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ORIGINAL ARTICLE

Correlation of energy and protein intake with nitrogen balance changes in late acute phase critically ill patients

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Abstract

Background: The hypercatabolic process due to metabolic stress in critically ill patients, especially in the acute phase, is very high, causing protein degradation. Inadequate intake and high protein losses will result in a negative nitrogen balance.
Objective: To analyze the correlation of energy and protein intake in the late acute phase with nitrogen balance changes.
Methods: This study’s method was cross−sectional with consecutive sampling, conducted in the ICU of the university of Indonesia hospital. Energy and protein intake were assessed for 7 days. On days 3 and 7 of treatment, 24−hour urine urea nitrogen levels and nitrogen balance (NB) were assessed. Twenty three subjects participants in this study.
Results: There was a positive correlation between energy and protein intake with NB on day 3 (r=0.5, p=0.01 ;r=0.6, p=0.003). The mean nitrogen balance changes was positive, namely 3.8 g. There was a significant correlation between energy and protein intake with NB changes (p>0.01)
Conclusion: Energy and protein intake were positively correlated with nitrogen balance in the early acute phase. The results show that the administration of energy and protein starting at low intake in the early acute phase and gradually reaching the target intake during the late acute phase leads to an improvement in nitrogen balance.

Keywords: critically ill patient, protein intake, energy intake, nitrogen balance changes

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Introduction

Critical illness is a state of multiorgan dysfunction that disrupts homeostasis and requires intensive medical intervention in the intensive care unit.[1] Critically ill patients vary widely due to factors like disease phase, level of metabolic stress, inflammation, other complicating conditions, and the severity of organ dysfunction.[2] The Society of Critical Care Medicine (SCCM) states that more than 5 million patients are admitted to the Intensive Care Units (ICUs) each year in the United States.[3] The recent COVID-19 pandemic has increased deaths due to critical illness in almost all countries and caused a 2-time increase in ICU demand. Critically ill patients in Indonesia in 2019 reached 33.148 with an ICU mortality rate of 36.5%. In 2021, ICU demand in Indonesia reached 52.719 beds.

Nutritional status and intake, particularly energy and protein intake, can lead to longer hospital stays and decreased functional capacity, including muscle function. Length of stay in the ICU is associated with higher mortality, morbidity, and medical costs.[5] In critical illness, metabolic stress increases catabolism to provide healing substrates and repair tissues, particularly during the acute phase, which lasts about 7 days. This phase includes an early acute phase (1-3 days) with high mortality risk and a late acute phase (up to 7 days). The body requires significant energy for catabolism, and if glycogen stores run out, proteins are broken down into amino acids for gluconeogenesis. The balance between intake and degradation of protein can be evaluated from the nitrogen balance. Nitrogen balance, often negative in critically ill patients during this phase, indicates protein losses exceed intake.[6-8]

Nitrogen balance is one of the most frequently used indicators to identify protein metabolic rate in critically ill patients. During proteolysis, amino acids produce ammonia, which the liver converts to urea for kidney excretion. A 24-hour urine urea nitrogen (UUN) test can assess protein excretion. Studies show a positive correlation between energy and protein intake with nitrogen balance in the early acute phase. While inflammation is intense in this phase, patients who survive may experience regression, allowing anabolic processes to balance catabolism.[9-11] This study needs to be conducted to explore the correlation between energy and protein intake with nitrogen balance changes in the late acute phase.

Methods

This study was performed in the ICU of the University of Indonesia Hospital from December 2023 to May 2024 with a cross-sectional design. Inclusion criteria: ICU patients aged 18-60 years, getting protein intake in the first 48 hours of treatment, and having a written family representative statement stating that they were willing for the subjects to be included in the research. Exclusion criteria: urine output <0.5 ml/kgBW/hour starting on day 2, receiving renal replacement therapy, chronic liver disease, BMI <18.5, or ≥30 kg/m2, APACHE II score >30, pregnant, and receiving norepinephrine treatment >0.3 mcg. Dropout criteria were subjects who had an average protein intake on days 3 to 7 <0.5 g/kgBW/day and died before the 7th day of treatment. The sample size was calculated using the sample size formula for correlative analytical research. The required sample size was 19 subjects and considering the dropout rate of 20%, the minimum sample size was 21 subjects. This study was approved by the Health Research Ethics Commission of the Faculty of Medicine, University of Indonesia / Dr. Cipto Mangunkusumo National General Hospital no. KET-1176/UN2.F1/ETIK/PPM.00.02/2023 and research permit no. ND-743/DIKLATLIT/RSUI/XI/2023 from University of Indonesia Hospital.

