

# A reappraisal of nitrogen requirements for patients with critical illness and trauma

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This study was presented, in part, at the Ninth Annual Nutrition Week of the American Society for Parenteral and Enteral Nutrition. February 11, 2010, in Las Vegas, Nevada. Address for reprints: Roland N. Dickerson, PharmD, Department of Clinical Pharmacy, University of Tennessee Health Science Center, 881 Madison Ave, Suite 345, Memphis, TN 38163; email: [rdickerson@uthsc.edu](mailto:rdickerson@uthsc.edu).

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<b>BACKGROUND:</b>	Studies regarding protein requirements for patients with critical illness are inconclusive owing to small sample size and population heterogeneity. The primary objectives of this study were to determine the amount of protein required to achieve nitrogen equilibrium or a positive nitrogen balance (NB, $-4$ g/d or better) and ascertain whether patients with traumatic brain injury (TBI) exhibit greater protein catabolism than those without TBI.
<b>METHODS:</b>	Adult patients admitted to the trauma center, given specialized nutrition support, and had an NB determination within 5 days to 14 days after injury were evaluated. Patients with obesity, incomplete urine collection, kidney disease, corticosteroid or pentobarbital therapy, or an oral diet were excluded.
<b>RESULTS:</b>	A total of 300 NB determinations from 249 patients were evaluated. Increasing the protein dosage generally resulted in improved NB; however, the data were highly variable. Of the patients who received a protein intake of 2 g/kg per day or greater, 54% achieved nitrogen equilibrium or positive NB ( $-4$ g/d or better) in contrast to 38% and 29% of patients who received 1.5 g/kg per day to 1.99 g/kg per day and 1 g/kg per day to 1.49 g/kg per day, respectively ( $p < 0.001$ ). There was no significant difference in NB between patients with and without TBI at similar protein intakes.
<b>CONCLUSION:</b>	A higher protein intake was generally associated with an improved NB; yet, many patients remained having a negative NB. A protein dosage of 2 g/kg per day or greater was more successful in achieving nitrogen equilibrium than were lower-dosage intakes. Patients with TBI do not exhibit significantly greater protein catabolism than do patients without TBI. ( <i>J Trauma Acute Care Surg.</i> 2012;73: 549–557. Copyright © 2012 by Lippincott Williams & Wilkins)
<b>LEVEL OF EVIDENCE:</b>	Prognostic study, level III.
<b>KEY WORDS:</b>	Enteral nutrition; parenteral nutrition; protein requirements; nitrogen balance; traumatic brain injury.

The metabolic response to traumatic injury is heralded by hypermetabolism and marked protein catabolism.<sup>1</sup> The clinical repercussions of an ineffectively abated protein catabolism is evident for patients with critical illness and trauma as prospective, randomized trials indicate decreased immunity, increased infections, and worsened survival when given inadequate or delayed nutrition therapy.<sup>2–7</sup> The primary objectives of this study were to determine the amount of protein required to achieve nitrogen equilibrium or a positive nitrogen balance (NB,  $-4$  g/d or better) and to ascertain whether patients with traumatic brain injury (TBI) exhibit greater protein catabolism than those without TBI.

## PATIENTS AND METHODS

### Patient Selection

Adult patients, at least 18 years, with traumatic injuries, admitted to the Presley Regional Trauma Center (trauma, neurosurgical, or general intensive care units) at the Regional Medical Center at Memphis and who received enteral or parenteral nutrition from June 2005 to June 2009 were eligible for study inclusion. Patients must have had a 24-hour urine collection for determination of NB within 5 days to 14 days after admission to the hospital. Patients excluded were those with acute kidney injury according to the RIFLE criteria<sup>8</sup> or with chronic kidney disease, liver dysfunction (international normalized ratio,  $>1.5$  unresponsive to vitamin K), thermal injury, pregnancy, corticosteroid or pentobarbital pharmacotherapy, an ad libitum oral intake, or had received a hypocaloric, high protein regimen for obesity (body mass index,  $> 30$  kg/m<sup>2</sup>).

Patients were subcategorized based on the presence or absence of severe TBI. TBI was evident by a Glasgow Coma Scale score before sedation of less than 8 and a requirement for intracranial pressure monitoring. Injury Severity Score (ISS) and Abbreviated Injury Scale score (AIS) of the head and neck<sup>9</sup> were obtained from the trauma registry of the Regional

Medical Center at Memphis. Patients were identified as having sepsis or systemic inflammatory response syndrome according to the 2001 consensus guidelines of the American College of Chest Physicians/Society of Critical Care Medicine.<sup>10</sup>

The study was approved and conducted in accordance with the guidelines established by the University of Tennessee Health Science Center Institutional Review Board and the Regional Medical Center Office of Medical Research. The requirement for informed consent was waived.

