protein.

and body mass index were significantly lower in patients than in controls. The mean body weight of patients was significantly less than their ideal and usual body weight. Anthropometric and biologic data indicated a status of protein-energy depletion with an absence of inflammation in 12 of 13 patients, as determined by CRP serum levels.

Results of indirect calorimetry measurements are listed in Table 3. There was a statistically significant difference between estimated and measured REE both in malnourished patients (paired t test, $t = 3.35$, $P < .01$) and in control subjects (paired t test, $t = 3.47$, $P < .01$). However, differences between estimated and measured REE in malnourished patients ($-15.7\% \pm 16.9\%$) and control subjects ($-12.8\% \pm 11.7\%$) did not reach statistical significance ($t = 0.45$, NS). When expressed in kilocalories per day, estimated and measured REE were significantly less in patients than in controls. When measured REE was related to FFM, no difference was observed between malnourished patients and controls. There was a positive correlation between measured REE and FFM in control subjects ($r = .733$, $P < .02$) and in malnourished patients ($r = .710$, $P < .01$). The predictive equation for measured REE based on FFM was REE = (18.3 × FFM) + 455 in control subjects and REE = (15.7 × FFM) + 487 in malnourished patients (Fig 1). When patients' measured REE was calculated using the correlation equation derived from our group

Table 2. Anthropometric Data of Malnourished Patients and Healthy Control Subjects

Patient	Age (yr)	Sex	Body Weight (kg)	Sum of 4 Skinfolds (mm)	FFM (kg)	%UBW*	%IBW†	BMI (kg/m²)
A	35	M	40.5	8.9	38.9	70	64	14.4
B	70	F	37.5	17.8	30.1	83	70	13.9
C	25	F	32.3	21.4	27.3	89	70	14.9
D	40	M	46.6	19.7	41.0	85	75	17.1
E	20	F	34.0	27.6	27.7	81	62	13.3
F	19	F	45.0	25.1	37.3	75	83	15.9
G	38	F	41.7	10.2	37.8	73	76	14.8
H	29	F	34.0	14.7	30.6	71	64	12.3
I	60	M	55.0	16.8	49.5	85	82	17.8
J	68	M	61.2	37.6	47.9	82	97	21.9
K	52	F	50.5	24.1	38.5	78	95	18.3
L	25	F	38.0	19.9	32.7	73	73	14.5
M	34	M	50.0	31.9	41.6	88	75	16.1
Mean ± SD	39.6 ± 17.6		43.6 ± 8.8	21.2 ± 8.1	37.0 ± 7.1	79.5 ± 8.5	75.9 ± 11.0	15.8 ± 2.5
Control (n = 10, 4F/6M)								
Mean ± SD	32.4 ± 6.0		64.3 ± 8.0	41.2 ± 11.2	50.8 ± 8.7	100.2 ± 1.2	100.3 ± 4.5	21.7 ± 1.5
P	NS		<.001	<.001	<.001	<.001	<.001	<.001

Abbreviations: UBW, usual body weight; IBW, ideal body weight; BMI, body mass index.

*Expressed as % of pre-illness body weight.

†Expressed as a percentage of IBW.

Table 3. Results of Indirect Calorimetry Measurements in Patients and Controls in the Postabsorptive State

Patient	EREE (kcal/24 h)*	MREE (kcal/24 h)	MREE/FFM (kcal/kg/24 h)	Nu (g/24 h)
A	1,227	1,111	28.6	2.8
B	988	1,028	34.1	2.9
C	1,119	729	26.7	3.2
D	1,200	1,172	28.6	7.2
E	1,187	1,009	36.4	4.6
F	1,307	1,034	27.7	4.4
G	1,187	968	25.6	6.6
H	1,109	1,024	33.4	11.9
I	1,340	1,292	26.1	20.1
J	1,284	1,330	27.8	2.9
K	1,202	1,133	29.4	6.7
L	1,201	1,142	34.9	8.7
M	1,322	916	22.0	8.1
Mean ± SD	1,206 ± 97	1,068 ± 157	29.3 ± 4.2	6.9 ± 4.8
Control (n = 10)				
Mean ± SD	1,555 ± 199	1,382 ± 211	27.5 ± 3.3	9.7 ± 3.2
P	<.001	<.001	NS	NS

