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Daily Protein Intake and Patient Outcomes in Severe Acute Kidney Injury: Findings of the Randomized Evaluation of Normal versus Augmented Level of Replacement Therapy (RENAL) Trial

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Key Words
Protein intake · Acute kidney injury · Hemofiltration · Nitrogen balance · Nutrition

Abstract
Background and Aims: We aimed to examine the association between daily protein intake (DPI) and outcomes in patients from the Randomized Evaluation of Normal versus Augmented Level (RENAL) trial. ***Methods:*** We analyzed the association between DPI and clinical outcomes using multivariable logistic regression, Cox proportional hazards models and time-adjusted analysis. ***Results:*** During ICU stay, mean DPI was 37.6 g/day among survivors and 37.7 g/day among nonsurvivors (p = 0.96; DPI of 0.5 g/kg/day). Only 159 (10.9%) of the patients received a mean DPI of >1 g/kg. Patients with a DPI above the median had a 43.1% mortality compared with 46.1% for a DPI below the median (p = 0.25). On multivariate analysis, a lower DPI was not associated with increased odds ratios for 90-day mortality or any secondary outcomes. Cox proportional hazards models and time-adjusted analysis confirmed these findings. ***Conclusions:*** In the RENAL study, mean DPI was low. Within the confines of such low DPI, greater amounts of DPI were not independently associated with improved clinical outcomes.
Video Journal Club "Cappuccino with Claudio Ronco" at http://www.karger.com/?doi=363175.

Introduction

Achieving an adequate daily protein intake (DPI) is widely considered beneficial in critically ill patients in general and in patients with acute kidney injury (AKI) in par-

The Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group and The George Institute for International Health. The members of the Writing Committee listed above take responsibility for the content of this article. The names and affiliations of the RENAL Study Investigators are listed in the Appendix.

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ticular [1–3]. Accordingly, in these patients, nutritional guidelines recommend consideration of intravenous parenteral amino acids and the early administration of enteral nutrition whenever possible, targeted to achieve a protein intake of at least >1 g/kg/day and preferably >1.5 g/kg/day [4–6].

Unfortunately, all studies of protein intake in AKI conducted so far have been small and single center [7–13]. Thus, there are no large multicenter observational studies to (a) describe current practice and (b) assess whether protein intake in patients receiving renal replacement therapy (RRT) carries an independent association with patient-centered outcomes.

This lack of knowledge is problematic because protein intake may be a determinant of outcome and is modifiable. Moreover, critically ill patients with AKI receiving RRT represent close to 5% of all ICU patients and are typically some of the most acutely ill patients treated in ICU [14]. Such patients may represent a testing ground for the association between protein intake and outcome in the most critically ill patients in general.

The Randomized Evaluation of Normal versus Augmented Level (RENAL) study [15–19] is the largest randomized study of AKI treatment to date. It offers a unique opportunity to explore the independent association between DPI and outcome. Thus, we conducted a secondary analysis of the RENAL study findings focusing upon the relationship between DPI and primary and secondary clinical outcomes. We hypothesized that greater DPI would be independently associated with improved clinical outcomes.

Methods

The RENAL study was a multicenter, prospective, randomized trial of two levels of intensity of continuous RRT (CRRT) in 1,508 critically ill patients with AKI conducted in 35 ICUs in Australia and New Zealand (ANZ) [15] (ClinicalTrials.gov No.: NCT00221013). The Human Research Ethics Committees of the University of Sydney and all participating institutions approved the study.

The methodological details of the RENAL study were recently reported [19]. In brief, patients were eligible for enrollment if they were critically ill adults who had AKI, were deemed to require RRT by the treating clinician and fulfilled predefined criteria. Eligible patients were randomly assigned to continuous venovenous hemodiafiltration with effluent flow at 40 ml/kg/h (higher intensity) or 25 ml/kg/h (lower intensity). Study treatment was discontinued on death, discharge from ICU, or recovery of renal function. The primary study end point was death from any cause by day 90.

Daily Protein Intake

In all patients, DPI was calculated as the sum of all protein administered either by parenteral route, enteral route or both on each study day. Such data were prospectively collected as part of a standardized case report form.