### Nutritional Regimen

Patients were assigned energy and protein goals of 126 kJ/kg per day to 134 kJ/kg per day and 2 g/kg per day to 2.5 g/kg per day, respectively. Protein intake was increased to 2.5 g/kg per day to 3 g/kg per day if the patient exhibited an NB of greater than  $-6$  g/d while receiving 2 g/kg per day to 2.5 g/kg per day. Patients were preferentially given enteral nutrition intragastrically. If the patient's ISS was greater than 20, an enteral formula (1.3 kcal/mL, 78 g protein/L) containing glutamine, arginine, dietary nucleotides, and  $\omega$ -3 fatty acids was initiated. Other patients received a conventional polymeric (1 kcal/mL, 62 g protein/L) or diabetic formula (1.2 kcal/mL, 60 g protein/L). Liquid protein supplements were also given. Parenteral nutrition was provided if enteral nutrition was contraindicated or if the patient was unable to tolerate enteral feeding despite prokinetic pharmacotherapy and postpyloric feeding was not possible. Energy intake was decreased and protein intake was maintained for those who received a propofol infusion containing 10% lipid emulsion. Preresuscitation body weight was used to determine target nutritional goals. Blood glucose concentrations were maintained between 70 mg/dL and 150 mg/dL.

### Measured Variables and NB

A 24-hour urine collection for the determination of NB and creatinine clearance was conducted within 5 days to

14 days after hospital admission during the mid-to-late flow phase response to their initial injuries.<sup>11</sup> Urine samples were assayed for urea nitrogen and creatinine by the hospital laboratory. The urine collection was considered reliable if the measured creatinine clearance was 90% or greater of what was predicted<sup>12</sup> and the laboratory volume measurement and nursing record of urine output were within approximately 10% of each other. NB was estimated by the following equation:<sup>13</sup>

$$\text{NB (g/d)} = \text{Nitrogen intake (g/d)} \\ - \text{Urinary urea nitrogen (g/d)/0.85} - 2(\text{g/d})$$

Two grams of nitrogen was an assumption of integumental and insensible nitrogen losses.<sup>13,14</sup> If a change in serum urea nitrogen concentration of more than 3 mg/dL occurred during the balance study, body urea nitrogen appearance was included in the nitrogen loss.<sup>13</sup> Nitrogen equilibrium was defined as an NB within  $-4$  g/d to  $+4$  g/d. Positive NB was defined as greater than  $+4$  g/d. A negative NB was indicated by worse than  $-4$  g/d.

## Statistical Analysis

Continuous data were expressed as mean (SD). Data analysis was conducted using IBM SPSS Statistics version 19 (IBM Corporation, Somers, NY). A  $p < 0.05$  was established as statistically significant. Comparison of interval data between two independent groups was performed by the  $t$  test or Mann-Whitney  $U$  test. Differences between groups with nominal data were determined using  $\chi^2$  analysis. One-way analysis of variance was used to detect differences in NB for protein intake groups. The Tukey's honestly significant difference method was used for post hoc, multiple pairwise comparisons. Two-way analysis of variance was used to detect differences in NB by protein groups for those with and without TBI. Goodness of fit of the linear model between two variables was assessed by Pearson correlation analysis. Data were interpolated for a nonlinear relationship using TableCurve 2D, version 5.01 (SYSTAT Software Inc., Point Richmond, VA). Variables that correlated with NB at a significance level of  $p < 0.05$  from the univariate analysis were identified for multivariate logistic regression analysis using a backward stepwise elimination procedure. Analysis of covariance was used to ascertain if differences in NB at various protein intakes were different between those with and without TBI.

## RESULTS

### Patient Population

Two hundred forty-nine patients with critical illness and trauma were enrolled into the study. Most of the patients were male, admitted to the hospital as a result of injuries from a motor vehicle collision and survived. One third of patients experienced severe TBI ( $n = 83$ ), whereas 166 patients were without TBI. Patients with TBI were younger ( $p < 0.002$ ), exhibited a lower body weight ( $p < 0.001$ ) and body mass index

( $p < 0.001$ ), and had a greater ISS ( $p < 0.001$ , Table 1). Details of patient characteristics are given in Tables 1 and 2.

### Nutrition Support and NB

Most of the patients (85%) received enteral nutrition alone (Table 3). A total of 300 NB determinations were used in the analysis. One hundred three determinations were from patients with TBI (24% contributed a second NB). The remaining 197 NB determinations were from patients without TBI (17% contributed a second NB). An increase in serum urea nitrogen concentration, necessitating an adjustment in nitrogen loss, occurred in 9% of the NB studies.

### Influence of Protein Intake Upon NB and Creatinuria

Significant protein catabolism was evident by a mean NB of  $-11$  g/d ( $-135$  mg/kg/d) while receiving an mean protein intake of  $1.3$  g/kg per day (Table 3). Nitrogen equilibrium or positive NB was achieved in 28% of the 300 studies (Table 4). Mean protein intake for patients that achieved nitrogen