The data used in this research are primary and secondary data. Data on energy and protein intake as well as route for intake were obtained from medical records and interviews with the nutritionist on duty and collected during 7 days of treatment. Energy intake data was presented in % energy expenditure (EE). The calculation of EE as a target energy intake was 25 kcal/kgBW/day using actual body weight or adjusted body weight for subjects with a BMI >25kg/m2. Protein intake data was presented in g/kgBW/day based on actual body weight or ideal body weight for subjects with a BMI >25kg/m2. The nitrogen balance value was obtained from the formula: (Protein Intake/6.25) - (UUN 24 hour+4). In subjects with burn trauma, nitrogen loss was multiplied by 1.25 as an estimate of nitrogen loss through the wound.[10,12] The UUN 24-hour results were obtained from laboratory tests conducted twice, namely on day 3 and day 7 of treatment. Nitrogen balance changes were derived by subtracting the nitrogen balance on day 7 with that on day 3.

Descriptive data were reported as percentages for categorical data while numerical data were reported as means and standard deviation (SD), or median and min-max if non-normally distributed. This study was analyzed using SPSS 26. Bivariate analysis methods used include independent samples T test or Mann-Whitney test, one-way ANOVA or Kruskal-Wallis test, paired T-test or Wilcoxon test, and Pearson or Spearman correlation test.

Results

In total 23 subjects met the inclusion and exclusion criteria for the study, 2 subjects dropped out due to death before day 7 of the study, leaving 21 subjects for analysis. The characteristics of the study subjects are presented in **Table 1**.

Patients' average age was 45 years. Patients' sex were predominantly female (57%) while men were 43%. The number of medical and surgical patients were nearly equal. The mean APACHE II score was 16. Patients with APACHE II scores between 11 to 20 were more dominant (62%). Patients' IMT were predominantly normal. Patients who received a combination of oral and enteral nutrition were highest at 52.4%. The majority of patients did not receive mechanical ventilation support (62%).

The mean energy and protein intake for the first 3 days were 78% EE and 0.8 g/kgBW/day. The mean energy and protein intake for day 3 to day 7 were 110% EE and 1.1 g/kgBW/day. The mean UUN 24h levels and nitrogen balance on day 3 were 8.1 g and -5.3 g. On day 7, the data were presented as median due to non-normally distributed with one outlier. The median UUN 24h levels and nitrogen balance on day 7 were 4.2 g and -0.4 g. The mean nitrogen balance changes was positive, namely 3.8 g.

Significant differences were found in nitrogen balance between males and females on days 3 and 7 ($p < 0.05$). This result was slightly influenced by body composition, as skeletal muscle mass in males was greater than in females. The differences in metabolism caused by underlying diseases had a more significant effect on the nitrogen balance of critically ill patients, as evidenced by the APACHE II scores in male subjects being higher than in female subjects, at 19 and 13, respectively. There was no significant differences in nitrogen balance among groups of admission diagnosis, APACHE II score, BMI, routes of administration, and mechanical ventilation (**Table 2**)

The differences in mean energy intake and protein intake between day 3 and day 7 were analyzed using paired T tests, and significant differences were found ($p<0.0001$). There was a strong positive correlation between energy intake and protein intake on day 3 and day 7, $p < 0.001$ (**Figure 1**).

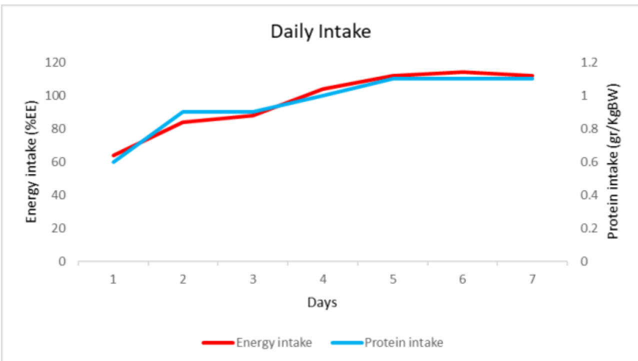

Figure 1. Daily Intake graph

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Table 1. Subject characteristics

