The Effect of Burn Wound Size on Ureagenesis and Nitrogen Balance

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Hypermetabolic burn patients are frequently in negative nitrogen balance despite provision of estimated caloric needs. We studied 18 thermally injured adult patients in order to evaluate the relationship of burn wound size to urea production and nitrogen balance. We selected data from 147 patient-days when the patients received 100 ± 25% of their estimated caloric needs. Three significantly different burn size groups (by body surface area [BSA]) were identified by calculation of the catabolic index (CI): group 1, 0–10% BSA (CI = −0.1); group 2, 11–30% BSA (CI = 6.4); and group 3, 31–60% BSA (CI = 10.5). The urine urea nitrogen (UUN) for groups 1, 2, and 3 was 11.1, 18.9, and 25.3 gm/day, and nitrogen balance was 1.0, −3.9, and −5.8 gm/day, respectively. When nitrogen was given in a calorie:nitrogen ratio of 150:1, only those patients in group 1 were able to achieve positive balance. We conclude that large burn wounds are associated with increased ureagenesis and impaired nitrogen retention. The protein intake, at the customary calorie:nitrogen ratio of 150:1, may not provide adequate nitrogen to achieve equilibrium, even when energy demands have been met, in patients with burn wounds greater than 10% BSA.

THE STATE OF HYPERMETABOLISM, which follows major thermal injury, is characterized by an increased energy requirement and accelerated ureagenesis. An increased rate of urea production and a decreased nitrogen intake are the major factors in the customary negative nitrogen balance of the burned patient. It is generally agreed that burned patients require supranormal caloric intake[1] in order to achieve positive nitrogen balance. Curreri's formula attempts to estimate each patient's caloric requirements by taking into consideration the basal caloric requirement as well as the burn size.[2]

Nitrogen requirements over and above the basal requirements and the optimal calorie:nitrogen ratio in burn patients have not received similar emphasis. Soroff showed an increase in both the nitrogen requirement for equilibrium and the obligatory nitrogen loss in severe burns.[3] Nitrogen metabolism subsequently returns towards normal late in the postburn period as the wounds heal, but the size of the open wound has not been correlated with nitrogen balance.

We studied burn patients with various wound sizes whose calorie requirements had been met according to the Curreri formula. We evaluated the relationship of the size of the burn wound to urea nitrogen production and nitrogen balance.

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Materials and Methods

We studied 18 adult patients admitted to the Cook County Hospital Burn Unit who sustained cutaneous burn injuries initially greater than 20% of the total body surface area (BSA). All patients signed informed consents for participation in the study.

The clinical management of the patients was standardized within the limits dictated by the clinical course. All patients were initially resuscitated using the Parkland formula. The wounds were treated with occlusive dressings and topical silver sulfadiazine. Full-thickness or tangential excisions were performed as deemed necessary in the early postburn period.

Caloric requirements were estimated using the formula of Curreri: ideal calorie intake = 25 × weight (kg) + 40 × per cent body surface area burn.[2] The estimated calorie requirements were adjusted daily in each patient according to changes in the size of the open wound. In an attempt to meet these requirements, the patients were fed high-protein, high-calorie hospital diets containing 3,200 Kcal and 20–24 gm nitrogen per day. In addition, oral dietary supplements were provided using Sustacal® (Mead-Johnson, Evansville, IN) or Ensure®/Ensure-Plus® (Ross, Columbus, OH). Patients whose oral intake did not meet estimated caloric requirements were given additional tube feedings using Isocal® (Mead-Johnson) or Vivonex-HN (Eaton, Nor-

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wich, NY). When necessary, parenteral hyperalimentation was provided via central or peripheral venous catheters. The nutritional composition of these feedings is shown in Table 1.

The estimated nitrogen requirement was calculated based on a calorie:nitrogen ratio of 150:1. Plasma and albumin were not used to supplement nitrogen intake, per se. These blood products were used when necessary in the perioperative period only.

Daily measurements of calorie and nitrogen intake and blood urea nitrogen as well as continuous 24-hour urine collections were begun upon admission and continued until the date of discharge or death. Oral, enteral, and parenteral intakes were recorded daily by the nursing staff. Urine was pooled in 24-hour collections and refrigerated without added preservative.

