Protein and Energy Balance Following Femoral Neck Fracture in Geriatric Patients

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To elucidate the effect of total peripheral parenteral nutrition (TPPN) on protein kinetics following injury, we compared the whole-body leucine kinetic response using a primed-constant infusion of L-[1-^{14}C]leucine in 33 elderly patients (aged 82 ± 1.0 years) following hip fracture and 33 healthy elderly control subjects (aged 75 ± 0.7 years). Following a 36-hour fast, leucine release from protein breakdown was 1.2 ± 0.10 μmol · kg^{-1} · min^{-1} and leucine incorporation into protein was 0.94 ± 0.095 μmol · kg^{-1} · min^{-1} in control subjects, and in injured subjects leucine release from protein breakdown was 1.3 ± 0.14 μmol · kg^{-1} · min^{-1} and leucine incorporation into protein was 0.97 ± 0.092 μmol · kg^{-1} · min^{-1}. Control and injured subjects were then administered TPPN (protein, 1.5 g amino acids · kg^{-1}; carbohydrate, 10.0 kcal · kg^{-1}; lipid, 15.0 kcal · kg^{-1}) for 24 hours, and leucine kinetics were redetermined. Compared with protein kinetics in the fasting state, leucine release from protein decreased to 1.0 ± 0.14 μmol · kg^{-1} · min^{-1} and leucine incorporation into protein increased to 1.16 ± 0.097 μmol · kg^{-1} · min^{-1} in control subjects. Injured patients also responded to TPPN with a decrease in leucine release from protein breakdown (1.12 ± 0.156 μmol · kg^{-1} · min^{-1}) and an increase in leucine incorporation into protein (1.29 ± 0.164 μmol · kg^{-1} · min^{-1}). These results indicate that in a geriatric population, whole-body leucine kinetics following hip fracture and the anabolic response to TPPN are not significantly altered from those of uninjured subjects. The overall metabolic response of energy expenditures and efficiency of nitrogen retention does suggest a mild catabolic response that may be reversed by nutritional intervention.

INDIVIDUALS aged 65 years and over represent a rapidly growing cohort of the total population.[1] Fracture of the hip is one of the most common, devastating, and feared medical crises of older persons, threatening both survival and independence,[2] and has been described as having reached epidemic proportions in the United States,[3] as well as in other industrialized societies.[4] Because of the increasing number of elderly people in the United States, the total number of hip fractures in persons 50 years and older will increase from 238,000 to 512,000 by the year 2040, with a concomitant increase in avoidable deaths, disabilities, and medical costs.[5]

The information available on the energy and protein metabolism of elderly patients after surgery or trauma is sparse. Albanese[6] concluded that following hip fracture negative nitrogen balance persisted with intakes of 0.7 to 0.9 g protein · kg^{-1} · d^{-1} and that repletion of tissue protein was best achieved at 1.0 to 1.3 g protein · kg^{-1} · d^{-1}. Stableforth[7] reported that after surgery for femoral neck fractures spontaneous food intake was low and nitrogen balance was negative. Jallut et al[8] reported negative energy balance in a similar patient population. In the single reported account of protein turnover in the elderly following trauma, Phillips[9] evaluated five geriatric patients (mean age, 77.8 years) with a variety of injuries. They included one with a 15% burn, one with a femur fracture, one with inflammation of the joints, one with a pressure sore, one osteoarthritic with a flexion deformity of the knees, and a control group of five subjects (mean age, 70.8 years). While receiving approximately 1.1 g protein · kg^{-1} · d^{-1}, the stressed group showed a 40% increase in protein turnover, as well as increased protein synthesis and breakdown. Net protein synthesis was slightly positive in both groups.

The present study was undertaken to evaluate energy balance, leucine kinetics, and nitrogen balance in geriatric patients following hip fracture and in normal healthy geriatric controls during the basal state and in response to short-term total peripheral parenteral nutrition (TPPN) in an attempt to provide a more definitive assessment of the appropriate protein needs of such patients during convalescence.

SUBJECTS AND METHODS

Subjects

The subjects studied consisted of 33 patients (24 women, nine men) with a mean age of 81.7 ± 1.0 years (range, 70 to 92 years) who were admitted to the Baptist Medical Centers because of a fall resulting in a fractured femur, and a control group consisting of 33 nonhospitalized, ambulatory, healthy volunteers (24 women, nine men). The mean age of the control subjects was 75.5 ± 0.7 (range, 70 to 84 years). Before this hospitalization, all subjects were independent, free-living, ambulatory, mobile, healthy adults free of any metabolic or nutritional disease.

The protocol was approved by the Institutional Review Board of the Baptist Medical Centers. The nature, purpose, and risks of the study were explained in detail to all patients, and written informed consent was obtained from all individuals before the evaluation.

