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ORIGINAL COMMUNICATION

Postprandial rise of essential amino acids is impaired during critical illness and unrelated to small-intestinal function

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Abstract

Background: Postprandial rise of plasma essential amino acids (EAAs) determines the anabolic effect of dietary protein. Disturbed gastrointestinal function could impair the anabolic response in critically ill patients. Aim was to investigate the postprandial EAA response in critically ill patients and its relation to small-intestinal function.

Methods: Twenty-one mechanically ventilated patients and 9 healthy controls received a bolus containing 100 ml of a formula feed (Ensure) and 2 g of 3-O-Methyl-d-glucose (3-OMG) via postpyloric feeding tube. Fasting and postprandial plasma concentrations of EAAs, 3-OMG, total bile salts, and the gut-released hormone fibroblast growth factor 19 (FGF19) were measured over a 4-hour period. Changes over time and between groups were assessed with linear mixed-effects analysis. Early (0–60 minutes) and total postprandial responses are summarized as the incremental area under the curve (iAUC).

Results: At baseline, fasting EAA levels were similar in both groups: 1181 (1055–1276) vs 1150 (1065–1334) μmol·L−1, $P = .87$. The early postprandial rise in EAA was not apparent in critically ill patients compared with healthy controls ($iAUC_{60}$, −4858 [−6859 to 2886] vs 5406 [3099–16,853] μmol·L^{-1}·60 minutes; $P = .039$). Impaired EAA response did not correlate with impaired 3-OMG response (Spearman ρ 0.32, $P = .09$). There was a limited increase in total bile salts but no relevant FGF19 response in either group.

Conclusion: Postprandial rise of EAA is blunted in critically ill patients and unrelated to glucose absorption measured with 3-OMG. Future studies should aim to delineate governing mechanisms of macronutrient malabsorption.

KEYWORDS
amino acids, critical care, enteral nutrition, proteins

CLINICAL RELEVANCY STATEMENT

Enteral nutrition is part of routine care for mechanically ventilated critically ill patients in an effort to attenuate protein-energy deficits during intensive care unit (ICU) stay. However, gastrointestinal dysfunction is common among critically ill patients and can lead to impaired uptake of protein and carbohydrate. There is a paucity of data on protein malabsorption and its governing mechanisms in particular. As a result, protein malabsorption often occurs occult and is not accounted for in dosing of nutrition. This study demonstrated that postprandial rise of essential amino acids as a marker of protein uptake is impaired in ICU patients and that it is unrelated to intestinal function assessed by 3-O-Methyl-d-glucose uptake. This highlights that governing mechanisms of malabsorption likely differ between macronutrients and should be further delineated to optimize nutrition support of critically ill patients by improving the systemic availability of enteral nutrition.

BACKGROUND

Critical illness is characterized by a protein catabolic state, resulting in rapid loss of skeletal muscle mass.[1] Although the detrimental impact of skeletal muscle wasting on both short- and long-term outcomes of critically ill patients is well established, effective strategies attenuating muscle loss are currently lacking.[2,3] Dietary protein is an important driver of muscle anabolism in health and could potentially inhibit protein catabolism during critical illness.[4] However, the anabolic potential of dietary protein appears limited in critically ill patients, a phenomenon termed anabolic resistance.[5]

The anabolic effect of dietary protein on skeletal muscle is largely determined by the postprandial rise of plasma essential amino acids (EAAs).[6,7] Postprandial changes in plasma EAA concentrations reflect the uptake of dietary amino acids into blood.[8] Gastrointestinal (GI) dysfunction, which is common among critically ill patients, may diminish postprandial availability of diet-derived amino acids.[9] The contribution of intestinal dysfunction to carbohydrate absorption is well established.[10–13] Systemic availability of dietary protein also appears to be limited in critically ill patients, but there is a paucity of studies investigating the governing mechanisms of protein malabsorption.[14] Small-intestinal absorptive function can be quantified by using 3-O-Methyl-d-glucose (3-OMG), an analogue of glucose that uses the same intestinal active transport mechanism but is not metabolized by the liver and is renally cleared.[15] It is unclear whether intestinal glucose uptake is also a good marker for intestinal protein uptake.

