Estimating Energy and Protein Requirements of Thermally Injured Patients: Art or Science?

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INTRODUCTION
Thermal injury is one of the most hypermetabolic and hypercatabolic of all conditions encountered in clinical practice. Nutrition support may improve morbidity and mortality after severe thermal injury, but excessive caloric and protein intakes cannot overcome the catabolic response to critical illness and the detrimental effects of overfeeding are well established. Success of the nutritional management of the thermally injured patient may depend on how well this burn-related change in energy expenditure and nitrogen loss can be estimated and then matched by an appropriate amount of macronutrients.

ESTIMATING ENERGY REQUIREMENTS
Estimating energy requirements for thermally injured patients is challenging to the clinical practitioner because they are often variably hypermetabolic. As a result, extensive research regarding the pathogenesis and nature of the hypermetabolism has been conducted over the past few decades. The abundance of literature and predictive methods for estimating energy requirements in thermal injury has most likely led to further confusion rather than to clarity for clinicians involved in the management of these patients. To clarify this literature, we recently conducted a study to ascertain which of the 46 available methods in the literature most accurately predicted resting energy expenditure. We evaluated the bias and precision of those methods in 24 thermally injured (burn area > 20% of total body surface) adults who had their resting energy expenditures measured by indirect calorimetry. Patients were measured during the first 3 wk postinjury within the expected period of sustained hypermetabolism from thermal injury. The predictive method was considered precise if the 95% confidence interval (CI) for the root mean-square prediction error was within 15% of the measured energy expenditure. Unfortunately, none of the formulas met the criteria for being precise. None of the formulas’ CIs for error was within 20% of measured energy expenditure. Thirty-three percent of all of the methods were biased toward overpredicting measured energy expenditure, whereas about 20% of the formulas consistently underpredicted measured energy expenditure.

The most precise, unbiased methods for estimating resting energy expenditure in our population were the formulas of Xie et al. (18 ± 15% error, CI = 12–24%) and Milner et al. (16 ± 15% error, CI = 10–22%). Both methods included body surface area (BSA) and percentage of total body surface area burn (BSAB). The method of Milner et al. also included the number of days postinjury and the basal metabolic rate according to Fleish’s standards for normal subjects. Because of its practicality in ease of use without a substantial difference in error, we chose the formula of Xie et al. for estimation of goal caloric intake in our practice:

\[
\text{energy expenditure (kcal/d)} = \frac{(1000 \text{ kcal} \times \text{BSA [m}^2])}{(25 \times \%\text{BSAB})}
\]

Recent data have suggested that it is uncommon for the thermally injured patient to exceed a resting energy expenditure of greater than twice that of basal energy expenditure (e.g., Harris–Benedict equations). Also, many of the published formulas were designed to estimate energy expenditure during the acute hypermetabolic phase after thermal injury. Because thermally injured patients have sustained hypermetabolism for about 3 wks after injury, the predictive methods of Xie et al. and Milner et al. may not be appropriate and may lead to overfeeding in long-term, convalescent thermally injured patients. However, hypermetabolism and hypercatabolism may exist for several months after thermal injury in some patients.

Total energy expenditure may differ significantly from resting energy expenditure, particularly in thermally injured patients. In critically ill, mechanically ventilated, non-thermally injured patients, total energy expenditure is generally 5% to 10% above measured resting energy expenditure. However, thermally injured patients undergo activities and painful procedures such as physiotherapy and dressing changes that may alter their energy expenditures. The amount of increase in energy expenditure due to these procedures is variable and may partly depend on the extent of hypermetabolism the patient is experiencing at the time of the procedure. If the patient is considerably hypermetabolic before the procedure, it is unlikely that these procedures will have a substantial effect on further increasing total energy expenditure. Because of this variability and the modest predictive performance of these predictive methods, we chose the formula of Xie et al. as an estimation of total energy expenditure rather than resting energy expenditure. This conservative method, using resting energy expenditure predictions as an estimation of total energy expenditure, may result in a modest underestimation of energy needs in some patients. However, with this technique, we are probably less likely to experience overfeeding complications for those individuals where the predictive formula overestimates resting energy expenditure. For patients who require parenteral nutrition, this macronutrient regimen will not exceed a dextrose intake of 5 mg · kg⁻¹ · min⁻¹ or 25 kcal · kg⁻¹ · min⁻¹ to avoid overfeeding complications from excessive parental glucose intake.