Following surgical repair of the hip fracture for patients in the trauma group and following an overnight fast and admission to our clinical research unit for the control subjects, patients were placed on metabolic balance. The mean interval from injury to the beginning of the day 1 kinetic study was 72 hours. The control and hip-fractured groups received only electrolytes by intravenous infusion for 24 hours. This period was defined as day 1. At the end of this period, the control and hip-fracture groups had been without energy intake for approximately 36 hours. At the start of day 2 (12:00 AM), TPPN was initiated in both groups. The TPPN solution was infused at a rate to provide 1.5 g protein · kg^{-1} · d^{-1}

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(Aminosyn; Abbott Laboratories, Chicago, IL) and energy equivalent to 1.3 times the subjects' measured resting energy expenditure (REE) with a 44%:56% energy mixture of carbohydrate to lipid using glucose and a commercial lipid emulsion. These solutions were packaged for peripheral intravenous administration as a triple mixture yielding a solution that is 3.65 g amino acids, 9.8 g glucose, and 4.6 g lipid per 100 mL. The fluid volume delivered was compatible with the clinical status of the patient.

Nutritional Status

Nutritional status was assessed using standard anthropometric and biochemical parameters. Body composition was evaluated by anthropometry. Anthropometric measurements included upper-arm and wrist circumferences using a standardized tape measure. Triceps, biceps, suprailiac, and subscapular skinfold thicknesses were measured with a calibrated Lange caliper. Lean body mass was calculated from fat mass and fat-free mass (FFM) as estimated from the skinfold thicknesses using the tables developed by Durnin and Womersley.[10] Visceral protein status was determined from the plasma albumin concentration. Prior nutritional intake was assessed by interview with a trained research dietician.

Biochemical and hematologic indices of prior nutritional status measured included serum albumin, serum total protein, total lymphocyte count calculated from complete blood count with differential, hemoglobin, hematocrit, and serum cholesterol. These indices of prior nutritional status are routinely obtained for all patients upon admission to the hospital and were obtained from each patient's hospital chart.

Leucine Kinetics

Leucine kinetics were studied using the primed-constant infusion technique at the end of two consecutive 24-hour periods in each patient. The first estimate of leucine kinetics was made at the end of the 24-hour postabsorptive state. The second estimate of leucine kinetics was made at the end of the 24-hour period of TPPN. The isotope infused was L-[1-^{14}C]leucine (DuPont/New England Nuclear, Boston, MA). Solutions of [1-^{14}C]leucine were prepared in 0.45% NaCl and passed through 0.22-μm filters into sterile, pyrogen-free vials. The solutions were confirmed to be sterile and nonpyrogenic by an independent testing laboratory. For each infusion, an aliquot of the infusate was analyzed for the precise isotope concentration to calculate the infusion rate for each patient. Whole-body leucine appearance was estimated from the equation$Q = I/Sp_{LEU}$, where Q (flux) is the amount of leucine leaving and entering the plasma pool ($\mu mol \cdot kg^{-1} \cdot min^{-1}$), I is the radioisotopic infusion rate ($\mu Ci \cdot kg^{-1} \cdot min^{-1}$), and Sp_{LEU} is the specific activity of plasma free L-leucine ($\mu Ci \cdot \mu mol^{-1}$).

The simplest stochastic model of leucine kinetics contains two pools, the metabolic pool, in which plasma amino acid specific activity and free intracellular amino acid specific activity are assumed to be equivalent, and the protein pool. Because leucine is an essential amino acid, the sole source of leucine entering the plasma pool in the postabsorptive state is tissue breakdown. Q then provides an index of the rate of leucine release from tissue protein breakdown. The rate of protein synthesis is determined from the equation[11,12] $Q = synthesis + oxidation = breakdown + intake$, where Q is the rate of leucine turnover (or flux); synthesis is the rate of leucine incorporation into protein; oxidation is the rate of leucine conversion to CO_2 or catabolism; breakdown is the rate of leucine release from protein; and intake is the rate of exogenous leucine infusion. Results are expressed as micromoles per kilogram per minutes. This may be converted to grams of protein per kilogram per day using the conversion factor of 1,440/590 ($min \cdot d^{-1}/\mu mol$ leucine $\cdot$ g protein^{-1}), but this conversion is valid only if it is accepted that leucine is a reliable tracer for whole-body protein and that leucine represents 7.8% of mixed-body protein.[13] During infusion of leucine, Q represents the sum of the rates of entry of leucine into the plasma compartment from infused leucine and endogenous leucine; breakdown is then obtained by the difference between Q and the exogenous infusion rate. Leucine oxidation was calculated as oxidation = $\dot{V}(^{14}CO_2)/(Sp_{LEU} \times 0.8)$, where $\dot{V}(^{14}CO_2)$ is the production rate of $^{14}CO_2$ calculated as the product of the steady-state specific activity of expired CO_2 and the total rate of CO_2 production determined with the ventilated-canopy system[14]; the factor 0.8 corrects for nonexpired $^{14}CO_2$ from leucine converted to CO_2 but retained within the body bicarbonate pool. Nonoxidative disposal of leucine was calculated as the difference between Q and oxidation, and is taken as an index of leucine incorporation into protein.