As intestinal function is not routinely measured, protein-energy malabsorption cannot be quantified and accounted for in dosing of nutrition.[16] Endogenous biomarkers that accurately reflect intestinal function and malabsorption of nutrients could aid in improving adequate nutrition dosing. Although citrulline, which is generated from glutamine by the enterocyte, reflects intestinal absorption capacity in patients with short-bowel syndrome, altered glutamine metabolism during critical illness affects its accuracy in the intensive care unit (ICU).[17,18] Recent work from our group has established that the bile salt–induced gut hormone fibroblast growth factor 19 (FGF19) is a prognostic marker in chronic intestinal failure and that the postprandial response of FGF19 to a lipid challenge is blunted in critically ill patients.[19,20] Preclinical studies demonstrated that FGF19 exerts several metabolic actions, including stimulation of hepatic protein synthesis and preservation of the trophic state in skeletal muscle.[21,22] Because FGF19 is a gut-derived hormone and not a metabolite like citrulline, it may prove a more stable endogenous biomarker of gut function during critical illness.

The aim of this study was to investigate the systemic EAA response following an enteral meal and its relation to small-intestinal absorptive function measured by 3-OMG uptake. In addition, we evaluated the potential of measuring postprandial FGF19 response as an alternative marker for small-intestinal function.

MATERIALS AND METHODS

Participants and data collection

Stored plasma samples collected from patients and healthy volunteers initially enrolled in a prospective comparison study investigating glucose absorption and intestinal transit time were analyzed.[13] Critically ill patients were recruited if they were ≥18 years old, mechanically ventilated, and able to receive enteral nutrition. Exclusion criteria included pregnancy, preexisting diabetes, admission after upper-GI surgery, receiving of erythromycin, or requirement for parenteral nutrition. Additional exclusion criteria for the healthy participants were contraindication to naso-duodenal feeding tube placement, GI motility–affecting drugs, previous GI surgery, or any history of GI disease. Plasma samples of 21 critically ill patients and 9 healthy controls were available for analysis.

The original study protocol was approved by the local ethics committee and adhered to the national legislation regarding medical research in incapacitated patients.The trial was registered in the Australian New Zealand Clinical Trials Registry (ACTRN12608000579392). Written informed consent was obtained from the next of kin.

Study design

In ICU patients, ongoing enteral nutrition was ceased at least 6 hours prior to study commencement, and a naso-duodenal feeding tube was placed using an electromagnetic guidance technique.[23] Postpyloric position of the tube was confirmed by abdominal x-ray. Arterial blood samples were collected at timed intervals (fasting and then 5, 15, 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes following administration of the test meal).

Healthy participants arrived at the motility laboratory in the morning after an overnight fast. A silicone rubber catheter (Mui Scientific, Mississauga, Ontario, Canada) was placed intragastrically and allowed to migrate into the duodenum. The postpyloric position of all distal

side holes of the feeding catheter was confirmed based on the antroduodenal transmucosal potential difference. Blood was sampled at similar time points as in ICU patients via an intravenous cannula placed in the antecubital vein.

After collection of a baseline sample in the fasted state, all participants received 100 ml of the same test meal, which was infused over a 5-minute period. The enteral test meal consisted of 100 ml of a nutrient liquid (Ensure 1 kcal/ml: 54% carbohydrate; 15.9% protein; 30.1% fat; Abbott Australia, Botany, Australia) with an added 3 g of 3-OMG (Sigma-Aldrich, Castle Hill, Australia) to assess glucose uptake. The 100-ml bolus that participants received contained 4.0 g of protein (84% casein and 16% soy protein), of which 1.64 g consisted of EAAs (Table S1). Leucine was the most abundant EAA, representing 21% of total EAA content in the test meal.

Sample processing and analysis

Blood samples were collected in 5-ml tubes, centrifuged (3200 rpm, 15 minutes, 4 °C), and stored at −70 °C until analysis. The 3-OMG concentrations were assessed on-site using a liquid chromatography–mass spectrometry method.[13] For further analysis, plasma samples were transported on dry ice to Maastricht University. For amino acid analysis, aliquots of plasma samples were deproteinized using 5-sulfosalicylic acid. Plasma amino acid concentrations were determined using a high-performance liquid chromatography method.[24] Total bile salt concentrations were analyzed using an enzymatic cycling assay (Diazyme Laboratories). Concentrations of FGF19 were determined using a sandwich enzyme-linked immunosorbent assay developed in-house.[25]

Statistical analysis

Results are expressed as median (interquartile range) (as shown in tables) or mean ± SE (in figures and data derived from linear mixed-effects [LME] analysis). Data were visualized and analyzed using R v3.6.2. Baseline values were compared using Mann-Whitney *U* test or Fisher exact test as appropriate.[26]

To analyze plasma concentrations over time, we used LME analysis, using group, time, and their interaction as fixed effects and participants as random effects with a random intercept. To locate differences at specific time points, time was used as a categorical value with the baseline (T = −5) time point as reference value.