On those 147 patient-days when the patients received 100 ± 25% of the calculated caloric requirements, the data were selected and analyzed for the effect of wound size on urea nitrogen production and nitrogen balance. Estimates of the size of the open wound were made every five days until the time of discharge or death. Open areas were defined as: unhealed partial thickness wounds, all full-thickness wounds, and all unhealed donor sites. Wound sizes on intermediate days were determined by interpolation. Days of operation and the first 72 hours of resuscitation were excluded from the study.

Calorie and nitrogen intakes were calculated by the ward dietician. It is controversial whether blood products should be included in nitrogen intake calculations. We did not do so in this study; however, no patients received more than 5 gm of nitrogen per day in this form. Determinations of 24-hour urine urea nitrogen (UUN) were made using the Clinicard Analyzer IL 368.[4] Total urea nitrogen (TUN) produced was calculated from UUN corrected for the change in blood urea nitrogen (BUN) for that day.[5] Total nitrogen output was then calculated by adding TUN to the estimated value of 4 gm/day for other nitrogen losses (wound exudate, feces, and other nitrogen containing compounds present in the urine).[6] This estimated value was not adjusted for wound size, but was assumed to be constant. Nitrogen balance was calculated as the difference between dietary nitrogen intake and total nitrogen output.

Nitrogen output depends on both nitrogen intake and nitrogen retention; the latter is influenced by the magnitude of catabolic stress. Therefore, in order to assess the effects of catabolic stress on nitrogen retention, Bistrian proposed the catabolic index (CI): UUN $- (0.5 \times$ dietary nitrogen intake $+ 3$ gm). This index minimizes the effect of nitrogen intake on nitrogen output and indicates the magnitude of catabolic stress. An index of less than zero represents no significant stress; an index of zero to five, moderate stress; and an index greater than five, severe stress.[7] We calculated the catabolic index on each patient-day for comparison with the calculated nitrogen balance on that day.

Student's t-tests were used to determine the level of statistical significance of the data.

TABLE 1. *Nutritional Composition of Supplemental Feedings*

Source	Kcal/L	Grams N/L
Sustacal	1,000	9.60
Ensure	1,060	5.92
Ensure-Plus	1,500	8.80
Isocal	1,040	5.44
Vivonex-HN	1,000	6.67
Central IV hyperalimentation	1,000	6.25
Peripheral IV hyperalimentation	500	6.25

Results

Each patient-day was placed into one of ten categories of open wound size: 0–10%, 11–20%, *etc.*, body surface area (BSA). Using the catabolic index, three significantly different groups were defined as follows: group 1, 0–10% BSA; group 2, 11–30% BSA; and group 3, 31–60% BSA.

All of the individual patient data was then pooled according to these burn size groups. Means of catabolic index, calories required, actual calorie intake, per cent of calorie requirement received, estimated nitrogen requirement, actual dietary nitrogen intake, Kcal:N ratio, UUN, total nitrogen output, and nitrogen balance were calculated for groups 1, 2, and 3 as defined by BSA (Table 2). The catabolic indices of groups 1, 2, and 3 were all significantly different ($p < 0.05$): −0.1, 6.4, and 10.5, respectively. The three burn size groups were comparable in that the Kcal:N ratios and the actual calories received, as a percentage of the estimated requirement, were not significantly different.

The presumed nitrogen requirements (based on a calorie:nitrogen ratio of 150 to 1) for each group were 15.0, 16.9, and 22.3 gms per day, respectively. The means of actual nitrogen intake for groups 1, 2, and 3 were 16.3, 19.0, and 23.6 grams per day, respectively. In each group, actual nitrogen intake exceeded the presumed requirement.

Individual data points of nitrogen intake and UUN are shown for each group in Figure 1. The mean UUN was 11.1, 18.9, and 25.3 gm per day, respectively. Urea nitrogen losses increased significantly in groups 2 and 3. The difference between TUN and UUN was insignificant in all three groups. Total urea nitrogen was only used in the calculations of total nitrogen output and nitrogen balance.

