Brief Report

Effects of different energy intakes on nitrogen balance in patients with acute renal failure: a pilot study

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Abstract

Background. Thus far, there have been no controlled studies to examine optimal levels of energy provision in critically ill patients with acute renal failure (ARF) receiving artificial nutrition.

Methods. After a 24 h nitrogen-free regimen (20% dextrose), we assigned during an open-label, AB/BA-crossover-trial, 10 ARF patients receiving both total parenteral nutrition (TPN) and renal replacement therapy (seven males; mean age 72 years, range 60–83; mean APACHE II score 27.1, range 23–34, mechanical ventilation 8/10) to a lower calorie-TPN regimen (30 kcal/kg/day) and to a higher calorie-TPN regimen (40 kcal/kg/day), each for 3 days. Nitrogen intake was 0.25 g/kg/day for both regimens. We estimated nitrogen balance, protein catabolic rate and urea generation rate by urea kinetic methods based on both timed blood samples of serum urea and direct urea quantification from dialysis fluid.

Results. Two patients were excluded from the analysis (due to death and serum triglycerides above 5.1 mmol/l, respectively). Compared with the lower calorie-TPN, the higher calorie-TPN regimen did not improve estimated nitrogen balance [+1.55 g/day (95% confidence interval: −0.95 to +4.05, P = 0.18)], protein catabolic rate [−0.10 g/kg/day (−0.33 to +0.14, P = 0.35)], or urea generation rate [−1.3 mg/min (−5.2 to +2.7, P = 0.46)], whereas it increased serum triglycerides [+1.36 mmol/l (+0.53 to +2.19, P = 0.007)], glucose [+1.15 mmol/l (+0.07 to +2.24, P = 0.041)], insulin need [+20.4 U/day (+8.3 to +32.6, P = 0.006)] and nutritional fluid administration [+468 ml/day (+370 to +566, P < 0.001)].

Conclusions. The present study, conducted in a small group of subjects, shows that in critically ill patients with ARF on a nitrogen intake of 0.25 g/kg/day, an energy provision of 40 kcal/kg/day does not improve nitrogen balance estimates compared with a 30 kcal/kg/day intake; instead, it may increase the risk of artificial nutrition-related side-effects.

Keywords: acute renal failure; critical illness; dialysis; nitrogen balance; parenteral nutrition

Introduction

Although artificial nutrition in critically ill patients with acute renal failure (ARF) may provide important benefits [1] for these patients that are often malnourished [2] and highly catabolic [3], it may also increase the risk for complications, such as hyperglycaemia, hypertriglyceridaemia and fluid overload [3].

The optimal administration of nutrients in ARF patients has not yet been defined. Nutritional regimens for ARF in the late eighties and early nineties, which were primarily based on protein intakes of < 1 g/kg/day, had led to recommendations from authoritative reviews [4] of calorie:nitrogen ratios ranging from 150:1 to 600:1 [5–7] and all the way to 30–45 kcal/kg. Since then, recommended energy intakes for ARF patients have been progressively lowered, and this is in agreement with what is currently being suggested for critically ill patients [8], ranging from 25 to 30 kcal/kg/day [3,9]. Macias et al. [10] used a regression model to explore the interaction between energy and protein provision over a wide range of energy intakes (20–50 kcal/kg/day). They suggested that the optimal nutritional regimen for patients with ARF may include a higher protein intake (1.5–1.8 g/kg/day) along with a relatively low (as compared to the past) energy content (25–35 kcal/kg/day), which is in accordance with recent studies [11,12]. However, experimental
energy for optimal amounts of energy intake in ARF patients still remains to be ascertained.

Given this background, we assessed in a cross-over design the impact of previously recommended high-energy intakes of 40 kcal/kg/day and of more recently indicated energy intakes of not more than 30 kcal/kg/day on nitrogen balance in ARF patients. To this purpose, we used isonitrogenous amounts of commercial parenteral solutions i.e. 0.25 g of nitrogen/kg/day, which corresponds to about 1.5 g of proteins/kg/day, an average value for protein catabolic rate in critically ill ARF patients [2]. We also examined whether higher energy provision by artificial nutrition is associated with an increased risk of specific adverse effects of artificial nutrition in ARF patients.