We divided patients into two groups according to their mean DPI. A 'low' DPI was considered present when individual mean DPI was below the median value for the study population and a 'high' DPI was considered present when individual mean DPI was above the median value for the study population.

According to study protocol, DPI data were obtained until the first occurrence of either death, or ICU discharge or the completion of 28 days from study randomization (study treatment time).

Statistical Analysis

Continuous variables were expressed as means with standard deviation for normally distributed variables and as median and interquartile range for nonnormally distributed variables. Comparisons were made using Student's t test or the Mann-Whitney test where appropriate. Categorical variables were expressed as proportions and compared with the χ^2 test or Fisher's exact test as appropriate.

Patients with low and high mean DPI were first compared by univariate analysis. Mean DPI was calculated and DPI-related variables and treatment group, APACHE (acute physiology and chronic health evaluation) III diagnostic groups, daily use of CRRT, allocation to high- versus low-dose CRRT, study center, age, daily calorie intake, time from ICU to randomization, presence of sepsis, Sequential Organ Failure Assessment (SOFA) respiratory score, SOFA coagulation score, SOFA liver score, SOFA cardiovascular score, SOFA renal score, presence of nonrenal organ failure, international normalized ratio for prothrombin time, activated partial thromboplastin time, platelet count, serum creatinine, PaO_2/FiO_2 ratio, $PaCO_2$, use of mechanical ventilation, mean daily fluid balance, clinical diagnosis of significant edema at randomization, and all other variables with a significant difference on univariate comparison were used to create backwards elimination multivariable models with a 5% threshold using survival to 90 days as the dependent variable. The models were tested for collinearity and were found to have a low variance inflation factor.

Multivariable linear regression analysis was used to assess the relationship between mean DPI and mechanical ventilation-free days, RRT-free days and ICU-free days at 90-day follow-up as the dependent variables. Analysis of time to death within 90 days of randomization used the Kaplan-Meier product limit estimates and compared survival curves using the log-rank test. Because data collection was censored at 28 days, we additionally assessed the relationship between DPI and 28-day mortality and because a DPI >1 g/kg/day is generally recommended, we also assessed the relationship between a DPI >1 g/kg/day and 28-day mortality.

To test the robustness of any association between mortality and DPI, we then applied Cox proportional hazards modeling with adjustment for the above variables and pattern analysis to assess whether pattern mixture modeling could be applied. As an additional analysis, we performed multivariable regression analysis for 90-day mortality after excluding patients who had died before 96 h. This choice was based on the finding that DPI appeared to plateau after day 4 and that early DPI was much lower. This difference created an artificial mortality bias against low DPI, because the achievement of full nutritional support was time-dependent and patients who died in the first few days were

Table 1. Key baseline characteristics and major outcomes of patients with a low (below median) versus high (above median) DPI