TABLE 1. Patient Characteristics and Clinical Outcomes

Variable	All Patients	With TBI	Without TBI	<i>p</i>
<i>n</i>	249	83	166	—
Survived/died, <i>n</i>	224/25	76/7	148/18	NS
Male/female, <i>n</i>	201/48	67/16	133/32	NS
Admission diagnosis, <i>n</i>				
Motor vehicle collision	157	55	100	0.054
Gunshot wound	28	4	24	
Pedestrian struck	18	8	10	
Fall	18	5	13	
Assault	12	7	5	
Miscellaneous	18	4	14	
Type of injury				
Blunt, <i>n</i> (%)	209 (84)	72 (87)	137 (83)	NS
Penetrating, <i>n</i> (%)	40 (16)	11 (13)	29 (17)	
Age, mean (SD), y	44 (18)	39 (16)	47 (19)	0.002
Weight, mean (SD), kg	81 (18)	76 (15)	85 (19)	0.001
BMI, mean (SD), kg/m <sup>2</sup>	26 (5)	25 (4)	27 (6)	0.001
Tmax, mean (SD), °C	38.6 (0.6)	38.7 (0.6)	38.5 (0.7)	0.04
GCS score, mean (SD)	9 (5)	6 (2)	11 (4)	0.001
Sepsis/SIRS, <i>n</i>	108/141	41/42	66/100	NS
ISS, mean (SD)	30 (12)	35 (10)	28 (12)	0.001
AIS score, head and neck, mean (SD)	2.9 (1.9)	4.5 (0.6)	2.1 (1.9)	0.001
Ventilator dependence, <i>n</i>	225	76	149	NS
Ventilator days, mean (SD), d	18 (25)	16 (10)	19 (30)	NS
ICU length of stay, mean (SD), d	24 (19)	24 (17)	23 (20)	NS
Hospital length of stay, mean (SD), d	35 (29)	36 (24)	35 (32)	NS

BMI, body mass index; GCS, Glasgow Coma Scale; ICU, intensive care unit; NS, not significant; SIRS, systemic inflammatory response syndrome; Tmax, maximum daily temperature.

**TABLE 2.** Admission Serum Laboratories

Variable	All Patients	With TBI	Without TBI	<i>p</i>
n	249	83	166	—
Admission lactate, mean (SD), mg/dL	2.8 (3.0)	1.6 (1.4)	3.9 (3.6)	0.001
WBC, mean (SD), cells/ $\mu$ L	13.1 (5.0)	14.4 (5.3)	12.5 (4.8)	0.008
Albumin, mean (SD), g/dL	1.8 (0.4)	1.9 (0.4)	1.8 (0.4)	NS
Prealbumin, mean (SD), mg/dL	9.9 (4.3)	11.2 (4.6)	9.3 (4.0)	0.001
Glucose, mean (SD), mg/dL	124 (26)	123 (26)	124 (25)	NS
SUN, mean (SD), mg/dL	18 (11)	17 (8)	18 (11)	NS
SCr, mean (SD), mg/dL	0.8 (0.3)	0.8 (0.2)	0.9 (0.3)	0.003

NS, not significant; SCr, serum creatinine; SUN, serum urea nitrogen; WBC, white blood cells.

equilibrium was significantly greater than those with negative NB (mean [SD], 1.7 [0.6] g/kg per day vs. 1.0 [0.7] g/kg per day, respectively,  $p < 0.001$ ). Timing of the NB determination after hospital admission was similar between those who achieved nitrogen equilibrium or had a positive NB and those who experienced catabolism (mean [SD], 8.9 [2.8] days vs. 8.2 [2.5] days, respectively,  $p = NS$ ).

The proportion of patients achieving nitrogen equilibrium or having a positive NB improved with each incremental

**TABLE 3.** NB, Creatinine Clearance, and Nutrition Therapy

Variable	All Patients	With TBI	Without TBI	<i>p</i>
n	249	83	166	—
Hospital day EN/PN initiated, mean (SD), d	2.7 (2.0)	1.5 (1.1)	3.2 (2.2)	0.001
EN/PN/both, n	212/26/11	78/3/2	134/23/9	0.02
Hospital day of NB, mean (SD), d	8.4 (2.6)	8.9 (2.2)	8.3 (2.7)	0.05
Protein intake during NB, mean (SD), g/kg/d	1.3 (0.7)	1.5 (0.7)	1.2 (0.7)	0.001
Nitrogen intake, mean (SD), g/d	15.9 (9.0)	17.6 (8.8)	15.1 (9.0)	0.02
Energy intake during NB, mean (SD), kcal/d	1,272 (771)	1,365 (746)	1,224 (781)	NS
Energy intake during NB, mean (SD), kcal/kg/d	16 (10)	18 (10)	15 (10)	0.023
Urine urea nitrogen, mean (SD), g/d	21.0 (9.2)	22.0 (8.4)	20.6 (9.6)	NS
SUN during NB, mean (SD), mg/dL	18 (10)	17 (8)	18 (11)	NS
NB, mean (SD), g/d	-11.0 (10.2)	-10.1 (8.6)	-11.5 (11.0)	NS
NB, mean (SD), mg/kg/d	-135 (127)	-134 (114)	-136 (133)	NS
Urine creatinine, mean (SD), mg/d	1,842 (678)	1,861 (624)	1,832 (706)	NS
Measured CrCl, mean (SD), mL/min	164 (68)*	174 (67)*	159 (72)*	0.001
Predicted CrCl, mean (SD), mL/min	126 (46)	136 (47)	118 (51)	0.01

\* $p < 0.001$ , measured CrCl versus predicted CrCl.

CrCl, creatinine clearance; EN, enteral nutrition; NS, not significant; PN, parenteral nutrition; SUN, serum urea nitrogen.