### Subjects and methods

#### Patients

This study was carried out at the Renal Intensive Care Unit (ICU) of the Parma Medical School Hospital, a six-bed specialized ICU for critically ill patients with ARF. Inclusion criteria were the presence of acute renal failure as previously defined [2], urinary output <200 ml/day, need of renal replacement therapy performed as daily 4 h haemodialysis, or 8 h sustained-low efficiency haemodialysis as previously described [13], an APACHE II score [14] of at least 23, and artificial nutrition provided exclusively by parenteral nutrition [9].

Informed consent was obtained from participants and/or next of kin, along with approval from the Institutional Human Ethics Committee of the Parma University Medical School.

#### Type of study, baseline definition and treatment assignment

The study was a two-treatment, two-period, open-label, cross-over trial (AB/BA cross-over), with each period lasting 3 days and without any ‘wash-out’ period between the two treatments. These were preceded by a 24 h time period, which we will refer to as ‘baseline’. During this phase, we administered 20 kcal/kg of 20% dextrose. Triglycerides were measured in the morning before initiation of the dextrose infusion. The remaining measurements were taken over the entire 24 h. On the morning of the first day of the experimental phase, we assigned the patients to either one of the two sequences, randomizing with a probability that ranged from 1:1 to 4:1 to minimize the imbalance.

#### Nutritional regimens

Two isonitrogenous regimens (0.25 g nitrogen/kg/day) were compared: a ‘lower calorie-total parenteral nutrition (TPN)’ regimen that provided 30 kcal/kg/day, and a ‘higher calorie-TPN’ regimen which provided 40 kcal/kg/day. We used two different total nutrient admixtures available at our hospital at the time of the study. They were Nutri-Special Lipid (1875 ml, 107.7 g amino acids, 15 g nitrogen, non-protein kcal/N ratio of 118.7, lipids 75 g as medium chain and long-chain triglycerides, lipid calories 39.8% of non-protein calories; Baxter S.p.A, Italy) and Clinomel-N7 (2000 ml, 80 g of amino acids, 13.2 g of N, non-protein kcal/N ratio of 158.3, lipids 80 g as long-chain triglycerides, lipid calories 38.5% of non-protein calories; B. Braun, Milan, Italy).

#### Measurements

Daily and cumulative (for each 3 day TPN regimen) nitrogen balance was calculated as the difference between nitrogen intakes and nitrogen losses (urea appearance + non-urea nitrogen losses). Urea appearance was calculated from total urea nitrogen in the dialysate/ultrafiltrate fluid and from blood urea level changes between dialysis sessions; non-urea nitrogen losses were estimated as 4 g/day when stool loss was present or otherwise as 2 g/day [11]. For these analyses, we measured urea content of dialysis fluid, as well as serum urea levels from blood samples taken at the start, at the end, and at 60 min after the end of dialysis. Total urea nitrogen content in the dialysis fluid was obtained using the partial dialysate collection method [15], in conjunction with a continuously sampling micropump connected to the dialysis fluid drain. Equilirate urea generation (Gu, in mg/min) and protein catabolic rate normalized for body weight (nPCR) were estimated according to published formulas [10,15]. Total body water was calculated as 60% of actual body weight. Serum glucose levels were measured at least six times a day, and serum triglycerides were measured once a day at 8 a.m.

#### Data analysis

We excluded from the main analyses two patients who were withdrawn after 1 and 2 days, respectively, from start of the study. The outcome variables were computed as the average of each 3 day period. All analyses were performed using the statistical package GenStat release 7.2 (2003; VSN International, Hemel Hempstead, UK). We examined the effects of the two nutritional regimens on each outcome variable by means of mixed-effect ANOVA models for unbalanced experiments [16]. These models allowed for adjusting estimates of the difference between the two nutritional regimens for the ‘period effect’. We also made plots showing individual patient differences between the two nutritional regimens after having eliminated the period effect. Differences for each outcome variable between the baseline and the experimental phase were examined by t-tests for paired data. We also used the multivariate version of the same analyses described above to test for a combined difference between the two nutritional regimens in glucose level and insulin use. A two-sided P-value <0.05 was considered statistically significant.