TABLE 2. *Summary of Data for the Burn Size Groups* (Mean ± SEM) (Group 1, 0–10%; Group 2, 11–30%; Group 3, 31–60% BSA)

	Group 1		Group 2		Group 3
No. of pt-days	51		76		20
Catabolic index*	−0.1 ± 0.7	a†	6.4 ± 0.8	f	10.5 ± 2.2
Estimated calories required	2243 ± 36.5	a	2541 ± 76.0	c	3351 ± 87.9
Calories received	2282 ± 40.4	b	2595 ± 99.1	c	3353 ± 155.1
Per cent required calories received	102.8 ± 2.1	NS	101.0 ± 1.7	NS	99.9 ± 3.6
Est. gm nitrogen required (cal/150)	15.0 ± 0.2	b	16.9 ± 0.5	c	22.3 ± 0.6
Gm nitrogen received	16.3 ± 0.4	b	19.0 ± 0.9	e	23.6 ± 1.5
Cal:N ratio	144.4 ± 4.3	NS	145.6 ± 4.4	NS	154.1 ± 13.0
Urine urea nitrogen (gm/day)	11.1 ± 0.7	a	18.9 ± 1.0	d	25.3 ± 2.4
N-out‡	15.3 ± 0.7	a	22.9 ± 1.0	d	29.5 ± 2.4
N-balance (gm/day)	1.0 ± 0.8	a	−3.9 ± 0.8	NS	−5.8 ± 2.3

* Catabolic index = UUN − (0.5 × dietary nitrogen intake + 3).

† a: group 1 compared to group 2, $p < 0.001$; b: group 1 compared to group 2, $p < 0.01$; c: group 2 compared to group 3, $p < 0.001$; d: group 2; compared to group 3, $p < 0.01$; e: group 2 compared to group 3, $p < 0.02$; f: group 2 compared to group 3, $p < 0.05$.

‡ N-out = TUN + 4; TUN = UUN + (change in BUN[mg/dl] × 0.006 × body weight [kg]).

Nitrogen balance in each group is depicted in Figure 2. The means of total nitrogen output for groups 1, 2, and 3 were 15.3, 22.9, and 29.5 gm/day, respectively. The mean nitrogen balance was 1.3, −3.9, and −5.8 gm/day, respectively. Despite a significant increase in dietary nitrogen intake between groups 1 and 2 ($p < 0.01$), nitrogen balance became negative ($p < 0.001$). In comparing groups 2 and 3, nitrogen intake was again significantly increased ($p < 0.02$); though nitrogen balance became more negative, this difference was not significant ($p > 0.05$).

Discussion

Increased nitrogen loss is a characteristic feature of the metabolic response to injury, including burns. Increased catabolism under stress, perhaps due to a persistent elevation of serum catecholamines and glucagon,[8,9] reduces net protein retention and increases nitrogen excretion proportionally.[7]

Soroff has correlated nitrogen balance with the postburn course. He defined four phases: (1) catabolic, beginning on the seventh postburn day; (2) anabolic, beginning on the 13th; (3) postgrafting anabolic, beginning on the 60th; and (4) convalescence, beginning on the 90th. He concluded that the obligatory nitrogen loss and the requirements for nitrogen equilibrium decreased as the postburn course progressed through convalescence.[3]

We assumed a uniform amount of nitrogen loss from the wounds for all groups of patients (2 gm/day). It is reasonable to assume that nitrogen loss from the wound is greater in patients with larger wounds. If the actual nitrogen loss from the wound had been measured, this tendency toward a positive nitrogen balance in those with small wounds and negative nitrogen balance in