For determination of leucine kinetics in the postabsorptive state, subjects were infused with saline at a rate of 80 mL $\cdot$ h^{-1} or as clinically indicated. The saline infusion began at 12:00 AM on the day following surgery for injured subjects and on the day of admission to the clinical nutrition research unit for control subjects. Injured subjects had been without food before surgery; control subjects were admitted following an overnight fast. Leucine kinetics were assessed after a fast of approximately 36 hours. After 20 hours of saline infusion, subjects were administered a bolus injection of sterile, pyrogen-free ^{14}C-$NaHCO_3$ (0.2 μCi/kg) and L-[1-^{14}C]leucine (0.16 μCi/kg) followed by a constant infusion of L-[1-^{14}C]leucine at 0.0023 $\mu Ci \cdot kg^{-1} \cdot min^{-1}$ for 4 hours. Samples of blood and breath were obtained at half-hour intervals during the last 2 hours of [1-^{14}C]leucine infusion for determination of plasma leucine specific activity and breath CO_2 specific activity for calculation of basal leucine kinetics.[15,16]

The TPPN was initiated upon completion of the estimation of leucine kinetics in the fasting state. After 20 hours of TPPN, a blood and breath sample was obtained for determination of residual ^{14}C content. Protein kinetics were reevaluated with a primed-constant infusion of [1-^{14}C]leucine.

Leucine Specific Activity

The specific activity of plasma leucine was determined in the plasma samples after separation of the formed elements by centrifugation. Samples were deproteinized by addition of 0.050 mL sulfosalicylic acid (2.75 mol/L)/mL plasma. Amino acids were separated from plasma using a cation ion-exchange resin column. They were eluted with 1-mol/L NH_4OH, and the ammonia was removed by evaporation. An aliquot of the eluate was used for quantitation of amino acid concentration on an automatic amino acid analyzer (model no. 6300, Beckman Instruments, Palo Alto, CA). Radioactivity was determined by counting a separate aliquot of the amino acid eluate from the ion-exchange column in a liquid scintillation counter.[17] This technique allows for an accurate assessment of low levels of radioactivity in the plasma sample.

The specific activity of expired CO_2 was calculated from the indirect calorimetry system.[14] This system provides minute-by-minute analysis of expired CO_2 and also the radioactivity in expired CO_2. Mean values from each of these measurements were used to calculate the mean specific activity of expired CO_2.

It should be pointed out that plasma leucine specific activity was used to calculate protein turnover rates. When labeled amino acid is intravenously infused, amino acid enrichment is higher in the extracellular plasma compartment than intracellularly because the label is infused directly into the extracellular space, whereas unlabeled amino acid from protein breakdown enters directly into the intracellular compartment. Whole-body leucine kinetics have been determined in humans by a relatively short continuous

infusion of L-[1-^{14}C]leucine under a variety of metabolic conditions. This approach requires precursor ^{14}C specific activity for calculation of whole-body leucine flux and oxidation rates, and indirectly, the rate of leucine incorporation into protein through synthesis. The true precursor for leucine oxidation is the intracellular leucine or its ketoanalog α-ketoisocaproic acid. When relative changes in whole-body leucine kinetics are being evaluated, the simpler measurement of plasma [^{14}C]leucine specific activity is acceptable, since Matthews et al[18] have shown that the ratio of α-ketoisocaproic acid to leucine enrichment remained the same (77% ± 1%) over a wide range of dietary intake of proteins and in both the fed and postabsorptive states. Protein synthesis and breakdown were calculated from the blood and breath data before and during the infusion of nutrients.

Nitrogen Balance

The procedures for determining daily nitrogen balance require that all nitrogen intake, as well as losses, be measured. Daily 24-hour urine samples were digested using a micro-Kjeldahl procedure, and the resulting ammonia salt was assayed for total nitrogen using the method described by Geiger et al.[19]

Indirect Calorimetry

Energy expenditure was determined with a computerized, open-circuit, indirect calorimetry system using a ventilated canopy.[14] The oxygen level was measured with a Sybron-Taylor OA 540 Servomex oxygen analyzer (Norwood, MA). The carbon dioxide level was measured with a Mine Safety Appliance LIRA Model 202 infrared analyzer (Mars, PA). REE was calculated from the nonprotein respiratory quotients using equations described by Jequier and Felber[20] and Ferrannini.[21] The total energy expended in 24 hours (TEE) was estimated according to calculations described by Jallut et al[8] and Long.[22] The equation used to calculate TEE was TEE = (REE × 0.9 × 8) + (REE × 16 × 1.3), where REE is expressed as kilocalories per hour, 0.9 corrects for the reduction in energy expenditure during the 8 hours the subject is asleep, and 1.3 is an activity factor to correct for increases in energy expenditure due to activity during the 16 hours the subject is awake.

Analysis of Blood Samples

Blood samples were collected, and the plasma was immediately separated by centrifugation at 4°C. Aliquots of plasma were placed in tubes containing EDTA and Trasylol (FBA Pharmaceutical, New York, NY) and stored at −80°C for hormone determinations. All hormone levels were determined by radioimmunoassay. The glucagon level was determined using Unger's 30K antibody. Insulin and cortisol levels were determined with radioimmunoassay kits. Plasma for catecholamine analysis was transferred to tubes containing reduced glutathione, frozen, and stored at −80°C until analyzed. Catecholamines were analyzed using high-performance liquid chromatography and electrochemical detection (Bioanalytical Systems, West Lafayette, IN).