ESTIMATING PROTEIN REQUIREMENTS
Protein needs are increased after thermal injury due to accentuated and persistent muscle catabolism and wound losses.

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and tissue repair. Urinary urea nitrogen excretion tends to parallel the extent of burn injury;20 however, catabolism does not consistently increase linearly with thermal injuries above 40% total BSAB.19 Although numerous investigators have discussed the increased protein needs of the thermally injured patient, finding a clear recommendation for a goal regimen is more problematic. Matsuda et al.22 gave thermally injured patients a nutritional regimen based on a non-protein calorie:nitrogen ratio of 150:1 or 100:1. Patients were stratified according to extent of thermal injury (≤10%, 11–30%, or >30% BSAB). Each group received a protein intake of 1.3 or 1.8 g·kg⁻¹·min⁻¹, 1.6 or 2.2 g·kg⁻¹·min⁻¹, or 2.0 or 2.9 g·kg⁻¹·min⁻¹, respectively. The patients who received a lower NPC:N2 ratio (greater protein intake) for each stratified group had significantly better nitrogen balances. Wound losses and non-urea nitrogen losses in the urine were not accounted for; thus, nitrogen balance determinations were likely overestimated for all patients. Wolfe et al.23 assessed the protein metabolic response to a protein intake of 1.4 g·kg⁻¹·min⁻¹ versus 2.2 g·kg⁻¹·min⁻¹ in thermally injured patients. When the protein intake was increased from 1.4 to 2.2 g·kg⁻¹·min⁻¹, the protein kinetic studies indicated that there was no further increase in net protein synthesis. However, the nitrogen excretion data demonstrated a significant improvement in nitrogen balance with the higher protein intake. Based on these data, an empiric goal protein intake of 2.5 g·kg⁻¹·day⁻¹ was selected by our institution for critically ill thermally injured patients without significant renal or hepatic disease. We use conventional amino acids rather than products enriched with branched-chain amino acids because formulas using branched-chain amino acids do not appear to offer any significant advantages over conventional formulations in thermally injured patients.24 There is a limitation in the extent to which nutrition alone can optimize the thermally injured patient’s metabolic status.23 During the catabolic phase of injury, critically ill patients will remain in net protein catabolism despite intervention with aggressive nutrition support.23 As a result, trials with adjuvant pharmacotherapy combined with nutrition support as a means to reduce catabolism or further stimulate protein synthesis are currently being investigated for patients with thermal injury.25,26

**ASSESSING EFFICACY OF THE NUTRITIONAL REGIMEN**

Once calorie and protein goals are assigned and a nutritional regimen designed, how does the clinician assess the efficacy of that regimen? The determination of nitrogen balance, despite its limitations, tends to be the “gold standard” among clinicians for assessing adequacy of a nutritional regimen, particularly when evaluating whether the protein intake is sufficient. Nitrogen balance is simply the difference between nitrogen intake and excretion. One of the most common formulas for determining nitrogen balance in clinical practice follows:27:

\[
\text{nitrogen balance (g/d)} = \text{protein intake (g/d)} / 6.25 - (\text{urine urea nitrogen (g/d)} + 4)
\]

This equation assumes 16% nitrogen content in the protein source, 2 g of non-urea nitrogen in the urine and 2 g for stool, and integumentary and other insensible losses. Some clinicians alternatively estimate total urinary nitrogen as 1.25 times the urine urea nitrogen excretion rate.28 Nitrogen balance studies are often fraught with error due to an overestimation of intake and underestimation of excretion due to an inadequate urine collection. These errors favor overestimation of actual nitrogen balance. Meticulous care must be taken on the part of the nursing staff and nutrition support service regarding accurate recording of intake and complete collection of 24 h urine, stool, and other losses. On a practical basis, for routine clinical care of the patient, only the urine is collected and analyzed. Other losses, such as stool and drainages, are recorded but not sent to the laboratory for analysis.

The amount of nitrogen in the protein intake depends on the quality of the protein or the amount of the essential amino acids in the protein. Protein is considered to contain an average of 16% nitrogen and explains this nitrogen calculation: \(\text{nitrogen intake} = \text{protein intake} / 6.25\). However, this may be erroneous, particularly with parenteral nutrition or specialized enteral diets. Close inspection of the nitrogen content of commercially available intravenous amino acid solutions showed a range of 12% to 17% in the nitrogen content of protein.29 Therefore, an alteration in the method of estimation of nitrogen intake from protein intake may be necessary in certain circumstances.