Characteristics	n(%)	n=21 Mean±SD /Median (min-max)
Age (years)	-	45.5±11.3
Gender		
Male	9(42.9)	-
Female	12(57.1)	-
Admission diagnosis		
Surgical	11(52.4)	-
Medical	10(47.6)	-
APACHE II score		16.3±4.8
0-10	2(9.5)	-
11-20	13(61.9)	-
21-30	6(28.6)	-
BMI (kg/m^2)		
Normal	10(47.6)	-
Overweight	4(19)	-
Obese I	7(33.4)	-
Routes of administration		
Enteral only	7(33.3)	-
Oral + Enteral	11(52.4)	-
Oral+Enteral+Parenteral	3(14.3)	-
Mechanical ventilation		
Yes	8(38.1)	-
No	13(61.9)	-
Energy intake (% EE)		
Day 1-3	-	78.6±26.0
Day 4-7	-	111.0±20.5
Protein intake (g/kgBW/day)		
Day 1-3	-	0.8±0.2
Day 4-7	-	1.1±0.2
UUN 24h (g)		
Day 3	-	8.1±5.2
Day 7	-	4.2(1.5-24.9)
Nitrogen balance (g)		
Day 3	-	-5.3±5.7
Day 7	-	-0.4(-22.6-6.9)
Nitrogen balance changes (g)		3.8±5.3

Significant differences were found in nitrogen balance, but there was no significant differences in UUN levels. However, if the analysis of UUN levels excluded one outlier, significant differences would be found with a p-value <0.05. There was no significant correlation between energy and protein intake with UUN levels on day 3 or day 7 (p>0.05). However, a strong positive correlation was found between energy and protein intake from day 1 to day 3 with nitrogen balance on day 3 (p<0.05), but no significant correlation was found between intake and nitrogen balance on day 7. Further analysis was conducted to assess the correlation between mean intake from day 4 to day 7 with nitrogen balance changes, but no significant correlation was found (p>0.05).

Discussion

In this study, the mean energy intake for the first 3 days was 78% EE, increasing to 110% EE from day 4 to day 7. This intake was slightly higher than the European Society for Clinical Nutrition and Metabolism (ESPEN) recommendation of <70% EE during the early acute phase and 80-100% EE after day 3.[13] The findings align with Koekkoek et al.,[14] who reported <80% in the early phase and 80-110% in the late phase, but are lower than Bendavid et al.,[15] report of 88% EE. During the early acute phase, the administration of nutrition focuses on providing optimal energy while avoiding overfeeding, aiming to provide energy for the catabolism of macronutrient storage in the body. In the late acute phase, protein intake is increased to mitigate muscle wasting.[16,17] Nutritional intake also considers the patient's hemodynamic status and gut function. In this study, the most common administration method was a combination of oral and enteral feeding, in line with ESPEN guidelines that prioritize oral intake when possible. Enteral feeding is preferred within 48 hours if oral intake isn't feasible, and parenteral nutrition considered from days 3 to 7 if enteral feeding is contraindicated.[13]

Table 2.The nitrogen balance (NB) comparisons of each variable group

Variable	Day 3 NB (g)**	Day 3 p	Day 7 NB (g)***	Day 7 p
Gender				
Male	-8.2±6.8		-3.4(-22.6-6.9)	
Female	-3.1±3.9	0.04*	1.7(-6.1-3.3)	0.02*
Admission diagnosis				
Surgical	-6.5±6.0		0.9(-9.5-3.3)	
Medical	-3.9±5.4	0.3	-0.5(-22.6-6.9)	0.6
APACHE II score				
0-10	-2.6±1.8		2.4(1.6-3.3)	
11-20	-5.0±5.8		-0.6(-22.6-3.0)	
21-30	-6.7±6.7	0.6	-0.5(-4.0-6.9)	0.3
BMI				
Normal	-4.3±6.3		1.2(-9.5-6.9)	
Overweight	-7.0±6.7		-3.7(-6.1-3.0)	
Obese I	-5.6±4.9	0.7	-1.6(-22.6-3.3)	0.3
Routes of administration				
Enteral only	-5.5±8.1		0.6(-9.5-6.9)	
Oral + Enteral	-4.9±4.5		-0.6(-7.2-3.3)	
Oral+Enteral + Parenteral	-5.8±5.6	0.9	1.6(-22.6-2.8)	0.7
Mechanical ventilation				
Yes	-7.7±6.8		-1.1(-9.5-6.9)	
No	-3.7±4.7	0.1	0.6(-22.6-3.3)	0.9

*significant ($p<0.05$); **mean±SD; ***median(min-max)

Table 3. The Differences in energy intake, protein intake, UUN 24h, and nitrogen balance between day 3 and day 7

Variable	Day 3	Day 7	p
Energy intake (% EE)**	78.6±26.0	110.7±19.8	0.000*
Protein intake (g/kgBW/day)**	0.8±0.2	1.1±0.2	0.000*
UUN 24h (g)***	8.1±5.2	4.2(1.5-24.9)	0.2
Nitrogen balance (g)***	-5.3±5.7	-0.4(-22.6-6.9)	0.004*