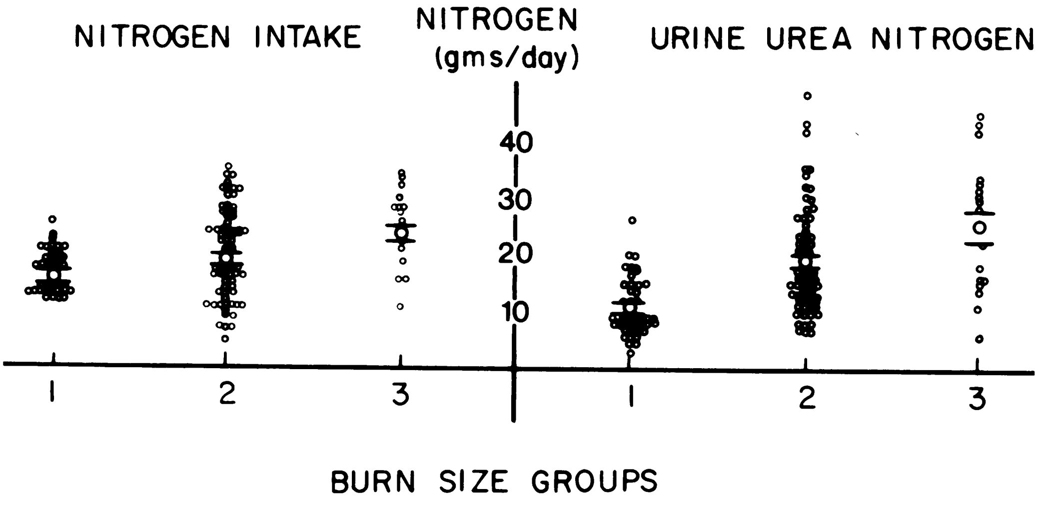

FIG. 1. Scattergram of nitrogen intake and 24-hour UUN in the three burn size groups: group 1, 0–10%; group 2, 11–30%; and group 3, 31–60% BSA. Mean and SEM are superimposed as the large circle and horizontal bars, respectively.

those with larger wounds wound have been even more obvious.

An analysis of our data showed a strong positive correlation between UUN and wound size. The UUN was greatest in patients with large wounds (groups 2 and 3). As wound size diminished, UUN excretion decreased.

The UUN is a unique variable because it is not affected by nitrogen loss from the wound. It is, in effect, a measurement of internal nitrogen metabolism. Nitrogen losses in wound exudates, which are difficult to measure, do not necessarily reflect changes in internal nitrogen metabolism. The use of a formula such as the catabolic index, rather than nitrogen balance, may therefore be justified in the analysis of the effect of catabolic stress on internal nitrogen metabolism.

The catabolic index is the difference between measured and predicted UUN.[7] The catabolic index did increase significantly in our patients with larger open wounds (groups 2 and 3). These differences were not as apparent and, in fact were not significant, when only nitrogen balance was analyzed.

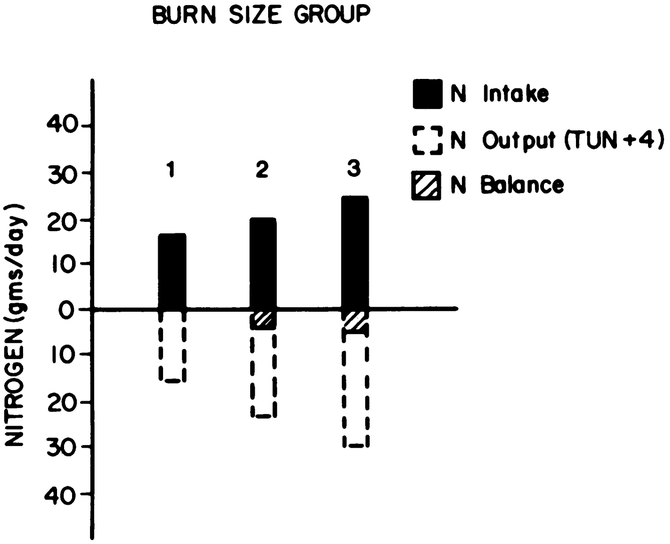

FIG. 2. Bar graphs of mean nitrogen intake, total nitrogen output, and nitrogen balance for the three burn size groups: group 1, 0–10%; group 2, 11–30%; and group 3, 31–60% BSA. N-in: group 1 vs. 2, $p < 0.001$; 2 vs. 3, $p < 0.02$. N-out: group 1 vs. 2, $p < 0.01$; 2 vs. 3, $p < 0.01$. N-bal: group 1 vs. 2, $p < 0.01$; 2 vs. 3, NS.

Accelerated ureagenesis is the final consequence of the hypermetabolic response to injury. The accelerated rate of hepatic gluconeogenesis, which is characteristic of stress, necessitates the increased use of amino acids (particularly alanine) as glucose precursors. Studies using radiolabeled alanine have shown that accelerated skeletal muscle proteolysis occurs with increased production of alanine and other three-carbon precursors from branched chain amino acids in muscle (Fig. 3). The amino-N generated from the hepatic transamination is, for the most part, converted to urea and excreted in the urine.[12]