**TABLE 4.** Effect of Protein Intake Upon Achievement of Nitrogen Equilibrium or Positive NB

Protein Intake, Range, g/kg/d	Protein Intake, mean (SD), g/kg/d	Energy Intake, mean (SD), kcal/kg/d	Serum Urea Nitrogen, mean (SD), mg/dL	NB Studies, n	Nitrogen Equilibrium, n, (%)
<0.5	0.2 (0.2)	4 (4)	15 (9)	47	0 (0%)
0.5–0.99	0.7 (0.1)	8 (4)	19 (14)	60	8 (13%)
1–1.49	1.2 (0.2)	15 (4)	17 (10)	73	21 (29%)
1.5–1.99	1.7 (0.1)	22 (5)	18 (7)	61	23 (38%)
2–2.49	2.2 (0.1)	28 (5)	18 (8)	47	23 (49%)
$\geq 2.5$	2.7 (0.2)	33 (6)	23 (16)	12	9 (75%)

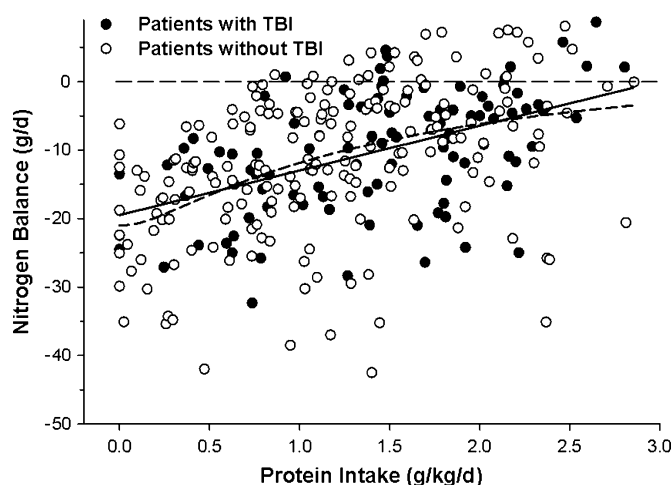
The proportion of patients achieving nitrogen equilibrium for the various protein dosages was significantly increased by increasing protein intake ( $\chi^2 = 50.919$ ,  $p < 0.001$ ). No statistically significant difference in serum urea nitrogen concentration was noted among protein intake groups.

increase in protein intake (Table 4). More than half (32 of 59, 54%) of those who received a protein intake of 2 g/kg per day or greater achieved nitrogen equilibrium or had a positive NB in contrast to 38% and 29% of patients who received 1.5 g/kg per day to 1.99 g/kg per day and 1 g/kg per day to 1.49 g/kg per day, respectively ( $p < 0.001$ ; Table 5). The association between NB and protein intake was modest for linear and nonlinear regression models ( $r = 0.46$  and  $r = 0.45$ , respectively;  $p < 0.001$  for each, Fig. 1). NB improved when protein intake increased ( $p < 0.001$ , Fig. 2) and appeared to plateau within 1.7 g/kg per day to 2.2 g/kg per day although further increases in protein intake resulted in a modest improvement ( $p = NS$ , Fig. 2). These changes in NB were not confounded by differences in mean serum urea nitrogen concentrations (19 [14] mg/dL, 15 [9] mg/dL, 17 [10] mg/dL, 18 [8] mg/dL, 18 [7] mg/dL, and 23 [16] mg/dL, respectively;  $p = NS$  for each protein intake, respectively).

**TABLE 5.** Univariate Correlation Analysis Between NB and Associated Variables

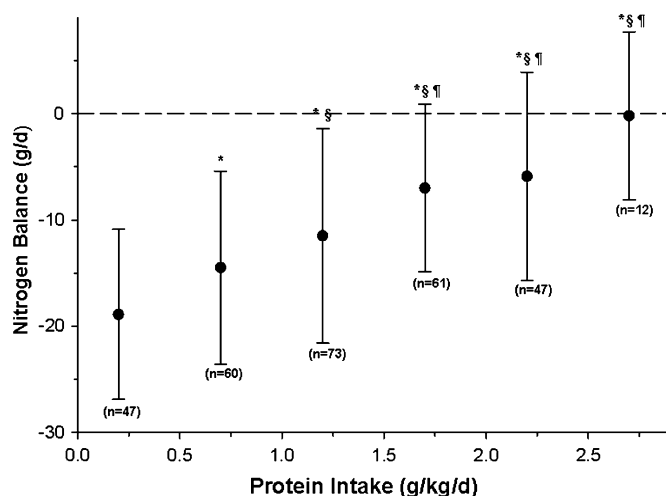
Variable	<i>r</i>	<i>p</i>
Protein intake, g/kg/d	0.460	<0.001
Day of NB	0.130	<0.03
Measured CrCl, mL/min	-0.212	<0.001
TBI	0.067	NS
ISS	0.054	NS
Sex (male)	-0.287	<0.001
Age, y	0.140	<0.02
Weight, kg	-0.258	<0.001
WBC, cells/ $\mu$ L	0.130	<0.03
Tmax, $^{\circ}$ C	-0.116	<0.05
GCS score	-0.066	NS
Albumin, g/dL	-0.092	NS
Prealbumin, mg/dL	-0.111	NS
Glucose, mg/dL	-0.028	NS

CrCl, creatinine clearance; GCS, Glasgow Coma Scale; NS, not significant; Tmax maximum daily temperature; WBC, white blood cell.