Table 1. Nutritional Status of Control Subjects and Trauma Patients

	Control	Trauma	P*
Age (yr)	75 ± 0.7	82 ± 1.0	<.001
Weight (kg)	61 ± 1.6	58 ± 2.2	.291
Height (cm)	165 ± 1.7	164 ± 1.6	.609
Percent ideal weight	103 ± 2.0	98 ± 2.5	.090
Body mass index (kg/m^2)	22.4 ± 0.44	21.6 ± 0.61	.250
FFM (kg)	39.6 ± 1.44	38.5 ± 1.56	.327
Fat mass (kg)	19.8 ± 0.83	17.5 ± 1.18	.125
Percent body fat	32.4 ± 1.23	30.6 ± 1.47	.344
Albumin (g/dL)	3.9 ± 0.08	2.8 ± 0.08	<.001
White blood cells (×10^3 cells/μL)	7 ± 0.7	10.8 ± 0.64	.004
Total lymphocytes (×10^3 cells/μL)	29 ± 3.5	11.7 ± 1.3	<.001

NOTE. Values are the mean ± SEM for 33 control and trauma subjects.

*Student's *t* test *P* for hip-fracture patients *v* controls.

Table 2. Plasma Electrolyte Concentrations (mmol/L) of Control Subjects and Trauma Patients

	Control	Trauma	P*
Calcium	2.20 ± 0.015	2.02 ± 0.032	<.001
Chloride	107 ± 0.6	104 ± 0.9	.007
Potassium	4.2 ± 0.06	4.0 ± 0.12	.050
Sodium	140 ± 0.5	135 ± 0.8	<.001

NOTE. Values are the mean ± SEM for 33 control and trauma subjects.

*Student's *t* test *P* for hip-fracture patients *v* control subjects.

Analysis of Data

Data obtained during the postabsorptive and TPPN periods for control and injured subjects were analyzed using a two-way ANOVA; however, because some subjects were not able to complete the second evaluation of protein kinetics, a repeated-measures analysis was not used. The Bonferroni procedure was used to make pairwise comparisons.[23] Student's *t* test was used to test for differences between hip-fracture patients and their controls. Values are reported as the mean ± SEM. Differences between groups were considered statistically significant if *P* was less than .05.

RESULTS

General characteristics and nutritional parameters of control subjects and injured patients are presented in Table 1. Injured patients were older than control subjects, but otherwise were well matched to control subjects with respect to weight, height, and body composition. Injured patients had a lower albumin level than control subjects. Compared with control subjects, the white blood cell count of injured patients was elevated with a depressed lymphocyte count; however, they remained within normal clinical ranges for this age group. Plasma electrolytes of injured patients were consistently less than those of control subjects (Table 2). The heart rate and systolic blood pressure of injured subjects were elevated, but the diastolic pressure remained normal (Table 3).

Plasma substrate and hormone concentrations measured in control and injured subjects after a 36-hour fast and after 20 hours of TPPN are presented in Tables 4 and 5. After the 36-hour fast, the plasma glucose of trauma patients was not significantly different ($P = 0.113$) from that of control

Table 3. Cardiovascular Status of Control Subjects and Trauma Patients

	Control	Trauma	P*
Heart rate (beats per min)	73 ± 1.5	93 ± 3.0	<.001
Systolic blood pressure (mm Hg)	129 ± 2.8	145 ± 4.5	.003
Diastolic blood pressure (mm Hg)	71 ± 1.6	70 ± 2.6	.722

NOTE. Values are the mean ± SEM for 33 control and trauma subjects.

*Student's *t* test *P* for hip-fracture patients *v* control subjects.

Table 4. Plasma Substrate Concentrations in Control Subjects and Trauma Patients

Substrate	Control		Trauma	
	Day 1 Fasting	Day 2 TPPN	Day 1 Fasting	Day 2 TPPN
Glucose (mmol/L)	4.4 ± 0.1 (33)	6.4 ± 0.16 (31)*	5.1 ± 0.21 (21)	7.2 ± 0.36 (19)*†
Lactate (mmol/L)	1.3 ± 0.04 (32)	1.3 ± 0.04 (28)	1.3 ± 0.06 (20)	1.7 ± 0.08 (15)*†
Pyruvate (μmol/L)	36 ± 5.4 (32)	49 ± 5.9 (28)	72 ± 10.6 (20)	111 ± 12.8 (15)*†
Free fatty acids (μmol/L)	890 ± 81 (33)	696 ± 109 (31)	788 ± 87 (21)	512 ± 84 (19)
Triglycerides (mmol/L)	1.35 ± 0.089 (33)	1.94 ± 0.158 (31)*	1.06 ± 0.097 (21)	1.47 ± 0.51 (19)
Acetoacetate (μmol/L)	33 ± 6.8 (32)	2.7 ± 0.98 (28)*	26 ± 7.8 (20)	1.5 ± 1.47 (15)
β-Hydroxybutyrate (μmol/L)	111 ± 23.4 (32)	13.9 ± 1.82 (28)*	55.9 ± 9.22 (20)	10.9 ± 2.21 (16)
Total ketones (μmol/L)	144 ± 30.1 (32)	16.7 ± 2.70 (28)*	82.0 ± 15.6 (20)	12.4 ± 3.47 (15)
Cholesterol (mmol/L)	5.33 ± 0.219 (30)		4.02 ± 0.207 (26)†	

NOTE. Values are the mean ± SEM (n).