#### Results

We enrolled 10 consecutive patients from September 2002 to October 2003. Mean age was 72.6 years (range 60–82) and mean APACHE II score was 27.1 (range 23–34); four patients received SLED, eight patients required mechanical ventilation, and four patients eventually died. Five were assigned to the higher calorie–lower calorie-TPN sequence and five to the lower calorie–higher calorie-TPN sequence.
Because two patients were withdrawn after study entry, only eight patients completed the study. One patient died on day 1 of the experimental phase because of refractory upper gastrointestinal tract haemorrhage; the other patient was withdrawn on day 2 because triglycerides raised to levels above 5.1 mmol/l (450 mg/dl); both patients were on the higher calorie-TPN regimen. All patients received the planned nutrient intake during the study period.

Table 1 shows nutritional and biochemical indexes during baseline and their averages over the course of the experimental phase. Estimated nitrogen balance, which was as low as −15.5 g/day, showed a striking improvement during the experimental phase (+1.08 g/day, \( P < 0.001 \)), whereas protein catabolic rate and urea generation rate did not significantly change.

Table 2 illustrates comparisons between the higher calorie-TPN and lower calorie-TPN regimens. There was no substantial difference between the two regimens in estimated nitrogen balance (+1.55 g/day, \( P = 0.18 \)), protein catabolic rate (−0.10 g/kg/day, \( P = 0.35 \)) or urea generation rate (+1.3 mg/min, \( P = 0.46 \)). Figure 1A depicts these findings in more detail by showing differences between the two regimens in single patients.

On average, all of the biochemical indexes worsened from the baseline to the experimental phase, and nutritional fluid intake increased by +460 ml per day.

However, these parameters differed markedly during the higher calorie-TPN and lower calorie-TPN regimens (Table 2). For example, glucose levels were about 1.2 mmol/l (21 mg/dl) higher on the higher calorie-TPN than on the lower calorie-TPN regimen (\( P = 0.041 \)) despite an increased insulin use of about +20 U per day (\( P = 0.006 \)). Likewise, triglyceride levels were about 1.4 mmol/l (120 mg/dl) greater on the higher calorie-TPN than on the lower calorie-TPN regimen (\( P = 0.007 \)). As shown in Figure 1A, glucose levels and insulin use were higher on the higher calorie- than on the lower calorie-TPN regimen in seven out of the eight patients, whereas triglycerides were higher on the higher calorie-TPN regimen in all eight patients. The higher calorie-TPN regimen also increased the amount of fluid administered by about 500 ml per day in comparison with the lower calorie-TPN regimen (\( P < 0.001 \), Table 2). Interestingly, in patients on the lower calorie-TPN regimen, all of these parameters were remarkably similar to those observed during baseline (Table 1).

**Discussion**

The present study demonstrates that an energy intake of 40 kcal per kg of body weight per day, in contrast to 30 kcal, does not substantially improve estimated nitrogen balance, and did not ameliorate protein catabolism in critically ill patients with ARF receiving artificial nutrition and a fixed nitrogen intake of 0.25 g/kg/day. Rather, the increased energy provision appears to enhance the risk of artificial nutrition-related side effects.

There were several limitations in the present study, which were related to design, the type of TPN regimens being compared and the measurements that were taken. As with every study having a cross-over design, ours may have been be flawed by the ‘carry-over’ effect. However, we do not believe that this was a major concern since ongoing metabolic modifications, such as those investigated in the present study, show a waxing and waning that does not persist over periods of days. As a second limitation, the cross-over design may be unsuited for the ICU setting because of the substantial probability of drop-out due to death or other reasons. As a matter of fact, two of the 10 enrolled patients dropped out during the first period due to complications. However, since both of these patients developed