**Figure 1.** Linear and nonlinear relationships between NB and protein intake for all patients. The *solid line* indicates the linear relationship:  $NB = 6.69 (\text{Protein intake}) - 19.5$  ( $r = 0.46$ ,  $p < 0.001$ ). The *dashed line* indicates the log normal cumulative nonlinear equation:  $NB = 12.25 \operatorname{erfc}[-\ln(\text{Protein intake}/1.47)/(1.67)] - 21$  ( $r = 0.47$ ,  $p < 0.001$ ). A mean protein intake of more than 2 g/kg per day was necessary to achieve nitrogen equilibrium or have a positive result for NB.

Urinary creatinine excretion paralleled nitrogen excretion ( $r = 0.61$ ,  $p < 0.001$ , Fig. 3A) and inversely correlated with NB ( $r = 0.47$ ,  $p < 0.001$ , Fig. 3B). Measured creatinine clearance was inversely proportional to NB ( $p < 0.001$ , Table 5). Serum creatinine concentrations were similar among protein intake groups (1.0 [0.4] mg/dL, 0.9 [0.3] mg/dL, 0.8 [0.2] mg/dL, 0.8 [0.2] mg/dL, 0.8 [0.2] mg/dL, and 0.7 [0.3] mg/dL, respectively).



**Figure 2.** Effect of a graduated increase in protein intake upon NB for all patients. Mean (SD) protein intake (g/kg/d) was 0.2 (0.2), 0.7 (0.1), 1.2 (0.2), 1.7 (0.1), 2.2 (0.1), and 2.7 (0.2) for each categorized protein intake, respectively. A significant improvement ( $p < 0.05$ ) in pairwise comparisons for NB was observed for 1.7 g/kg per day, 2.2 g/kg per day, and 2.7 g/kg per day when compared with 0.2 g/kg per day, \* 0.7 g/kg per day, § and 1.2 g/kg per day. ¶

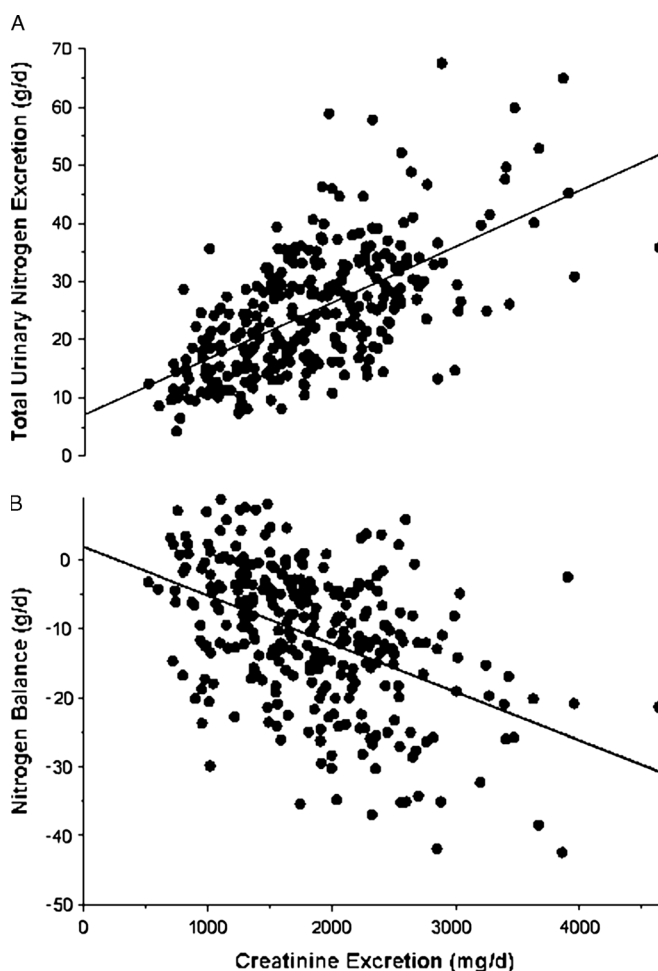
### Association Between NB and Other Variables

Protein intake exhibited a positive correlative relationship with NB ( $p < 0.001$ , Table 5), whereas measured creatinine clearance, male sex, and body weight were inversely associated ( $p < 0.001$ ). Backward stepwise logistic regression analysis resulted in the following probability models ( $r = 0.60$ ,  $p < 0.001$ ):

$$\text{Males: } NB (\text{g/d}) = (\text{Protein intake} \times 7.13) - (0.044 \times \text{mCrCl}) - 14.1$$

$$\text{Females: } NB (\text{g/d}) = (\text{Protein intake} \times 7.13) - (0.044 \times \text{mCrCl}) - 8.3$$

whereas protein intake is in gram per kilogram per day and mCrCl is measured creatinine clearance in milliliter per minute.