To summarize plasma responses, incremental area under the curve (iAUC) values were calculated using the trapezoidal rule and by correcting plasma concentrations for the baseline (fasted) value, as these values more accurately represent the response to a dietary challenge.[26,27] Because the postprandial response is peaked, with a rapid peak during the first 60 minutes, iAUC values were divided into an early (first 60 min) and total response ($iAUC_{60}$ and $iAUC_{240}$, respectively).[13] Summary values between the groups were compared using Mann-Whitney *U* test, with significance set at $P < .05$. Correlations were tested using Spearman correlation coefficient.

TABLE 1 Baseline characteristics of the study population

Demographics	ICU (n = 21)	Healthy (n = 9)	*P*
Age, years	47 (40–60)	37 (19–73)	.304
BMI, kg/m^2	24.2 (21.6–28.9)	23.9 (22.2–25.1)	.625
Sex, n (%)			1.000
Male	15 (71)	6 (67)	
Female	6 (29)	3 (33)	
APACHE II score	20 (15–23)	–	NA
ICU length of stay, days	6 (4–9)	–	NA
Primary admission diagnosis, n (%)			NA
Pneumonia/ respiratory failure	7 (33)	–	
Trauma	6 (28)	–	
Cerebral hemorrhage	3 (14)	–	
Septic shock	1 (5)	–	
Pancreatitis	1 (5)		
ARDS	1 (5)		
Burns	1 (5)		
CABG	1 (5)		
Sepsis, yes	10 (48)		NA
Sedated, yes	17 (81)		
Creatinine on study day, μmoL/L	58 (46–86)		

Note: Values are presented as median (first quartile to third quartile) or N (%). Data were tested using Mann-Whitney *U* test or Fisher exact test as appropriate.
Abbreviations: APACHE, Acute Physiologic and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; BMI, body mass index; CABG, coronary artery bypass graft; ICU, intensive care unit; NA, not applicable.

RESULTS

Participants

For novel biochemical analyses, plasma samples were available for 21 ICU patients (15 males) and 9 healthy controls (6 males). Only 4 samples were missing (1.1%) for analysis and were assumed missing at random.

Baseline characteristics of the population studied here are detailed in Table 1. There were no significant differences between the groups at baseline for age, sex, or BMI. ICU patients had a median APACHE II score of 22 (15–23) and were admitted to the ICU for a median of 6 (4–9) days.

TABLE 2 Fasted plasma amino acid, bile salts, and FGF19 concentrations at baseline

Fasted plasma concentrations	ICU (N = 21)	Healthy controls (N = 9)	*P*
Total amino acids, μmol/L	3111 (2682–3378)	3390 (3278–3535)	.07
Essential amino acids, μmol/L	1150 (1066–1335)	1181 (1055–1277)	.87
Branched-chain amino acids, μmol/L	496 (437–610)	463 (430–506)	.48
Nonessential amino acids, μmol/L	1847 (1582–2075)	2221 (2095–2344)	.01
Total bile salts, μmol/L	2.85 (1.73–8.28)	3.00 (1.99–2.68)	.38
FGF19, ng/ml	0.10 (0.07–0.18)	0.11 (0.11–0.34)	.16

Note: Data are presented as median (first quartile–third quartile) and tested using Mann-Whitney *U* test.
Abbreviations: FGF19, fibroblast growth factor 19; ICU, intensive care unit.

EAA concentrations

Fasted plasma concentrations of EAAs were not significantly different between the healthy controls and ICU group (1181 [1055–1276] vs 1150 [1065–1334] μmol·L−1, $P = .87$) (Table 2). Postpyloric infusion of the test meal resulted in an early peak of EAA in the healthy controls at 15 and 30 minutes, which was absent in the ICU group (Figure 1A). This resulted in a significant difference in the early EAA response between both groups ($iAUC_{60}$: 5406 [3099–16,853] vs −4858 [−6859 to 2886] μmol·L^{-1}·60 minutes, $P = .039$, Figure 1B). After the initial 60 minutes, EAA concentrations gradually dropped below baseline levels with between-group differences in the total iAUC value ($iAUC_{240}$ $P = .48$). Individual EAA concentrations show a similar pattern of a more evident early peak response in healthy controls vs ICU patients (Figure S1), with a more notable response in those amino acids that are more abundant in the test meal (leucine, lysine, and valine).