Baseline characteristics	Low DPI (n = 727)	High DPI (n = 730)	p
Age	65.8±14.5	63.3±15.1	0.0012
Male sex	455/727 (62.6%)	486/730 (66.6%)	0.114
Weight	79.8±12.8	81.5±13.0	0.0142
Mechanical ventilation	432/727 (59.4%)	644/730 (88.2%)	<0.0001
Time from ICU admission to randomization, h	27.2±52.9	75.9±156	<0.0001
Source of admission to ICU			
Accident and emergency department	185/687 (26.9%)	163/678 (24.0%)	0.0277
Hospital floor/ward	212/687 (30.9%)	175/678 (25.8%)	
Transfer from another ICU	49/687 (7.1%)	60/678 (8.8%)	
Transfer from another hospital, except from ICU	70/687 (10.2%)	84/678 (12.4%)	
Admitted from operating room/recovery following emergency surgery	86/687 (12.5%)	118/678 (17.4%)	
Admitted from operating room/recovery following elective surgery	85/687 (12.4%)	78/678 (11.5%)	
Nonoperative admission diagnosis			
Cardiovascular	252/539 (46.8%)	280/507 (55.2%)	<0.0001
Genitourinary	177/539 (32.8%)	52/507 (10.3%)	
Gastrointestinal	36/539 (6.7%)	39/507 (7.7%)	
Hematology	8/539 (1.5%)	14/507 (2.8%)	
Metabolic/endocrine	14/539 (2.6%)	11/507 (2.2%)	
Neurologic	4/539 (0.7%)	6/507 (1.2%)	
Respiratory	44/539 (8.2%)	102/507 (20.1%)	
Transplant	4/539 (0.7%)	1/507 (0.2%)	
Trauma	0/539 (0.0%)	2/507 (0.4%)	
Severe sepsis at baseline	302/727 (41.5%)	417/730 (57.1%)	<0.0001
APACHE III score	104.0±25.8	100.9±25.5	0.018
SOFA respiration score	2.5±1.1	3.0±0.7	<0.0001
SOFA coagulation score	0.8±1.0	1.1±1.2	<0.0001
SOFA cardiovascular score	2.7±1.6	3.0±1.4	<0.0001
SOFA renal score	2.9±1.1	2.6±1.0	<0.0001
Last creatinine concentration, μmol/l	369.7±228	299.7±147	<0.0001
Bicarbonate, mmol/l	17.1±5.7	19.5±5.7	<0.0001
Creatinine, μmol/l	374.0±248	298.9±151	<0.0001
pH	7.2±0.1	7.3±0.1	<0.0001
Base excess, mEq/l	−9.8±6.8	−6.8±6.8	<0.0001
eGFR	52.3±30.9	60.8±30.5	<0.0001

Continuous variables are expressed as means ± SD and nominal variables as numbers with percentages in parentheses. MV = Mechanical ventilation; eGFR = estimated glomerular filtration rate.

more likely to receive a low DPI thus creating an artificial association between lower DPI and mortality. We further tested for this effect by performing a time-dependent Cox proportional hazards model with or without exclusion of patients who died in the first 96 h.

A two-sided $p < 0.05$ was taken to indicate statistical significance. Statistical analyses were performed and independently checked with the use of SAS software, version 9.1.

Results

Of 1,508 patients enrolled in the RENAL study, complete DPI data were available for 1,457 (96.6%). The characteristics of these patients divided according to a mean DPI above (high) or below (low) the median DPI for the entire cohort are presented in table 1. In the overall cohort, mean daily caloric intake was 867 kcal/day, with a

Table 2. DPI according to survival status at 90 days after randomization

Baseline characteristics	All patients (n = 1,464)	Nonsurvivors (n = 654)	Survivors (n = 810)	p
DPI during time in ICU				
Patients, n	1,456	649	807	0.9673
Mean ± SD, g/day	37.7±33.3	37.7±35.0	37.6±32.0	
Q1/Q2/Q3, g/day	3.7/36.4/59.7	5.0/34.6/58.7	2.4/37.3/60.3	
Missing, n	8	5	3	
Weight-adjusted DPI during time in ICU				
Patients, n	1,456	649	807	0.5251
Mean ± SD, g/kg/day	0.5±0.4	0.5±0.5	0.5±0.4	
Q1/Q2/Q3, g/kg/day	0.1/0.5/0.7	0.1/0.4/0.7	0.0/0.5/0.7	
Missing, n	8	5	3	
Patients with a weight-adjusted mean DPI >1 g/kg/day				
No	1,297/1,456 (89.1%)	573/649 (88.3%)	724/807 (89.7%)	
Yes	159/1,456 (10.9%)	76/649 (11.7%)	83/807 (10.3%)	

Table 3. Multivariate logistic regression for 'death at day 90'

Variable name	Effect (discrete variable)	OR	95% CI	p
Median DPI during ICU admission	high vs. low	1.103	0.58–2.11	0.7673
Mean DPI during ICU admission		0.998	0.99–1.01	0.6413
Mean fluid balance, input-output (liters)		2.016	1.61–2.53	<0.0001
Median daily calorie intake during ICU admission	high vs. low	1.079	0.55–2.13	0.8275
Mean daily calorie intake during ICU admission		1.000	1.00–1.00	0.0636
Patient age		1.037	1.03–1.05	<0.0001
Patient weight (kg)		0.989	0.98–1.00	0.0394
Time from ICU admission to randomization (days)		1.002	1.00–1.00	0.0047
SOFA liver score	failure vs. normal	3.384	1.55–7.38	0.0022
INR		1.200	1.03–1.39	0.0172
Hemoglobin (g/l)		0.992	0.98–1.00	0.0353
Albumin (g/l)		0.977	0.96–1.00	0.0300
$PaCO_2$ (mm Hg)		1.016	1.00–1.03	0.0249