Estimation of urinary nitrogen losses is derived most often from urea nitrogen because urea is the main excretory product of nitrogen metabolism and it is a commonly available assay. Two grams of urinary non-urea nitrogen excretion is assumed as part of the “fudge factor” of 4 g in the traditional nitrogen balance computation. Urinary non-urea nitrogen would include substances such as ammonia, creatinine, uric acid, peptides, purines, creatine, 3-methylhistidinone, and other amino acids. However, the assumption that urinary non-urea nitrogen losses is 2 g/d or a constant percentage of total nitrogen excretion may be in error. Shaw-Delanty et al.30 found that urinary non-urea nitrogen excretion averages 1.3 ± 0.5 g/d for normal subjects (n = 37), 1.6 ± 0.8 g/d for nutritionally depleted patients (n = 67), 2.0 ± 1.2 g/d for ambulatory individuals (n = 96), 2.8 ± 1.3 g/d in injured patients (n = 43), and 3.1 ± 1.7 g/d for patients with sepsis (n = 31). There was a modest correlation between total urinary nitrogen excretion and urinary non-urea nitrogen excretion (r = 0.56); however, the slope of the regression was extremely flat (slope = 0.06).30 Data of Velasco et al. suggested the fudge factor of 4 g underestimates total nitrogen output in patients with high urinary urea nitrogen excretion (>30 g/d) and they recommended that a factor of 6 g (rather than 4 g) would provide a better indicator of non-urea and insensible nitrogen output due to the increased urinary non-urea nitrogen excretion in highly catabolic patients.31 Thermally injured patients are often highly catabolic and may exhibit a large variability in non-urea nitrogen excretion in the urine. Konstantinides et al. examined the amount of urea nitrogen and total nitrogen in 24 h urine collections from 27 thermally injured patients.32 Urea nitrogen averaged only 63 ± 12% of total nitrogen in the urine and ranged from 33% to 82%. In contrast, Milner et al. found that the predicted total urinary nitrogen (derived from the equation: \(\text{total urinary nitrogen} = 1.25 \times \text{urea nitrogen excretion}\)) correlated extremely well with total nitrogen (r = 0.936, P < 0.001) in 200 urine samples from 45 thermally injured patients.28 Urea nitrogen content was 77 ± 10% of total nitrogen in the urine samples. Use of the predicted total urinary nitrogen excretion in the calculation of nitrogen balance in these patients resulted in a mean error of only 0.6 g/d when compared with measured total urinary nitrogen, and the researchers suggested that those differences were not clinically relevant. However, the investigators pointed out six cases in which marked differences between predicted and actual nitrogen excretion resulted in significant error. Close inspection of their data showed a trend toward more variability when comparing predicted versus measured total urinary nitrogen excretion when the total urinary nitrogen excretion exceeded 20 g/d. Therefore, estimation of total urinary nitrogen may be less reliable in those patients with greater levels of hypercatabolism. If urinary urea nitrogen is used for assessing nitrogen excretion or balance, the clinician should have a high index of suspicion that the data may reflect an error in estimation of total urinary nitrogen excretion, particularly in those with severe hypercatabolism.

The remaining 2 g of the 4 g fudge factor in the nitrogen balance equation accounts for stool and integumentary and insensible losses. This factor can substantially underestimate nitrogen losses in critically ill patients, especially thermally injured patients. The presence of drainages and diarrhea can
variably influence nitrogen excretion. Average nitrogen losses for drainage and diarrea for patients requiring parenteral nutrition were reported as 1.1 ± 0.9 g/d and 2.7 ± 1.4 g/d, respectively; however, those losses were variable.30 Integumentary or dermal nitrogen losses are considered minimal in normal sedentary men, accounting for approximately 0.5 g/d, or 0.01 g · kg⁻¹ · d⁻¹. With thermal injury, dermal losses can be much more substantial. Studies from the early 1960s attempted to quantify protein losses from thermal wounds by extracting protein from all the wound dressings and bed linens. This was extremely difficult to do and was prone to error. Waxman et al. studied protein loss across burn wounds in 68 studies in 29 thermally injured patients (15% to 53% total BSAB) during the first 17 d postinjury.22 Wound loss of protein was measured by applying a 2- × 2-inch sterile cotton gauze dressing to the test site, followed by a cotton dressing sponge, followed by an occlusive covering. Samples were removed after 30 min and the protein was extracted from the sponge. The procedure was repeated for another 30 min and the rate of protein loss was calculated. Losses were greatest during the first 3 d postburn but reduced to stable rates of loss thereafter for the subsequent 2 wk. Rates of protein loss were similar across partial- and full-thickness burns and extent of thermal injury did not influence protein loss rate from the individual wound site.21 The investigators developed the following formula to estimate nitrogen losses from the thermally injured wound for postburn days 4 to 16:

\[
\text{nitrigen loss (g/d)} = 0.1 \times \text{BSA (m²)} \times \% \text{burn}
\]