Relationship between amino acid and 3-OMG absorption

Overall, 3-OMG concentrations were greater in the healthy controls when compared with those in the ICU group, especially in the early postprandial period (Figure 1C). Consequently, both early (0–60 minutes) and total 3-OMG uptake were significantly impaired in the critically ill patients ($iAUC_{60}$: 24.5 [20.7–24.6] vs 16.6 [9.9 - 16.7] μmol·L^{-1}·60 minutes, $P = .02$; $iAUC_{240}$: 83.2 [81.5–89.9] vs 67.9 [45.5–63.7] μmol·L^{-1}·240 minutes, $P = .03$) (Figure 1D). There was no significant correlation between plasma concentrations of EAA and 3-OMG ($\rho = 0.35$, $P = .09$) (Figure 2).

Total bile salts and FGF19 levels

Fasting plasma levels of total bile salts and FGF19 were similar between ICU patients and healthy controls: 2.85 (1.74–8.28) vs 3.00 (1.99–3.58) μmol·L−1, $P = .38$; and 0.10 (0.07–0.13) vs 0.11 (0.11–0.22) ng·mL−1, $P = .15$, respectively (Table 2). Following the postpyloric nutrient bolus, bile salt levels peaked at 15 and 30 minutes in healthy controls and ICU patients, respectively, with similar absolute elevations (Figure 3A). There were no between-group differences at any time point.

FGF19 concentrations peaked at 90 minutes to similar levels in both groups, but the change from baseline was only significant for the ICU group (Figure 3B). Although FGF19 levels reached statistically different levels between the 2 groups at 150 and 180 minutes, this did not represent a significant postprandial response from baseline for either group (Figure 3B).

DISCUSSION

Disturbed GI function could impair the anabolic effect of enteral nutrition in critically ill patients. In this context, we investigated the postprandial EAA, total bile salts, and FGF19 response following an enteral nutrient infusion and its relation to small-intestinal absorptive function measured by 3-OMG uptake. We have shown that the postprandial increase in EAA is blunted in critically ill patients and that plasma uptake of protein and carbohydrate correlated poorly in critical illness.

In our study, we measured EAA concentrations to quantify the diet-derived plasma response. In contrast to non-EAAs, which often undergo major splanchnic metabolism, a rise in EAAs can only result from protein breakdown or from dietary protein.[28] Although minor variations in individual EAA absorption exist, postprandial changes in total EAA concentrations reflect uptake of diet-derived amino acids.[8,29] The discordance between amino acid and glucose absorption demonstrated in the current study suggests that malabsorption of macronutrients during critical illness is governed by different mechanisms. Absorption of glucose (a monosaccharide) and sucrose (a disaccharide) have been shown to be markedly impaired when infused directly into the small intestine during critical illness.[11,30] Whereas mucosal architecture and luminal enzyme concentrations are relatively preserved,[11] down-regulation of glucose transporters in the apical and basolateral membrane of small-intestinal enterocytes is likely the dominant mechanism governing carbohydrate malabsorption.[10] Moreover, whereas fasting small-intestinal blood flow appears to be greater in hemodynamically stable critically ill patients than in healthy participants, demand-mediated increase in small-intestinal blood flow in