Only protein intake and calorie intake variables and variables with $p < 0.05$ are presented. INR = International normalized ratio for prothrombin time.

value of 883 kcal/day among survivors versus 847 kcal/day among nonsurvivors (p = 0.3185).

Among patients with a low mean DPI, 335 (46.1%) had died 90 days after randomization, compared with 314 (43.1%) patients with a higher mean DPI (p = 0.24). In addition, survivors and nonsurvivors had a similar DPI (table 2). During treatment, mean DPI among survivors was 37.6 versus 37.7 g/kg/day among nonsurvivors (p = 0.96) for a weight-adjusted mean DPI of 0.5 g/kg/day for both groups. Only 159 (10.9%) patients received a mean DPI of >1 g/kg on only 26.8% of study days. Overall, 382 patients received only parenteral nutrition for a total of 1,667 (13.8%) study days, and 200 patients received a combination of enteral and parenteral nutrition for a total of 2,055 (17.1%) study days. The daily DPI for survivors and nonsurvivors for the first 14 days of observation is compared in figure 1. DPI was similar in both groups and increased over time in both, reaching a plateau by day 4.

On multivariable logistic regression analysis, several variables were independently associated with 90-day

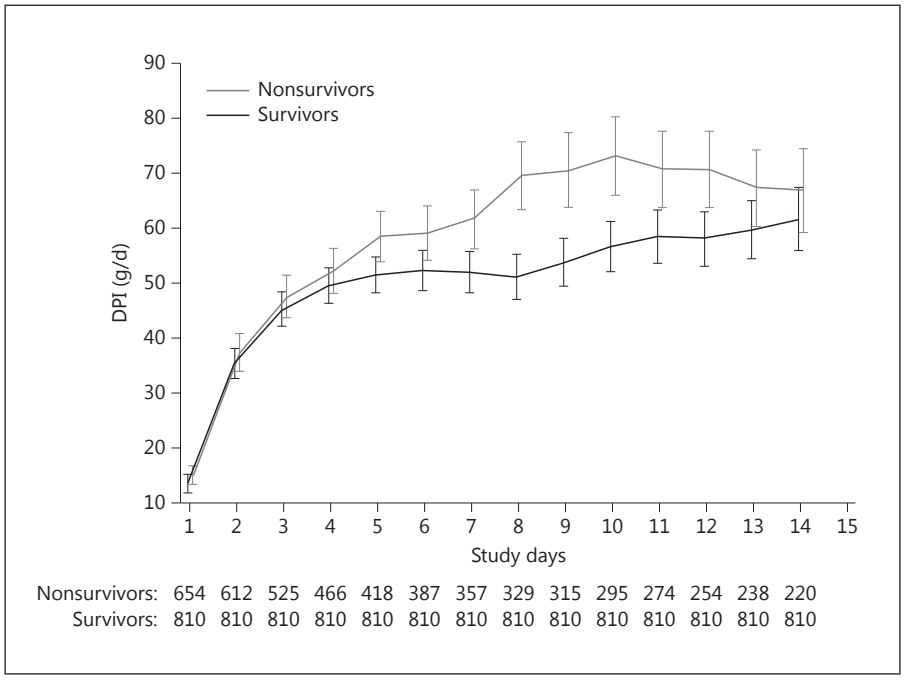

Fig. 1. Graphic representation of mean DPI (and 95% CI) over the first 2 weeks of observation after randomization according to survival status at 90 days. As can be seen, survivors had a lower DPI than nonsurvivors from day 7 to day 12.