*$P < .05$ *v* fasting value.

†$P < .05$ *v* control value.

subjects. The effect of TPPN was to increase plasma glucose in both control and injured subjects ($P < .001$). After 20 hours of TPPN, the plasma glucose of injured subjects was significantly greater ($P = .024$) than that of control subjects. The fasting plasma pyruvate of trauma patients was elevated ($P = .008$) and increased with TPPN only in the injured patients ($P = .021$). Fasting plasma triglycerides in injured patients were not significantly different from those of control subjects ($P = .738$). Plasma triglycerides increased during TPPN in control subjects ($P = .003$) but not in injured subjects ($P = .093$). Although there was a 43% decrease in plasma ketone bodies following trauma, there was no statistical difference between control and injured subjects while fasting ($P = .236$). In response to TPPN, plasma ketone bodies decreased to approximately 10% of the fasting concentration. The insulin concentration was not different between the two groups in the fasting condition ($P = 1.000$) and increased in response to TPPN ($P < .001$). Fasting plasma glucagon was not lower in injured subjects ($P = 1.000$). Plasma glucagon did not increase in response to TPPN in either control ($P = .262$) or injured ($P = 1.000$) subjects. There was not a difference between the two groups with respect to the cortisol concentration. Fasting plasma norepinephrine ($P = .497$) and epinephrine ($P = 1.000$) in the trauma group were not different from those in the control group. Plasma norepinephrine in the injured group receiving TPPN was significantly greater ($P = .045$) than that in the control group receiving TPPN. Cholesterol was decreased to 75% of normal in the injured subjects ($P < .001$).

The REEs of control subjects and injured patients are presented in Table 6. ANOVA indicated no effect of injury on REE expressed as kilocalories per day ($P = 1.000$) or as kilocalories per kilogram lean body mass per day ($P = .111$); however, there was a significant effect of injury on energy expenditure when REE was expressed in terms of body weight ($P = .017$). There was not an effect of TPPN on energy expenditure. The REE predicted by the Harris-Benedict equation[24] was 1,220 ± 25.6 kcal/d for control subjects and 1,148 ± 26.6 for injured subjects. The REE in control subjects after an overnight fast was 6.8% ± 1.99% greater than predicted by the Harris-Benedict equation ($P < .001$, paired *t* test). The REE measured in injured subjects was 19.6% ± 3.11% greater than predicted by the Harris-Benedict equation ($P < .001$, paired *t* test). ANOVA indicated a significant effect of injury on the increase in REE above that predicted by the Harris-Benedict equation ($P = .005$).

The TEE of control subjects was calculated to be 1,551 ± 46.9 kcal/d while receiving TPPN at a rate of 1,875 ± 23.7 kcal/d. They were in a positive energy balance of 334 ± 53.0 kcal/d. The TEE of injured subjects was calculated to be 1,584 ± 72.6 kcal/d while receiving TPPN at a rate of 1,798 ± 62.3 kcal/d. They were in a positive energy balance of 206 ± 106 kcal/d.

The substrate utilization by control subjects and trauma patients before and during TPPN is presented in Table 7. Under fasting conditions, control subjects and trauma patients derived approximately 60% of their energy from the oxidation of lipids and 25% to 30% from the oxidation of carbohydrates, with the balance being from protein oxidation. In response to TPPN, both control and trauma

Table 5. Plasma Hormone Concentrations in Control Subjects and Trauma Patients

Substrate	Control		Trauma	
	Day 1 Fasting	Day 2 TPPN	Day 1 Fasting	Day 2 TPPN
Insulin (pmol/L)	77 ± 15.5 (33)	319 ± 52.2 (30)*	106 ± 17.8 (21)	343 ± 35.1 (19)*
Glucagon (ng/L)	318 ± 38 (25)	447 ± 74 (19)	249 ± 18 (20)	300 ± 41 (16)
Cortisol (nmol/L)	390 ± 25.9 (20)	370 ± 29.4 (21)	476 ± 84.1 (20)	483 ± 66.6 (17)
Norepinephrine (mmol/L)	1.62 ± 0.217 (25)	1.58 ± 0.272 (26)	2.54 ± 0.385 (11)	3.27 ± 1005 (7)†
Epinephrine (pmol/L)	181 ± 28.6 (21)	170 ± 31.6 (25)	212 ± 47.4 (8)	273 ± 81.8 (6)

NOTE. Values are the mean ± SEM (n).

*$P < .05$ *v* fasting value.

†$P < .05$ *v* control value.