**Figure 3.** A, Parallel relationship between total urinary nitrogen excretion and urinary creatinine excretion ( $y = 7.1 + (0.0097 \times \text{urinary creatinine excretion})$ ,  $r = 0.61$ ,  $p < 0.001$ ). B, Inverse relationship between NB and urinary creatinine excretion ( $y = 1.83 - 0.007 \times \text{urinary creatinine excretion}$ ,  $r = 0.47$ ,  $p < 0.001$ ).

## Impact of Severity of Injury and the Presence of TBI Upon NB

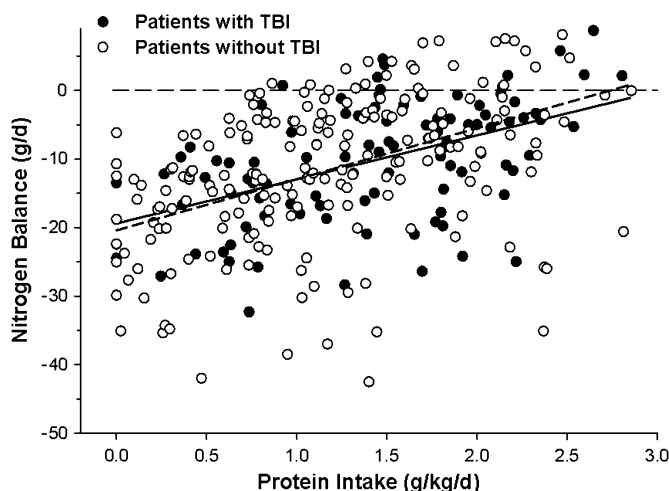
ISS had no relevant association with NB ( $r = 0.054$ ,  $p = \text{NS}$ ; Table 5). Of the patients, 86 had an ISS of less than 25 (mean [SD], 17 [5]) and 163 had an ISS of 25 or greater (mean [SD], 37 [10];  $p < 0.001$ ). Despite similar mean protein intakes (1.2 [0.7] g/kg per day vs. 1.3 [0.7] g/kg per day, respectively;  $p = \text{NS}$ ), NBs were not different between ISS groups ( $-11.1$  [11.8] g/d vs.  $-11.0$  [9.5] g/d, respectively,  $p = \text{NS}$ ).

NB without protein intake was similar for both groups at  $-20$  g/d. As protein intake increased, NB improved for both TBI and non-TBI groups (Fig. 4). The correlative relationships between NB and protein intake were statistically significant ( $r = 0.50$ ,  $p < 0.001$  and  $r = 0.45$ ,  $p < 0.001$ , for TBI and non-TBI groups, respectively) but indicated wide variability (Fig. 2). Analysis of covariance with TBI as the covariate indicated no significant difference in the NB-protein intake continuum between the two populations. There were no significant differences in mean protein intake for each protein intake group or in NB (g/d) between patients with and without TBI (Fig. 5,  $p = \text{NS}$ ).

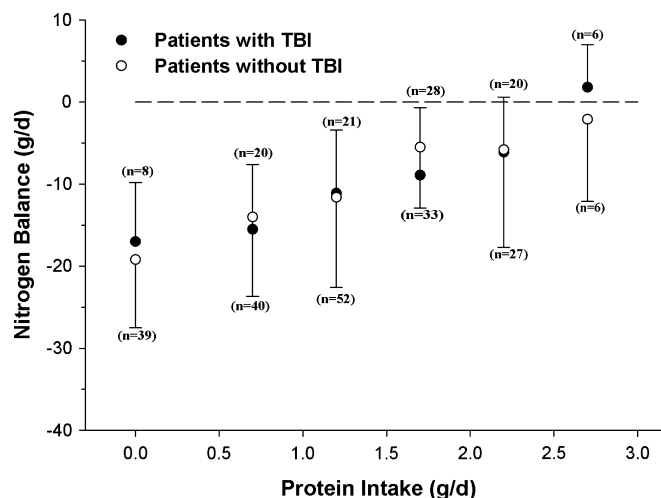
Twenty-eight NB determinations in 23 patients with isolated TBI and 75 NB studies in 60 patients with TBI and other injuries indicated that NB was significantly worse for the latter group ( $-5.7$  g/d vs.  $-11.7$  g/d, respectively,  $p < 0.001$ ; Table 6). A significantly worse NB persisted for patients with TBI and other injuries when adjusted for variability in protein intake ( $p = 0.015$ , Fig. 6). These findings were not attributable to differences in energy intake, days after the injury of the NB determination, head and neck AIS score, or other variables outside of the additional injuries and a higher ISS (Table 6).

## DISCUSSION

Our data indicate that nitrogen equilibrium for patients with critical illness and trauma was more often achieved at



**Figure 4.** Linear relationship between NB and protein intake for those with TBI (solid line;  $y = 6.4 \times - 19.4$ ,  $r = 0.50$ ,  $p < 0.001$ ) and without TBI (dashed line;  $y = 7.45 \times - 20.4$ ,  $r = 0.45$ ,  $p < 0.001$ ). Analysis of covariance indicated no significant difference between those with and without TBI.