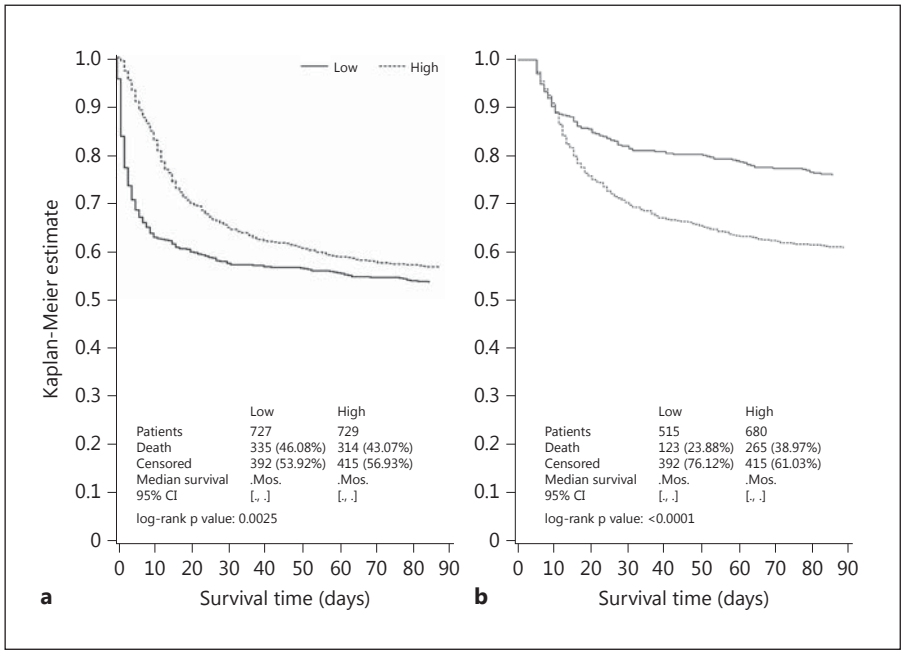

Fig. 2. a Kaplan-Meier graph of survival plots from randomization to day 90 stratified by the presence or absence of lower (below median) or higher (above median) DPI during the index ICU admission. **b** Kaplan-Meier graph of survival plots from randomization to day 90 among patients who survived >96 h stratified by the presence or absence of lower (below median) or higher (above median) DPI during the index ICU admission.

mortality (table 3) but mean daily DPI was not. When analysis was performed with 28-day mortality as the outcome, a DPI above the median carried an odds ratio (OR) of 0.98 (95% confidence interval, CI, 0.62–1.57; p = 0.95) and mean DPI carried an OR of 0.99 (95% CI 0.98–1.0; p = 0.15). Finally a DPI >1 g/kg/day had an OR for mortality of 0.63 (95% CI 0.36–1.13; p = 0.12). Time to event comparison using the log-rank test showed a significant difference in survival time in favor of patients with high mean DPI (fig. 2a). However, this effect was reversed once patients who died in the first 96 h were removed (fig. 2b).