Table 6. Energy Expenditure During Fasting and After TPPN in Control Subjects and Trauma Patients

REE	Control		Trauma	
	Day 1 Fasting (n = 33)	Day 2 TPPN (n = 31)	Day 1 Fasting (n = 26)	Day 2 TPPN (n = 22)
kcal/d	1,306 ± 38.7	1,329 ± 40.2	1,361 ± 57.0	1,358 ± 62.2
kcal · kg^{-1} · d^{-1}	21.4 ± 0.44	21.8 ± 0.48	23.8 ± 0.68†	24.0 ± 0.80
kcal · kg LBM^{-1} · d^{-1}	31.6 ± 0.68	32.3 ± 0.78	34.8 ± 1.16	35.4 ± 1.37
Percent difference from REE predicted by Harris-Benedict equation	6.8 ± 1.99	8.9 ± 2.14	19.6 ± 3.11†	20.2 ± 3.80†

NOTE. Values are the mean ± SEM.
Abbreviation: LBM, lean body mass.
*$P > .05$ *v* fasting value.
†$P > .05$ *v* control value.

subjects significantly decreased their energy derived from lipid ($P < .025$) to approximately 40% and increased their energy derived from protein to greater than 15% ($P < .001$). However, TPPN did not significantly increase the amount of energy derived from carbohydrate oxidation in either control ($P = .145$) or injured ($P = .154$) subjects. Under fasting or TPPN conditions, injured subjects derived the same proportion of energy from oxidation of carbohydrate, lipid, and protein as control subjects.

Nitrogen balances for control subjects and injured patients while fasting and during TPPN are presented in Table 8. During the fasting period, control and trauma subjects were in negative nitrogen balance with a urinary nitrogen excretion rate of 101 ± 4.7 and 116 ± 6.0 mg N · kg^{-1} · 24 h^{-1}, respectively. In response to TPPN, nitrogen balance became positive for both control subjects and trauma patients. Nitrogen balance increased to 85 ± 6.2 for control subjects and 48 ± 14.0 mg N · kg^{-1} · 24 h^{-1} for trauma patients. There was a significant difference between nitrogen balance for control subjects and trauma patients while receiving TPPN ($P = .022$).

Leucine kinetics while fasting and during TPPN in control and trauma subjects are presented in Table 9. Injury did not affect leucine kinetics. Leucine release from protein breakdown, leucine oxidation, and leucine incorporation into protein in injured patients were not different from values for control subjects ($P = 1.000$). In response to TPPN, leucine release from protein breakdown and leucine incorporation into protein did not change significantly in both injured and control subjects, whereas leucine oxidation increased in both groups ($P < .002$).

Table 7. Substrate Oxidation During Fasting and After TPPN in Control Subjects and Trauma Patients

Substrate Oxidized	Control		Trauma	
	Day 1 Fasting (n = 33)	Day 2 TPPN (n = 31)	Day 1 Fasting (n = 26)	Day 2 TPPN (n = 22)
Carbohydrate	27.2 ± 3.97	40.6 ± 4.46	29.2 ± 3.64	44.6 ± 5.90
Lipid	60.5 ± 4.02	42.7 ± 4.47*	58.3 ± 3.85	36.8 ± 6.25*
Protein	12.3 ± 0.64	16.7 ± 0.59*	12.5 ± 0.65	18.5 ± 1.09*

NOTE. Values are the mean ± SEM and are expressed as a percentage of REE.
*$P > .05$ *v* fasting value.

DISCUSSION

We evaluated a homogenous group of 33 geriatric patients following surgical fixation of the fractured hip in both a postabsorptive basal state and following TPPN and compared them with 33 age- and weight-matched healthy volunteer controls. The data as presented in Table 1 demonstrate the relatively good match between trauma and control subjects with respect to age, weight, height, and lean body mass. There was no correlation between age and any parameter. Therefore, the age difference between the two groups of subjects did not have a significant influence on the results. The lower plasma albumin levels of the trauma patients presented in Table 1 suggest that the injured geriatric population was malnourished before injury; however, this assumption is not supported by the body-composition data. Albumin levels following trauma may not be reliable indicators of malnutrition, since they are significantly decreased in younger populations following injury.[25] This may explain the low level observed in our elderly trauma population. In addition, fluids received during surgical fixation of the hip fracture may also contribute to the observed low plasma albumin.

The lower plasma cholesterol in injured geriatric subjects is consistent with similar changes observed in younger subjects after motor vehicle accidents[26] or burns.[27] Concomitant with the increase in plasma norepinephrine is a 27% increase in heart rate and a 12% increase in systolic blood pressure.

REE was measured at the end of each metabolic study period (basal and TPPN) in the morning before any activity by or to the patient. Control subjects were assessed in a similar fashion. The results presented in Table 6 demonstrate that the REE of the injured group was significantly increased over that of controls during both the basal and TPPN study periods when expressed on a weight basis (kilocalories per kilogram per day). When the measured REE was compared with the REE predicted by the Harris-Benedict equation, the REE of the trauma group was 20% greater than predicted, whereas the REE of the control group was less than 10% greater than predicted. These data compare favorably with our previous study showing an increase in measured REE over predicted REE in mildly stressed patients.[22] These results suggest that the injured

Table 8. Nitrogen Balance During Fasting and After TPPN in Control Subjects and Trauma Patients

	Control		Trauma	
	Day 1 Fasting (n = 33)	Day 2 TPPN (n = 33)	Day 1 Fasting (n = 33)	Day 2 TPPN (n = 33)
Nitrogen intake		227 ± 4.5*	6 ± 4.2	219 ± 15.1*
Nitrogen output	101 ± 4.7	142 ± 4.7*	116 ± 6.0	168 ± 10.2*†
Nitrogen balance	−101 ± 4.7	85 ± 6.2*	−110 ± 7.7	48 ± 14.0*†

NOTE. Values are the mean ± SEM and are expressed as mg N · kg^{-1} · 24 h^{-1}.