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**Table 1. Comparisons between the baseline and experimental phases (crude summary values)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline Average</th>
<th>Higher calorie-TPN Average</th>
<th>Lower calorie-TPN Average</th>
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</thead>
<tbody>
<tr>
<td>Nitrogen balance (g/day)</td>
<td>−15.47 (−26.94 to −7.56)</td>
<td>+1.08*** (−3.18 to +5.88)</td>
<td>+1.49*** (−4.82 to +6.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+0.67*** (−0.06 to +5.72)</td>
<td></td>
</tr>
<tr>
<td>Protein catabolic rate (g/kg/day)</td>
<td>1.37 (0.95 to 2.08)</td>
<td>1.47 (0.97 to 1.80)</td>
<td>1.46 (1.10 to 1.96)</td>
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<td></td>
<td></td>
<td>1.49 (0.84 to 2.19)</td>
<td></td>
</tr>
<tr>
<td>Urea generation rate (mg/min)</td>
<td>21.0 (9.9 to 37.11)</td>
<td>23.8 (16.9 to 34.2)</td>
<td>23.7 (16.8 to 35.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23.9 (14.2 to 37.3)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.07 (1.3 to 3.7)</td>
<td>2.74* (1.58 to 3.36)</td>
<td>3.36** (1.56 to 4.55)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.66 (1.56 to 4.55)</td>
<td>2.11 (1.60 to 2.73)</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>6.48 (6.0 to 7.7)</td>
<td>7.35** (6.61 to 8.08)</td>
<td>7.90** (6.95 to 8.47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.80 (5.88 to 8.82)</td>
<td></td>
</tr>
<tr>
<td>Insulin use (U/day)</td>
<td>25.5 (0 to 71)</td>
<td>36.5* (0 to 60)</td>
<td>47.5** (0 to 73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25.6 (0 to 57)</td>
<td></td>
</tr>
<tr>
<td>Volume (ml/day)</td>
<td>2216 (1764 to 2676)</td>
<td>2676* (2148 to 3132)</td>
<td>2910** (2304 to 3432)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2442 (1192 to 2832)</td>
<td></td>
</tr>
</tbody>
</table>

Symbols refer to the comparison with baseline, as follows: *\( P < 0.05 \), **\( P < 0.01 \), ***\( P < 0.001 \). The column baseline refers to the values taken the 24h preceding the experimental phase. The column average reports the mean value over the entire experimental phase. The remaining columns report the mean values when patients were on higher calorie-TPN and lower calorie-TPN regimens, whichever came first. These latter columns may not be directly used to estimate differences between the two nutritional regimens since these values are confounded by the ‘period effect’. The test for a combined change in glucose level and insulin use was significant for the comparison of baseline vs average and of baseline vs higher calorie-TPN (\( P = 0.02 \) for both comparisons), but not for baseline vs lower calorie regimen (\( P = 0.48 \)). To convert triglycerides to mg/dl, divide by 0.01129; to convert glucose to mg/dl, divide by 0.05551. Data are reported as mean (range).
complications while on the higher calorie-TPN regimen, it is unlikely that the results would have favoured this regimen had these patients completed the study. Third, the present pilot study was small and therefore had a low power to detect statistical differences; this limitation notwithstanding, we were still able to detect statistically significant differences in metabolic complications.

As a further limitation, the two total nutrient admixtures were not perfectly matched for composition of lipids, which were exclusively long-chain triglycerides in the higher calorie-TPN regimen and a physical mixture of long-chain and medium chain triglycerides (50:50 ratio) in the lower calorie-TPN. However, rather than preparing an ad hoc mixture for this study, we preferred using isonitrogenous amounts of all-in-one nutrient admixtures widely available on the market to make our results more readily applicable to daily clinical practice.

As for limitations in measurements, we did not directly assess energy expenditure in our patients. However, the energy intake of the lower calorie-TPN regimen (30 kcal/kg/day) was close to both the energy expenditure values directly measured in ARF patients [13,17], and to the number of calories, according to the model of Macias et al. [11], that is associated with a less negative nitrogen balance when the protein intake is held at 1.5 g/kg/day. Also, the absolute nitrogen balance values in our study should be considered as optimistic estimates since we did not directly measure other forms of nitrogen loss, such as loss of proteins, amino acids, creatinine and of uric acid into the dialysis fluid.

Compared with the lower calorie-TPN, the higher calorie-TPN regimen worsened metabolic control in

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**Table 2. Main results of the experimental phase**