Abbreviations: MREE, measured REE; Nu, urinary nitrogen excretion.
*Estimated from Harris-Benedict equation.

of control subjects, patients' measured REE appeared slightly decreased compared with calculated REE (paired *t* test, $t = 2.08, P = .06$).

Data for leucine and glutamine kinetics are listed in Table 4. Whole-body leucine turnover, leucine oxidation, and nonoxidative leucine disposal, obtained with either ^{13}C-leucine or ^{13}C-KIC enrichments, were not significantly different in seven malnourished patients and six normal volunteers. The ratio of KIC to leucine ^{13}C enrichment was similar in patients and normal volunteers (0.89 ± 0.17 and 0.90 ± 0.20, respectively).

Whole-body glutamine turnover was increased by 28% in seven malnourished patients as compared with six normal volunteers (unpaired *t* test, $t = 2.62$, $P = .02$). Glucose R_a was similar in the same seven patients and eight controls (2.9 ± 0.7 and 2.5 ± 0.2 mg · kg · min^{-1}, respectively).

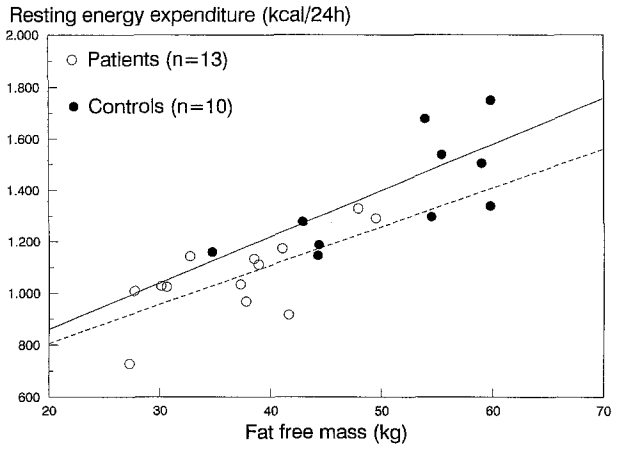

Fig 1. Correlation between FFM and REE in (○—○) patients ($r = .71$, REE = [15.7 × FFM] + 487) and (●—●) controls ($r = .73$, REE = [18.3 × FFM] + 455).

In malnourished patients, measured REE expressed per unit of FFM correlated positively with leucine turnover calculated using ^{13}C-leucine plasma enrichments ($r = .75$, $P = .05$) and glutamine turnover ($r = .79, P = .036$).

Postabsorptive blood glucose levels were 4.8 ± 0.4 mmol/L (range, 4.3 to 5.5), insulin levels were 7.9 ± 3.5 μU/mL (range, <5 to 13; normal range, <5 to 15), and serum cortisol levels were 646 ± 366 nmol/L (range, 237 to 1,280; normal range, 250 to 650). Only two patients had cortisol serum levels above the upper limit of normal range. Due to the small number of patients (n = 4) who had both determinations of substrate fluxes and hormone serum levels, correlation cannot be calculated.