*$P < .05$ *v* fasting value.

†$P < .05$ *v* control value.

elderly patients were mildly hypermetabolic following hip fracture and surgical fixation.

Jallut et al[8] studied energy and protein balances in 20 elderly female patients with a femoral neck fracture (mean age, 80.9 ± 0.94; range, 74 to 87 years). They reported a calculated 24-hour energy expenditure of 1,319 ± 44 kcal/d on the third postoperative day with a mean intake of 1,097 ± 74 kcal · kg^{-1} · d^{-1} providing a negative balance of 222 kcal/d. In the present study, the injured subjects were provided with 1,798 ± 62 kcal/d. The calculated TEE of injured subjects on TPPN averaged 1,584 ± 72 kcal/d. Based on this estimate of TEE, injured subjects were in positive energy balance by 214 ± 106 kcal/d. This is in line with the recommendation of Jallut et al[8] that 300-kcal supplements should be provided to the geriatric patient.

The combined effects of the injury and reparative surgery sustained by the trauma group in the present study appear not to have been of sufficient magnitude to produce a severe hypercatabolic response. The 24-hour urinary nitrogen excretion rates of 116 ± 6 in the trauma group and 101 ± 4.7 mg N · kg^{-1} · d^{-1} in control subjects during the postabsorptive study period are consistent with normal nitrogen excretion rates in fasted adult subjects. The protein intake of subjects on TPPN averaged 224 mg N · kg^{-1} · d^{-1}. The urinary nitrogen loss of the hip-fracture group reported here during TPPN was 168 ± 10.2 mg · kg^{-1} · d^{-1}, providing a positive nitrogen balance. The control group lost 142 ± 4.7 mg · kg^{-1} · d^{-1} during TPPN. Phillips[9] observed a mean urinary nitrogen loss of 151.5 mg · kg^{-1} · d^{-1} on an intake of 177.3 mg N · kg^{-1} · d^{-1} in their geriatric injured group. Jallut et al[8] reported urinary N losses of 148.0 mg · kg^{-1} · d^{-1} on an intake of 113.2 mg N · kg^{-1} · d^{-1}. From these data, they recommended supplementing the diet of geriatric patients with at least 20 g protein · d^{-1}. This would correspond to a protein intake of 1.1 g protein · kg^{-1} · d^{-1}. Combining the data presented by Jallut et al[8] with the results of the present study indicates that nitrogen balance can be achieved at a nitrogen intake of 1.0 g protein · kg^{-1} · d^{-1}. On a 70-kg basis, the trauma population showed approximately a 3.4-g positive nitrogen balance per day and the control group showed a 5.0-g positive nitrogen balance while receiving 1.4 g protein · kg^{-1} · d^{-1} from TPPN. The ability of the geriatric patient to retain nitrogen at these nitrogen intake levels is quite remarkable. These results are comparable to those for a growing adult, even though they are classified as geriatric data. These data highlight the efficiency of nitrogen retention in such an aged population.

A comparison of whole-body leucine turnover, leucine incorporation into protein, leucine release from protein breakdown, and leucine oxidation revealed no significant differences between injured geriatric patients and control subjects when the data were expressed per kilogram body weight or per kilogram FFM. This observation was consistent throughout both the basal fasting period and the TPPN

Table 9. Leucine Kinetics During Fasting and After TPPN in Control Subjects and Trauma Patients

	Control		Trauma	
	Day 1 Fasting (n = 31)	Day 2 TPPN (n = 28)	Day 1 Fasting (n = 20)	Day 2 TPPN (n = 18)
Total leucine flux	1.20 ± 0.104	1.70 ± 0.135*	1.26 ± 0.131	1.85 ± 0.177*
	(1.82 ± 0.133)	(2.50 ± 0.187)	(1.88 ± 0.171)	(2.79 ± 0.254)
Exogenous leucine flux (leucine infusion rate)		0.68 ± 0.026		0.73 ± 0.043
		(1.00 ± 0.04)		(1.15 ± 0.080)
Endogenous leucine flux (leucine release from protein breakdown)	1.20 ± 0.104	1.02 ± 0.139	1.26 ± 0.135	1.12 ± 0.156
	(1.82 ± 0.133)	(1.50 ± 0.194)	(1.88 ± 0.171)	(1.66 ± 0.225)
Leucine oxidation	0.26 ± 0.040	0.54 ± 0.057*	0.29 ± 0.047	0.61 ± 0.069*
	(0.40 ± 0.064)	(0.79 ± 0.080)	(0.43 ± 0.060)	(0.91 ± 0.091)
Leucine incorporation into protein	0.94 ± 0.095	1.16 ± 0.097	0.97 ± 0.092	1.29 ± 0.164
	(1.42 ± 0.115)	(1.71 ± 0.137)	(1.45 ± 0.125)	(1.97 ± 0.243)