<table>
<thead>
<tr>
<th></th>
<th>Higher calorie-TPN</th>
<th>Lower calorie-TPN</th>
<th>Estimated difference</th>
<th>95% CI</th>
<th><em>P</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen balance (g/day)</td>
<td>+1.85</td>
<td>+0.30</td>
<td>+1.55</td>
<td>−0.95 to +4.05</td>
<td>0.18</td>
</tr>
<tr>
<td>Protein catabolic rate (g/kg/day)</td>
<td>1.42</td>
<td>1.52</td>
<td>−0.10</td>
<td>−0.33 to +0.14</td>
<td>0.35</td>
</tr>
<tr>
<td>Urea generation rate (mg/min)</td>
<td>23.2</td>
<td>24.5</td>
<td>−1.3</td>
<td>−5.2 to +2.7</td>
<td>0.46</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>3.42</td>
<td>2.06</td>
<td>+1.36</td>
<td>+0.53 to +2.19</td>
<td>0.007</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>7.92</td>
<td>6.77</td>
<td>+1.15</td>
<td>+0.07 to +2.24</td>
<td>0.041</td>
</tr>
<tr>
<td>Insulin use (U/day)</td>
<td>46.7</td>
<td>26.3</td>
<td>+20.4</td>
<td>−8.3 to +32.6</td>
<td>0.006</td>
</tr>
<tr>
<td>Volume (ml/day)</td>
<td>2910</td>
<td>2442</td>
<td>+468</td>
<td>+370 to +566</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The first two columns report adjusted means during the higher calorie-TPN and lower calorie-TPN regimens, respectively. The third column reports differences between the higher calorie-TPN and lower calorie-TPN nutritional regimens. The fourth and fifth column display 95% confidence intervals and *P*-values associated with the differences between the higher calorie-TPN and lower calorie-TPN regimens, respectively. The combined difference of glucose level and insulin use between the higher calorie-TPN and lower calorie-TPN regimens was statistically significant (*P* = 0.032). To convert triglycerides to mg/dl, divide by 0.01129; to convert glucose to mg/dl, divide by 0.05551.

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**Fig. 1.** (A) The plots show for each patient differences between the higher calorie-TPN and lower calorie-TPN regimens in terms of nitrogen balance, protein catabolic rate and urea generation rate. Values above zero indicate higher values (e.g., less negative for nitrogen balance) during the higher calorie-TPN than lower calorie-TPN regimen. The short horizontal segment represents the mean difference. The *P*-value refers to the test that the mean difference is zero. (B) The plots show for each patient differences between the higher calorie-TPN and lower calorie-TPN regimens in terms of triglycerides, glucose and daily insulin use. Values above zero indicate higher values during higher calorie-TPN than lower calorie-TPN regimen. The short horizontal segment represents the mean difference. The *P*-value refers to the test that the mean difference is zero. To convert triglycerides to mg/dl, divide by 0.01129; to convert glucose to mg/dl, divide by 0.05551.
almost every patient. The risks of overfeeding critically ill patients with calories are well known. For example, calorie intakes of 40 kcal/kg/day or more increased the risk of infection in surgical patients with normal renal function [18]. Hyperglycaemia may play a major role in this setting, and this was supported by a recent large randomized-control trial which showed that tight control of glycaemic levels reduced the risk of sepsis and death in surgical ICU patients [19]. It is commonly believed that ARF per se generates increased calorie requirements. However, this belief is not supported by the available evidence, since there are no major changes in energy metabolism associated with ARF per se [17]; moreover, a recent study with ARF patients showed that energy expenditure was around 2300 kcal/day, which corresponded to an energy intake of not more than 35 kcal/kg/day [20].

There have been no studies that have investigated the concept of optimal nitrogen balance in ARF patients. It is also not clear whether the term 'optimal' refers to a numerical target (e.g., a positive value or the highest possible value) or to patient-related outcomes (i.e., the nitrogen balance level that significantly reduces the risk of malnutrition and of malnutrition-related complications). The benefits of pursuing, at all costs, a neutral or even positive nitrogen balance using extremely high protein intakes should be carefully balanced against possible metabolic side effects (such as increased urea generation, hyperphosphataemia, hyperkalaemia etc) and increased costs (additional nutrients and even more intensive renal replacement therapy). In fact, even though it was recently suggested that nitrogen balance values are correlated with hospital and ICU outcomes in ARF patients [12], there are no randomized and controlled trials which have demonstrated that moving nitrogen balance to positive values produces better outcomes. In this regard, the findings of the present pilot study may provide important estimates for the design of larger cross-over or parallel group trials.

In summary, we carried out pilot studies to examine the optimal artificial nutrition regimen for patients with ARF on renal replacement therapy. Although performed on a small group of subjects, we found that a relatively lower calorie intake, while probably protecting estimated nitrogen balance roughly as well as higher calorie regimens, may be safer by reducing the risk of metabolic complications.

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Conflict of interest statement. None declared.

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