DISCUSSION

This study used indirect calorimetry and infusion of stable-isotope–labeled glucose, leucine, and glutamine to assess protein-energy metabolism in malnourished patients with nonneoplastic gastrointestinal disease. Patients were studied after correction of dehydration and/or gross electrolyte disturbances and before initiation of nutritional restoration. The patients were not in a septic or postoperative state and did not have an ongoing inflammatory process, as shown by CRP values; two patients with inflammatory bowel disease had been cured of active lesions and were not given corticosteroids. All patients had normal postabsorptive glucose and serum insulin levels. Mean serum cortisol level was at the upper range of normal, a finding previously documented in energy- or protein-depleted patients.[21-25] The patients are therefore representative of chronic protein-energy malnutrition induced by gastrointestinal disease without superimposed clinical stress. In this population we found that rates of energy expenditure, glucose production, and protein turnover expressed per unit of body weight or FFM were similar in patients and controls, whereas whole-body glutamine turnover was increased by 28% in comparison to controls.

It has been proposed recently that expression of energy expenditure per unit of FFM introduces a mathematic bias, and that a comparison of slope and intercept of the regression lines between FFM and REE in different groups of subjects was more appropriate.[26] In our patients, measured REE was slightly reduced as compared with REE calculated using the slope and intercept of normal volunteers. However, the reduction in REE related to metabolic adaptation was not substantial and would represent, at most, 5%. Our results contrast with those of previous studies in starved individuals. The classic study performed by Keys et al[3] in normal volunteers undergoing a 24-week semistarvation period showed a significant reduction in REE, representing 14% of REE, when expressed per unit of FFM. Most studies performed in obese subjects undergoing very–low-calorie weight-reduction diets have also produced similar results.[27] Yet studies performed in spontaneously occurring deprivation or malnutrition states have yielded less clear-cut results. A reduction in REE related to lean body mass has been observed in Indian laborers

Table 4. Leucine Flux (R_a), Oxidation, and Nonoxidative Disposal and Glutamine Kinetics in the Postabsorptive State in Patients and Controls

Patient	Leu R_a (μmol/kg/h)		Leu Ox (μmol/kg/h)		NOLD (μmol/kg/h)		Protein Turnover (g/kg/d)*		Gln R_a (μmol/kg/h)
G	152.0	111.6	22.6	16.6	129.4	95.0	6.02	4.39	281.2
I	120.7	119.3	18.3	19.1	102.4	100.2	4.79	4.69	403.6
H	ND	167.5	ND	22.8	ND	144.7	ND	6.58	538.6
L	187.7	135.4	23.5	13.1	164.2	122.3	7.43	5.32	527.5
J	104.8	119.7	14.6	11.2	90.2	108.5	4.15	4.70	433.6
K	112.1	86.6	39.5	23.5	72.6	63.1	4.44	3.40	425.3
M	72.5	70.2	9.7	7.2	62.8	63.0	4.06	2.76	398.5
Mean	125.0	115.8	21.4	16.2	103.6	99.5	5.15	4.55	429.8
SD	40.0	31.7	10.2	6.1	37.8	29.8	1.32	1.25	86.8
Controls (n = 6)									
Mean	108.4	93.7	21.0	16.8	87.4	76.9	4.29	3.71	334.9
SD	22.7	8.0	6.0	7.8	23.6	12.4	0.90	0.32	15.9
P	NS		NS		NS		NS		.02

NOTE. Leucine turnover parameters were calculated from plasma enrichment in ^{13}C-KIC and ^{13}C-leucine: first and second, respectively.
Abbreviations: Ox, oxidation; NOLD, nonoxidative leucine disposal; ND, not determined.
*Estimated assuming a leucine content of 8 g/100 g in whole-body protein.

habituated to low intakes,[4] but could disappear with a longer duration of malnutrition.[28] Most studies concerning anorexia nervosa have given support to a reduction of REE per unit of lean body mass.[29] Data obtained in unstressed patients with gastrointestinal disease are scarce. Lindmark et al[6] compared malnourished noncancer patients (most of them suffering from gastrointestinal diseases) with controls; they did not observe any reduction in REE per unit of body mass using total-body potassium as an index of body cell mass. Our data indicate that the potential economy represented by an adaptation of energy metabolism to undernutrition is quantitatively negligible in chronically malnourished patients with gastrointestinal disease, without overt superimposed clinical stress.