NOTE. Values are the mean ± SEM in μmol · kg^{-1} · min^{-1}. Values in parentheses are expressed as μmol · kg FFM^{-1} · min^{-1}. This may be converted to g protein · kg^{-1} · d^{-1} using the conversion factor of 1,440/590 (min · d^{-1}/μmol leucine · g $protein^{-1}$). Total leucine flux includes the rate of leucine infusion from the TPPN; endogenous leucine flux is the difference between total leucine flux and the rate of leucine infusion from TPPN.

*$P < .05$ *v* fasting value.

period. These findings suggest that elderly patients experiencing fracture of the hip and surgical repair of the fracture are not highly hypercatabolic from this degree of injury.

Leucine kinetics and nitrogen excretion do not always change in the same direction. Nair et al[28] reported that total urinary nitrogen excretion did not significantly decrease after 72 hours of fasting, but that leucine oxidation increased from 16.0 to 23.4 $\mu mol \cdot kg^{-1} \cdot h^{-1}$. In the fasted state, leucine oxidation should be accompanied by an equivalent amount of oxidation of other protein-bound amino acids, and the leucine oxidation to N excretion ratio should reflect the leucine to N ratio of muscle and liver, ie, 3.93 μmol leucine/mg N.[29] Using this ratio, the amount of N excretion that should be expected from the rate of leucine oxidation was calculated and compared with the measured amount of N excretion. The predicted N excretion to measured N excretion ratio under fasting conditions was 1.05 ± 0.201 for control subjects and 0.98 ± 0.157 for injured subjects. The ratio increased with TPPN to 1.47 ± 0.158 for control subjects and 1.38 ± 0.204 for injured subjects. If the ratio is 1, there is good agreement between leucine oxidation and N excretion. If the ratio is greater than 1, excess leucine is being oxidized. During TPPN, the leucine being infused was 40% of the total leucine flux and the excess leucine was oxidized. Because leucine oxidation now represents oxidation of infused amino acid, as well as leucine, from muscle and liver, the leucine to N excretion ratio may no longer be 3.93 μmol leucine/mg N. Furthermore, transformation of the leucine oxidation rates measured over 2 hours to N excretion rates makes the assumption that the measured rates of leucine oxidation are similar to the average rate for 24 hours. The degree to which that is true will influence the calculation of the predicted rate of N excretion and the discrepancy between N excretion indicating a significant anabolic effect of TPPN and leucine kinetics indicating leucine balance.

Whole-body protein kinetic parameters are directly related to the level of nutrient intake in humans.[30] The transition from the postabsorptive state to the fed state initiated by infusion of TPPN at a rate of 1.5 g protein $\cdot kg^{-1} \cdot d^{-1}$ resulted in significant increases in whole-body leucine turnover and leucine oxidation in injured and uninjured subjects. Leucine release from protein breakdown decreased by 15% in control subjects and by 11% in injured subjects when TPPN was provided. Phillips[9] showed similar results in his injured geriatric patient population. Gelfand et al[15] and Fukagawa et al[16] examined the short-term effect of amino acid infusion on leucine kinetics in healthy young adults (aged 19 to 30 years) and geriatric men (72 to 87 years). Leucine kinetics measured before infusion of amino acids were not different from those in the present study. Leucine kinetics measured after 2 to 4 hours of infusion of amino acids at a rate of 4.8[15] or 4.4 $g \cdot kg^{-1} \cdot d^{-1}$ [16] showed changes that were qualitatively similar to the present study. There were 80% to 100% increases in whole-body leucine turnover, 250% to 300% increases in leucine oxidation, 40% to 55% increases in leucine incorporation into protein, and 12% to 63% decreases in leucine release from protein. The quantitative differences between the results of Gelfand et al,[15] Fukagawa et al,[16] and the present study are most likely due to the higher rates of amino acid infusion and shorter time of amino acid infusion.

The REE, hyperglycemia, and hormonal data suggest a degree of hypermetabolism from the injury and treatment, as well as less efficiency of nitrogen retention during TPPN. The plasma amino acid results previously reported[31] showed significantly lower fasting concentrations of total plasma amino acids, attributed mainly to lower nonessential amino acids. Of the essential amino acids, during fasting phenylalanine and methionine were increased and lysine was decreased by 21%. Phenylalanine levels are noted to be increased following trauma and sepsis.[32] The branched-chain amino acids were not different. Lysine continued to be significantly lower in the hip-fracture group during TPPN, but was not limiting for protein synthesis based on the calculated order of limiting amino acids patterns.

The overall response of the injured geriatric patient suggests a mild catabolic response that may be reversed by nutritional intervention. The results of the present study therefore suggest that prompt nutritional intervention in the injured geriatric population has the potential to reverse net protein breakdown, thereby preventing muscle wasting and its associated clinical complications.

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