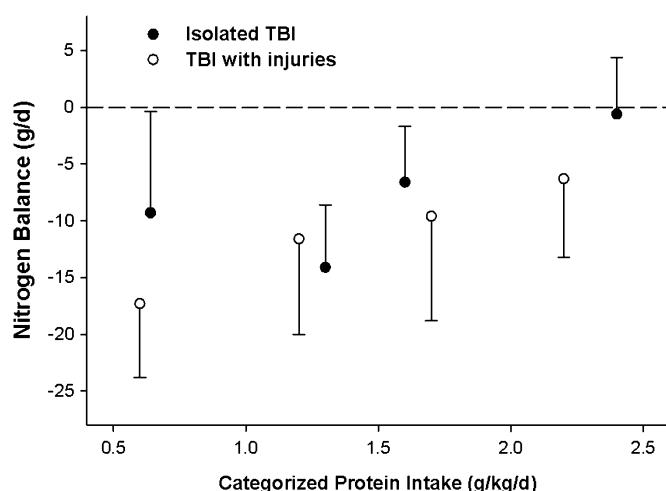


**Figure 5.** Influence of protein intake, stratified into an increment of 0.5 g/kg per day, upon NB for patients with and without TBI. Mean (SD) protein intake (g/kg/d) for TBI and non-TBI patients for each protein intake group was 0.3 (0.2) vs. 0.2 (0.1), 0.7 (0.1) vs. 0.7 (0.1), 1.2 (0.2) vs. 1.2 (0.1), 1.7 (0.2) vs. 1.7 (0.1), 2.2 (0.1) vs. 2.2 (0.1), and 2.7 (0.3) vs. 2.6 (0.2), respectively ( $p = \text{NS}$ ). There was no significant difference in NBs between TBI and non-TBI groups at equivalent protein intakes ( $p = \text{NS}$ ).

**TABLE 6.** Patient Characteristics of Those With Isolated TBI Versus TBI With Other Associated Injuries

Variable	Isolated TBI	TBI With Other Injuries	<i>p</i>
n	23	60	—
Survived/died, n	22/1	54/6	NS
Male/female, n/n	19/4	48/12	NS
ISS, mean (SD)	26 (7)	38 (10)	0.001
Type of injury, n (%)			
Blunt	14 (61)	58 (97)	0.001
Penetrating	9 (39)	2 (3)	
Age, mean (SD), y	41 (15)	39 (17)	NS
Weight, mean (SD), kg	75 (13)	77 (16)	NS
BMI, mean (SD), kg/m <sup>2</sup>	24 (4)	25 (4)	NS
AIS score, head and neck, mean (SD)	4.6 (0.5)	4.4 (0.6)	NS
GCS score, mean (SD)	5 (2)	6 (2)	NS
Protein intake during NB, mean (SD), g/kg/d	1.6 (0.7)	1.4 (0.7)	0.07
Energy intake during NB, mean (SD), kJ/d	6,142 (330)	5,548 (3059)	NS
Energy intake during NB, mean (SD), kJ/d	79 (42)	71 (42)	NS
NB, mean (SD), g/d	-5.7 (6.7)	-11.7 (8.7)	0.001
NB, mean (SD), mg/kg/d	-79 (95)	-155 (115)	0.002
Hospital day of NB, mean (SD), d	9.3 (2.3)	8.6 (2.4)	NS

BMI, body mass index; GCS, Glasgow Coma Scale, NS, not significant.



**Figure 6.** Influence of protein intake, stratified into an increment of 0.5 g/kg per day, upon NB for patients with isolated TBI and for those with TBI and other associated traumatic injuries. Mean (SD) protein intake (g/kg/d) for each stratified protein intake was 0.6 (0.2), 1.3 (0.1), 1.6 (0.2), and 2.4 (0.3) vs. 0.6 (0.3), 1.2 (0.2), 1.7 (0.2), and 2.2 (0.2), respectively. Patients with TBI and other traumatic injuries experienced a significantly worse NB than those with isolated TBI at similar protein intakes ( $p = 0.015$ ).

protein intakes of 2 g/kg per day or greater. A slowing of nitrogen accretion occurred at protein intakes within 1.7 g/kg per day to 2.2 g/kg per day, but modest improvement in NB was observed when protein intake was increased further. Patients with TBI are not more catabolic than those without TBI. The strength of our study was the large number of patients and a homogenous population of patients with trauma.

Traumatic injury is associated with a fourfold to fivefold increase in urinary nitrogen excretion compared with that of healthy subjects.<sup>15</sup> Whole-body protein synthesis increases 15% to 37%, and protein breakdown increases by 41% to 79% resulting in net protein catabolism.<sup>15–17</sup> Unabated protein catabolism during critical illness, attributed to inadequate nutrition therapy, results in impaired immunity, increased infections, and worsened survival.<sup>2–7</sup> Therefore, it is imperative that nutrition therapy be implemented early and continued throughout the patient's intensive care unit stay.