***significant ($p<0.005$); **paired T test; ****Wilcoxon test*

Table 4. Correlation test results of energy and protein intake with UUN 24h, nitrogen balance, and nitrogen balance changes

			UUN 24h Day 3**	UUN 24h Day 7***	Nitrogen balance Day 3**	Nitrogen balance Day 7***	Nitrogen balance changes**
Day 1-3	Energy intake	r	-0.2	-0.02	0.5	0.1	
		p	0.2	0.9	0.01*	0.7	
	Protein intake	r	-0.2	0.1	0.6	-0.001	
		p	0.2	0.4	0.003*	0.9	
Day 4-7	Energy intake	r		-0.2		0.3	0.3
		p		0.4		0.1	0.2
	Protein intake	r		0.004		0.2	0.3
		p		0.9		0.3	0.1

*significant ($p<0.05$); **Pearson correlation test; ***Spearman correlation test

The mean protein intake for the first 3 days in this study was 0.8 g/kgBW/day, increasing to 1.1 g/kgBW/day from day 4 to 7. Some participants did not exceed 0.8 g/kg BW/day due to kidney dysfunction, following Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations.[18] Hoffer and Bistrian noted that many critically ill patients received less than half the recommended protein intake in the first week. The mean protein intake in Bendavid et al.,[15] study was lower, at 0.64 g/kg BW/day.[15]

The mean 24-hour urine urea nitrogen (UUN) level in this study decreased from 8.1 g on day 3 to 7.2 g on day 7, and the mean nitrogen balance significantly improved from -5.3 g to -1.5 g, with an average change of 3.8 g. Seventeen of 21 subjects showed a more positive nitrogen balance. Higher UUN levels were reported in studies by Dupuis et al.,[19] likely due to differences in patient populations and disease severity, which impact protein degradation and nitrogen excretion. This explains that the severity of the disease, severe infection, and inflammatory status play crucial roles in increasing protein degradation and thus increasing urinary nitrogen excretion.[7,17,20]

There was a strong positive correlation between energy and protein intake and nitrogen balance on day 3, but not on day 7. While Ferrie et al. observed better nitrogen balance on day 3 with higher protein intake, no significant differences were noted on day 7.[11] Arabi et al.,[21] found no improvement in nitrogen balance on days 1, 7, and 14 with protein intakes of ≤0.8 g/kg BW and >0.8 g/kg BW. Additionally, no significant correlation existed between energy or protein intake during the late acute phase and nitrogen balance changes. This suggests that factors like inflammatory status, renal function, and comorbidities may influence protein degradation in this phase, despite anabolic processes and regression of inflammation.[20,21] During the early acute phase, the catabolic process is very high. Anabolic processes will begin to strive for balance in the late acute phase, although catabolism still predominates. The inflammatory process generally decreases during this phase, which should lead to improvements in nitrogen balance and positive nitrogen balance changes.[22] However, the severity of underlying diseases and the condition of kidney function in patients can disrupt this process, resulting in a negative nitrogen balance. In some patients, inflammation remains high even in the late acute phase.[23] Research results indicated a trend of improved nitrogen balance in most subjects; however, among the four subjects with worsening nitrogen balance, two had sepsis and two had diabetes-related complications. The high level of inflammation in these conditions could lead to catabolism being far more dominant than anabolism in patients. This had an impact on the overall results in a small sample. Nevertheless, energy and protein intake in this study could generally be associated with improvements in nitrogen balance, with significant increases in intake accompanied by improvements in nitrogen balance during the acute phase.

This study has limitations including a smaller number of subjects compared to other similar studies; as a result, even slight differences in data among subjects have a significant impact on the final analysis results. Additionally, UUN 24-hour and nitrogen balance were not calculated in the first 24 hours as a baseline metabolic rate, energy expenditure calculation did not use indirect calorimetry which is the gold standard, and there was no periodic assessment of kidney function and inflammation status to assess other factors that can influence the catabolism in the study subjects. Future research is expected to address these limitations, especially in the late acute phase.

Conclusion

There is a strong positive correlation between energy and protein intake in the early acute phase with nitrogen balance on day 3, but no correlation was found between intake with nitrogen balance changes during the late acute phase. Starting with a low intake of energy and protein in the early acute phase and gradually increasing to the target intake during the late acute phase contributes to improving nitrogen balance.

Conflict of interest

No conflict of interest was declared

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