In the same line of evidence, postabsorptive whole-body protein and glucose turnover rates were not reduced in our population of malnourished patients in comparison to normal volunteers. This finding differs from reports on obese patients undergoing a very–low-calorie weight-reduction diet, in whom protein and glucose fluxes declined during prolonged fasting.[2,30] On the other hand, Golden et al[1] showed in five malnourished starved infants that whole-body protein turnover studied with ^{15}N-glycine was significantly less when children were malnourished than after recovery. The absence of reduction in leucine and glucose fluxes might therefore be a feature of chronic undernutrition associated with gastrointestinal disease in adult patients, provided that further studies confirm these data.

It has been shown that in chronic undernutrition, muscle mass decreases linearly with severity of undernutrition while visceral mass shows little change.[31] Since glutamine kinetics were measured under steady-state conditions, elevation of whole-body glutamine turnover in our malnourished patients suggests an increase in both production and utilization of glutamine. In view of the role of glutamine as a preferred fuel for rapidly dividing cells such as those of the viscera,[32] it can be hypothesized that this increased utilization of glutamine takes place in the splanchnic territory. Such an increased delivery rate of glutamine, presumably from the skeletal muscle,[33] to the viscera might contribute to the preservation of visceral mass and/or function during chronic undernutrition and thus can be viewed as an adaptative mechanism to undernutrition. The increase in glutamine turnover rate was present even in four patients with a short bowel, a situation for which we have previously demonstrated a 20% reduction in glutamine turnover.[34] However, the latter result was obtained in a group of weight-stable patients with normal nutritional status.[34] This result therefore suggests that chronic malnutrition per se might lead to increased glutamine turnover.

It can be argued that in the present study, water and electrolyte depletion could have stimulated cortisol and catecholamine secretion and led to metabolic stress. Although this hypothesis cannot be excluded, since 24-hour urinary free cortisol and catecholamine levels were not measured, we think that this was not the case. First, mean serum cortisol levels were at the upper limit of normal in the subjects studied, but elevated serum cortisol levels have been documented in malnourished adults and children with marasmus rather than kwashiorkor,[23] without apparent dehydration. Since cortisol excess has been demonstrated to cause a significant increase of glutamine efflux,[35-36] we can hypothesize that elevated serum cortisol levels contributed to the increase in glutamine turnover rate in our chronically malnourished patients. Second, infusion of epinephrine, even at a high physiologic range such as seen in stress and trauma, increases REE but minimally affects glutamine flux,[37] a metabolic pattern different from that observed in our study. Third, dehydration had been corrected in a mean of 3 days (range, 1 to 6) before the metabolic study.

In summary, in this study performed in chronically malnourished, nonneoplastic gastroenterologic patients, there emerged a coherent metabolic pattern in which neither protein nor energy metabolism showed any evidence of hypometabolic adaptation. Although rates of energy expenditure and protein turnover were depressed when expressed on a whole-body basis (eg, kilocalories per day), this reduction was almost entirely attributable to the loss of FFM rather than to a reduction in the rates of energy, glucose, or protein metabolism per unit of body

weight. On the contrary, both energy production and proteolysis proceeded at normal rates, and release of the conditionally essential amino acid, glutamine, was accelerated. Taken together, these findings suggest that the saving process termed hypometabolic adaptation—although documented in healthy subjects submitted to hypocaloric diets or obese subjects submitted to voluntary starvation—is not operative during states of malnutrition due to gastrointestinal diseases. From our data, we cannot exclude that water and electrolyte disturbances associated with gastrointestinal disease represent a stress state driving the rates of protein, glutamine, and energy metabolism in the upward direction. However, the present results support the view that studies performed in starved volunteers cannot be extrapolated to states of chronic malnutrition observed in clinical settings.

ACKNOWLEDGMENT

We thank the nursing staff of the Saint Lazare Hospital nutrition unit for excellent care of the study subjects.

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