For example, in an averaged size individual with a BSA of 1.7 m² and 50% total BSAB, approximately 8.5 g of nitrogen could be expected to be lost every day. This is obviously markedly different than the approximately 0.5 g/d, or 0.01 g · kg⁻¹ · d⁻¹, that is anticipated in normal subjects. Protein loss is reduced in excised wounds covered with artificial skin or silver sulfadiazine or wounds that are grafted.21 Therefore, knowledge of the care and status of the wounds will need to be considered when estimating nitrogen losses from the burn wound.

If there is urea accumulation during the nitrogen balance determination due to renal impairment, that amount of urea must be incorporated into the nitrogen excretion or loss. A change of 5 mg/dL in serum urea nitrogen in a 70 kg man would amount to approximately 2 g of urea nitrogen accumulated and not excreted in the urine. Blumenkrantz et al.34 described a simple method for estimating urea nitrogen accumulation based on changes in serum urea nitrogen concentration and body weight (assuming body weight increases are due to water weight gain):

\[
\text{urea accumulation (g/d)} = 0.6 \times (\text{WT}_1 - \text{WT}_f) \times ([\text{SUN}_i - \text{SUN}_f] \times 0.01) + ([\text{SUN}_i \times 0.01] \times [(\text{WT}_i - \text{WT}_f)])
\]

where SUN_i and SUN_f are initial and final serum urea nitrogen concentrations (mg/dL), respectively; WT_i and WT_f are initial and final weights (kg), respectively; 0.6 L/kg is the assumed normal body water composition for males (0.55 L/kg for females); and the factor of 0.01 converts milligrams per deciliter to grams per liter.

The problem with this method is that it assumes a known body water composition. This can be particularly problematic for the thermally injured patient who undergoes massive fluid resuscitation followed by marked fluid fluxes due to loss of skin-barrier integrity and weeping wounds.

Because of these difficulties in achieving accurate nitrogen balance determinations in the thermally injured patient, some clinicians have integrated changes in serum proteins (e.g., prealbumin), clinical assessment of the patient, and estimated nitrogen balance as a means to assess nutritional recovery and response to a given regimen. That is the approach used at our institution. However, recovery of serum proteins such as prealbumin may not correlate well with nitrogen balance studies in thermally injured patients.33 Others have suggested an alternative approach by the use of indirect calorimetry and the achievement of positive caloric balance with a fixed protein intake.36 The macronutrient regimen was designed with 16% of the total calories from protein. This approach resulted in achievement of serum protein recovery and a reasonable nitrogen balance and it was suggested that it may be more accurate and more easily obtained than nitrogen balance.36 Unfortunately, many burn centers do not have the availability of indirect calorimetry for their routine clinical practice and this approach may not be a viable option.

Development of a plan for estimating energy and protein requirements of the thermally injured patient is a dynamic process as evolving innovations in their management may subsequently influence macronutrient requirements. Experimental adjuvant pharmacologic therapies, such as oxandrolone,25 propranolol,26 or testosterone,27 have reduced protein catabolism. Artificial skin substitutes have shortened length of hospital stay38 and perhaps altered energy and protein requirements. However, published clinical data regarding the effect of artificial skin substitutes on macronutrient metabolism are lacking.

CONCLUSIONS

Is the nutritional management of the critically ill, thermally injured patient art or science? Appropriate nutritional management of the thermally injured patient mandates the integration of the “art of clinical management” with science. The literature provides some guidance toward planning of macronutrient goals. Limitations in designing goal regimens and assessing adequacy of the nutrition support regimen in these patients dictates sound clinical judgment and close monitoring to ensure efficacy and prevent adverse effects. There are numerous methods that successfully integrate science and the art of clinical practice in the macronutrient planning of thermally injured patients. One practical evidence-based approach has been provided.

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