The impact of nutrition therapy toward modulating body protein loss during critical illness has been only modestly effective.<sup>1,17,18</sup> It has been established that the nonprotein energy intake is less likely to influence total body protein loss during critical illness than protein intake when protein intake is adequate or abundant.<sup>19,20</sup> However, the amount of protein intake whereby additional increases in dosage will not further attenuate body protein loss for the patient with critical illness is still debatable.<sup>16,17,21–23</sup> Studies in infected patients or patients with trauma<sup>16</sup> and patients with thermal injury<sup>24</sup> suggested no improvement<sup>24</sup> or an increase<sup>16</sup> in net protein catabolism when protein intake was increased from 1.5 g/kg per day to 2.2 g/kg per day. It is unlikely that increasing protein intake resulted

in increased endogenous protein catabolism, but rather the degradation of excess protein intake. These studies<sup>16,21,23,24</sup> provided the impetus for investigating optimal protein requirements for patients with critical illness and trauma.

NB reflects an overall assessment of nitrogen exchange but gives little insight into the internal dynamics of protein metabolism.<sup>15</sup> It is not known whether the higher protein doses resulting in improved NB observed in our study reflected reduced body protein loss, improved whole-body protein synthetic rate, decreased whole-body protein catabolic rate, or an expansion of the patient's labile amino acid pool. Urinary creatinine excretion and serum urea nitrogen concentration may provide a crude interpretation of internal protein dynamics. Posttrauma creatinuria was inversely related to NB, paralleled urinary nitrogen excretion (Fig. 3), and provided evidence of declining skeletal muscle breakdown by increasing protein intake. The highest protein intake (2.5–3 g/kg/d) had the highest mean serum urea nitrogen concentration (23 mg/dL vs. 17–19 mg/dL for the groups with protein intake of 0.5–2.5 g/kg per day, respectively) and greatest amount of variability in serum urea nitrogen concentrations (Table 4). This trend implies that some patients in the highest protein intake group may have achieved their maximal rate of net protein efficiency.

Previous literature suggested that dosing of protein for patients with TBI should be aggressive because TBI has historically been characterized as one of the most protein catabolic conditions during critical illness.<sup>11,25–28</sup> Petersen et al.<sup>29</sup> were the first to demonstrate that patients with and without TBI were similar in regard to severity of catabolic response as assessed by NB, urinary 3-methylhistidine excretion, and protein breakdown rate during the early flow phase of injury before implementation of nutrition therapy. Our data, derived from a larger patient population, confirmed their findings as applied to the mid-to-late flow phase of injury while patients were receiving nutrition therapy. This paradigm shift may be reflective of substantial improvements in the therapeutic management of patients with TBI, which include the use of propofol and avoidance of corticosteroids. Propofol decreases oxygen consumption by 25% to 40%.<sup>30</sup> It is possible that decreasing resting energy expenditure with propofol may also down-regulate urinary nitrogen excretion analogous to pentobarbital,<sup>11</sup> but data are lacking. Corticosteroids, now considered obsolete therapy for the management of TBI, increases urinary nitrogen excretion 30% to 50%.<sup>31</sup> These changes in therapeutic management are potentially plausible explanations for similar nitrogen excretion rates between patients with and without TBI when compared with earlier studies that indicated large differences in urinary nitrogen excretion.

Although previous studies indicated a lack of improvement in net protein catabolism with increased protein intake,<sup>16,24</sup> a 40% increase in whole-body protein synthesis occurred when the protein intake was increased.<sup>24</sup> An improvement in the absolute rate of whole-body protein synthesis may be considered beneficial during critical illness as long as there are no detrimental effects. In the absence of renal or hepatic failure, the physiologic effects of short-term administration of higher protein doses are unlikely to cause serious adverse effects.<sup>32</sup> Modest ureagenesis and an increase in net

titratable acid production will unlikely supersede the potential benefits of providing sufficient protein intake.

This study has some limitations. These data were derived predominately in males. Resting energy expenditure was not measured. The amount of insulin received by patients was not recorded; however, data are conflicting whether insulin administration significantly improves protein synthesis during critical illness owing to skeletal muscle insulin resistance.<sup>33</sup> A single NB may not reflect overall protein balance during the patient's hospital course. Cumulative protein deficit during their intensive care unit stay would be more reflective of the impact of nitrogen deficit upon clinical outcome. Steady-state NB measurements were not possible owing to interruptions in enteral nutrient delivery and day-to-day variability for the patients' clinical status. NB may also underestimate losses if the patient experiences diarrhea or abdominal fluid losses.<sup>14</sup> Finally, NB reflects only the net difference between intake and output. It does not reveal information regarding nitrogen distribution, synthesis, and catabolism among tissues and organs. Despite these shortcomings, the NB technique continues to serve as the basis for the determination of protein requirements<sup>34</sup> and is commonly used in clinical practice.

In conclusion, patients with critical illness and trauma exhibit a variable rate of protein catabolism. Patients with TBI are not significantly more protein catabolic than those without TBI. A protein dosage of 2 g/kg per day or greater was more successful in achieving nitrogen equilibrium than lower-dosage intakes. Ureagenesis was greater when protein intake exceeded 2.5 g/kg per day. Individualization of protein intake with close monitoring is warranted.

#### AUTHORSHIP

R.N.D. conceived of this project. All authors contributed to protocol development. R.N.D. and S.L.P. collected and entered the data, which R.N.D. analyzed and all authors interpreted. R.N.D. wrote the manuscript, which all authors critically reviewed.

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#### DISCLOSURE

The authors declare no conflicts of interest.

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