Our patients received approximately 100% of their

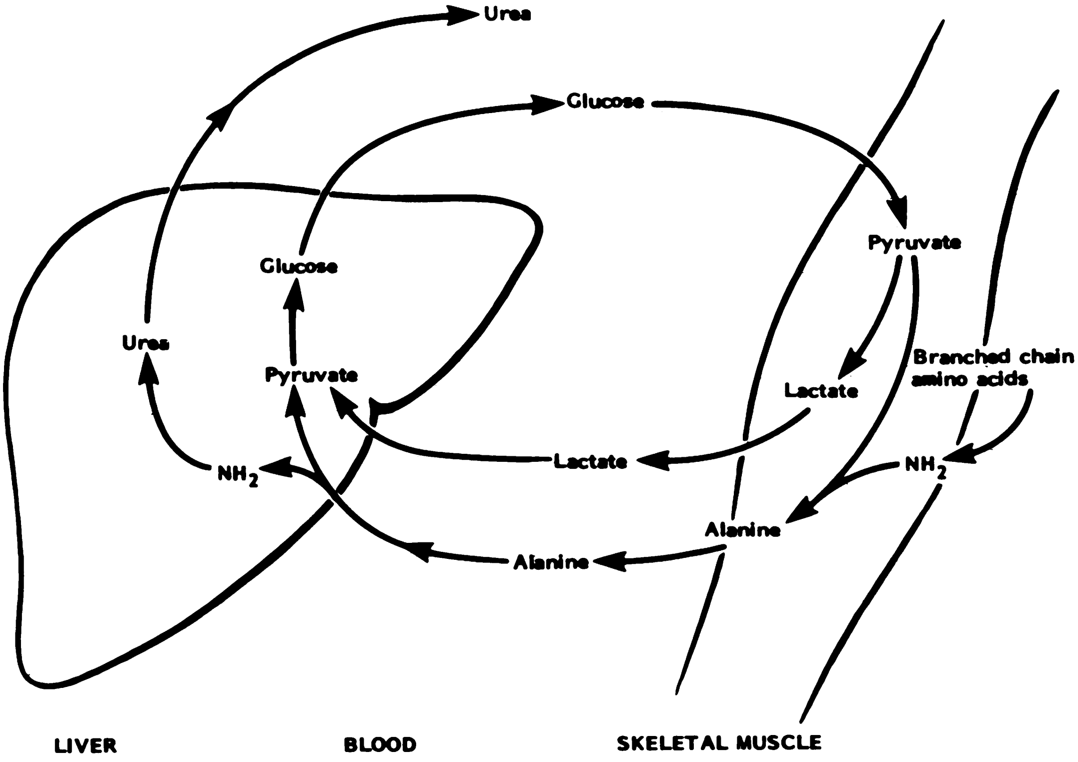

FIG. 3. The Cori cycle and glucose-alanine cycle in hepatic gluconeogenesis and ureagenesis (modified from Bondy[10] and Wilmore[11]).

targeted calories. Although there is great individual variation in the caloric requirements of burned patients, it is impractical to perform daily measurements of oxygen consumption. We estimated each patient's caloric requirement using Curreri's formula and assumed that this estimate would provide an adequate energy source. When nitrogen was given in a ratio of approximately 1 gm to 150 calories, nitrogen balance became progressively negative as the wound size increased. Only those patients with small burn wounds (group 1) were able to achieve a positive nitrogen balance (Table 2).

In normal active individuals, optimal efficiency of nitrogen use is obtained by administering 7-8% of the calories as protein (a calorie:nitrogen ratio of 300-350:1).[13] Hypermetabolic burn patients require supranormal calorie intakes to meet increased energy demands.[1] Wilmore has recommended that, in addition to the increased calorie intake, the quantity of protein in the diet be increased to 15-20% of the total calories (a calorie:nitrogen ratio of 150:1).[14] Alexander et al. have further suggested increasing the quantity of protein to 25% of the total calorie intake.[15] Hiebert has recently reported that, in severely hypermetabolic burn patients, only those receiving diets containing a calorie:nitrogen ratio of 100:1 were able to achieve positive nitrogen balance.[16]

The provision of adequate calories did not appear to suppress the increased stimulus for hepatic gluconeogenesis and increased ureagenesis in those patients with larger burns. Reduction of the burn wound size, per se, may decrease both urea nitrogen production and dietary nitrogen requirements by reducing catabolic stress. Early wound closure by aggressive surgical excision and grafting, then, may be very important in maintaining patients in good nutritional status. Those patients with large burns whose wounds cannot be reduced in size immediately by surgical intervention may require greater amounts of nitrogen relative to calorie intake (*i.e.*, lower Kcal:N ratio) in order to achieve nitrogen equilibrium.

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