Table 4. Multivariable linear regression models

Variable name	Estimates	SE	p
Multivariable linear regression model for RRT-free days			
Intercept	–40.32510	33.71933	0.2323
Mean DPI during ICU admission	**–0.01391**	**0.02507**	**0.5792**
Median DPI during ICU admission (high vs. low)	**0.99929**	**2.52307**	**0.6922**
Positive mean fluid balance	–4.09805	0.87492	<0.0001
Treatment intensity	–1.97170	0.85163	0.0210
Time from ICU admission to randomization (days)	–0.01644	0.00469	0.0005
SOFA liver score	–1.63540	0.44579	0.0003
APPT	–0.05581	0.02105	0.0083
pH	8.45062	4.27094	0.0484
Multivariable linear regression model for MV-free days			
Intercept	–23.71739	285.96733	0.9339
Mean DPI during ICU admission	**–0.02881**	**0.09283**	**0.7564**
Median DPI during ICU admission	**–3.16299**	**8.92563**	**0.7232**
Positive mean fluid balance	–19.28802	3.41162	<0.0001
Positive ventilation: no as reference group	–14.91985	5.71577	0.0094
Patient weight (kg)	0.53574	0.14153	0.0002
Last creatinine concentration	0.10963	0.04656	0.0190
Multivariable linear regression model for ICU-free days			
Intercept	–221.76773	281.51940	0.4313
Mean DPI during ICU admission	0.03687	0.08936	0.6801
Median DPI during ICU admission	–5.83877	8.44694	0.4898
Positive mean fluid balance	–19.69578	3.36383	<0.0001
Positive ventilation: no as reference group	–13.45268	5.58339	0.0165
Patient weight (kg)	0.45320	0.13896	0.0012
Time from ICU admission to randomization (days)	–0.03736	0.01756	0.0340
Last creatinine concentration	0.11279	0.04434	0.0114
Multivariable linear regression model for hospital-free days			
Intercept	25.05875	258.6057	0.9229
Mean DPI during ICU admission	–0.04355	0.08277	0.5991
Median DPI during ICU admission	0.80365	7.90876	0.9191
Positive mean fluid balance	–16.17529	3.08521	<0.0001
Patient weight (kg)	0.29499	0.12933	0.0231
Last serum urea concentration	–3.72244	1.85441	0.0454
Last creatinine concentration	0.09767	0.04131	0.0185
Glucose (mmol/l)	1.09456	0.50830	0.0319

SE = Standard error; APTT = activate partial thromboplastin time. Only DPI data and variables with a $p < 0.05$ are displayed.

Most of the death occurred in the low group within the first 96 h (212 deaths in the low group vs. 49 deaths in the high group). In this analysis, 341 patients did not receive any protein intake. Of all the 727 patients receiving a low (<median) protein intake, 335 (46.1%) died compared with 314 (43.15) of 729 patients among those receiving high (>median) protein intake. When patients who survived the first 96 h (time when DPI appeared to stabilize) were considered, 123 (23.9%) of 515 low DPI patients died compared with 265 (40%) of 415 patients receiving a high DPI ($p < 0.0001$).

Cox proportional hazards modeling failed to detect an independent association between DPI and 90-day mortality. Time-dependent Cox proportional hazards model

confirmed the findings of other models. Pattern analysis found that pattern mixture modeling could not be applied.

On multivariable linear regression analysis, mean DPI showed no association with decreased RRT-free days at day 90 after randomization, mechanical ventilation-free days, ICU-free days or hospital-free days (table 4). This lack of association with mortality and morbidity was confirmed when time-adjusted analysis was applied assessing the 1,183 patients who were alive after 96 h.

Discussion

Statement of Key Findings

Using data from a large, multicenter, randomized, controlled trial of the intensity of CRRT in critically ill patients with AKI, we assessed the association between mean DPI and clinically important outcomes. We found that DPI was generally low with a mean value of 0.5 g/kg/day and that only 10% of patients averaged a DPI of >1 g/kg/day. Within the confines of such a low DPI, patients with a DPI above or below the median had a similar mortality, and nonsurvivors had a similar DPI to survivors. In addition, DPI was not independently associated with decreased OR for mortality, or increased RRT-free days, mechanical ventilation-free days, ICU-free days and hospital-free days. Although unadjusted time to death analysis initially showed a favorable unadjusted association with DPI, this finding was biased by the time-dependent nature of DPI. Once the impact of such time-dependent effect was attenuated by time-adjusted analysis, this relationship was reversed. Moreover, Cox proportional hazards modeling confirmed the findings of the multivariable models. Finally, when patients who survived >96 h (the time when DPI stabilized) were analyzed separately, those receiving a higher DPI had a significantly greater mortality rate.

Comparison with Previous Studies

There are no epidemiological studies of current protein delivery practice in patients with AKI. In general critically ill patients, a recent multicenter observational found that mean DPI was 0.6 g/kg/day [20], a value similar to our study. Thus, current protein administration practice in ANZ appears to be similar to current ICU practice worldwide.

Authors [2, 3] and guidelines [1, 6] continue to recommend a protein intake of at least >1 g/kg/day in AKI patients, but the evidence supporting such recommendations is weak [7–13]. Moreover, although such recommendations appear reasonable from a nitrogen-balance point of view, especially given the loss of amino acids during CRRT [21–27], the only randomized controlled trial focusing on clinical outcomes was conducted in 1973 [28] and has little relevance to modern practice. Moreover, recent investigations have suggested that permissive underfeeding, trophic feeding, or delayed parenteral feeding may be equivalent or perhaps superior to currently recommended approaches [29–32].

Significance of Study Findings

Our findings expand our understanding of current practice and the relationship between DPI and outcome in severe AKI in the setting of essentially exclusive CRRT use. This aspect is important because during CRRT, volume control and full nutritional therapy are always possible [32]. Thus, DPI in this setting can be logically taken to reflect therapeutic choices rather than technical limitations [33, 34].

Our study demonstrates that current practice in ANZ delivers a low DPI, well below current guidelines, in the overwhelming majority of patients with severe AKI. This disconnect from published guidelines remains unexplained. Given that practice in ANZ ICUs is likely similar to other developed countries, it appears that low DPI in AKI patients may be common.

A low DPI is likely to be associated with a strongly negative nitrogen balance [33], and a negative nitrogen balance may be associated with increased mortality [34]. Our assessment, however, failed to provide evidence of an independent association between greater DPI and favorable outcome. Recent data suggest that more protein intake may inhibit autophagy and delay recovery in critically ill patients [35]. Moreover, studies of supplemental [36] and early parenteral nutrition [37] have delivered contradictory findings. Thus, it is not surprising that our understanding of optimal protein intake in renal disease, which is limited in patients with chronic kidney disease [38], in those on chronic dialysis [39], and in patients receiving continuous or intermittent extended RRT [40–42] generates great variability in feeding practices in ICU [20, 43].

A lack of association was seen despite the presence of a bias in favor of a high DPI. For example, patients who died in the first 2–3 days after randomization were most likely to receive little DPI because full nutritional therapy was typically achieved over time (about 4 days on average). Thus, those patients who achieved higher DPIs were essentially the same patients who had survived long

enough to achieve the higher rates of DPI delivered later in the course of ICU stay. However, sicker patients may have received endotracheal intubation for longer and nasogastric feeding at full dose for longer, while patients receiving early extubation may have also received less nasogastric feeding. These confounding and complex selection biases cannot be corrected by statistical techniques.

Study Strengths and Limitations

This study reports observational findings from the largest randomized controlled study of CRRT for AKI to date. The data were detailed and prospectively collected with specific attention to DPI and independently monitored for accuracy. As such, they provide the most comprehensive description of DPI during CRRT and of its association with outcomes to date.

On the other hand, we did not provide information on DPI prior to or after treatment. However, the time between ICU admission and randomization was <2 days, and the mean duration of study time was approximately 13 days, suggesting that the prerandomization period was unlikely to materially affect the study findings. In addition, it seems unlikely that DPI following ICU discharge would have biased our findings. In this regard, sensitivity analysis focusing on 28-day outcome was consistent with our primary 90-day mortality analysis. The use of high-dose CRRT might have led to greater protein loss and thus influenced the relationship between DPI and outcome. However, dose of CRRT was taken into account in multivariable models and showed no interaction with the relationship between DPI and outcome. We could not account for oral intake. However, such intake was uncommon in these patients while in ICU, and only nasogastric feeding nutritional data were recorded. Finally, we chose the mean dose of DPI as the metric for nutritional assessment. Other metrics (maximum daily dose or number of days above a given percentage of prescribed nutrition) could be used to analyze protein therapy in our study patients. However, it is unlikely that such metrics would materially alter our findings.

Conclusions

In the RENAL study, patients received a low DPI, markedly below current recommendations. Within the confines of such DPI, patients with a low DPI had similar mortality to those with a high DPI, and nonsurvivors had a similar DPI to survivors. After correction for multiple confounding variables and the application of different statistical modeling techniques, a low DPI was not independently associated with a decreased risk of death at 90 days or an increase in mechanical ventilation, RRT, ICU and hospital-free days.

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Disclosure Statement

Prof. Rinaldo Bellomo reports having received consulting fees as advisor for Gambro. There is no other potential conflict of interest relevant to this article.

Appendix

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