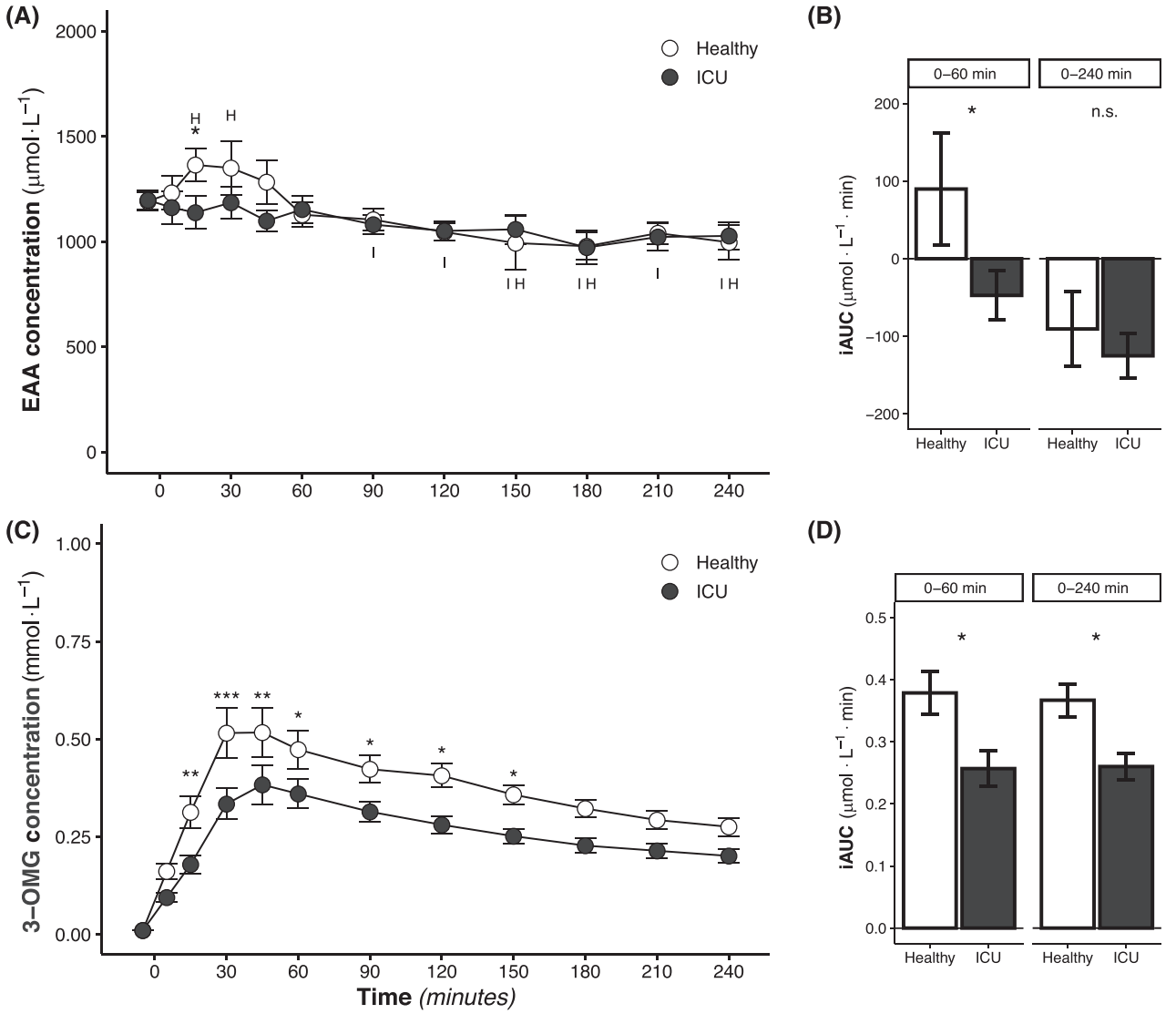

FIGURE 1 Postprandial essential amino acids (EAAs) (A) and incremantal under the curve (iAUC) values (B) and 3-O-methyl-d-glucose (3-OMG) (C) concentrations over time and iAUC values (D). Data are presented as mean ± SE. "H" or "I" marks significant changes from baseline for the healthy group (H) or intensive care unit (ICU) group (I), respectively, derived from the linear mixed-effects model (not shown for 3-OMG, as all concentrations were different from baseline). Significant differences between groups are marked with *($P < .05$), **($P < .01$), or ***($P < .001$)

response to luminal nutrient is attenuated and has been shown to correlate with carbohydrate absorption.[12]

Although mechanisms underlying carbohydrate malabsorption in the small intestine are well described, there is a paucity of studies assessing mechanisms for protein malabsorption. Similar to carbohydrate, the absorption of protein-derived amino acids and oligopeptides occurs by active transport through epithelial amino acid transporters.[31] Whether these transporters are comparably affected during critical illness is currently unknown. Similarly, although there is face validity that blood flow insufficiency may contribute to protein malabsorption on the intestinal level, evidence to support this hypothesis is lacking. Further studies are warranted to delineate architectural and molecular mechanisms governing intestinal protein malabsorption.

It is important to note that although 3-OMG is a relatively specific measure of intestinal absorption, the test meal in our study was a polymeric formula, containing intact protein rather than free amino acids or oligopeptides. Poor correlation between EAA and 3-OMG uptake could therefore also be attributed to maldigestion. Based on the high incidence of exocrine pancreatic insufficiency among ICU patients, there are grounds to assume that protein maldigestion could affect plasma amino acid appearance.[32] Only 1 study thus far has examined systemic availability of protein-bound amino acids, showing limited plasma appearance in ICU patients.[14] Other studies have assessed plasma appearance of dietary amino acids using isotopically labeled free amino acids.[8,33] These studies appear to show higher rates of appearance of diet-derived amino acids into the circulation, but the

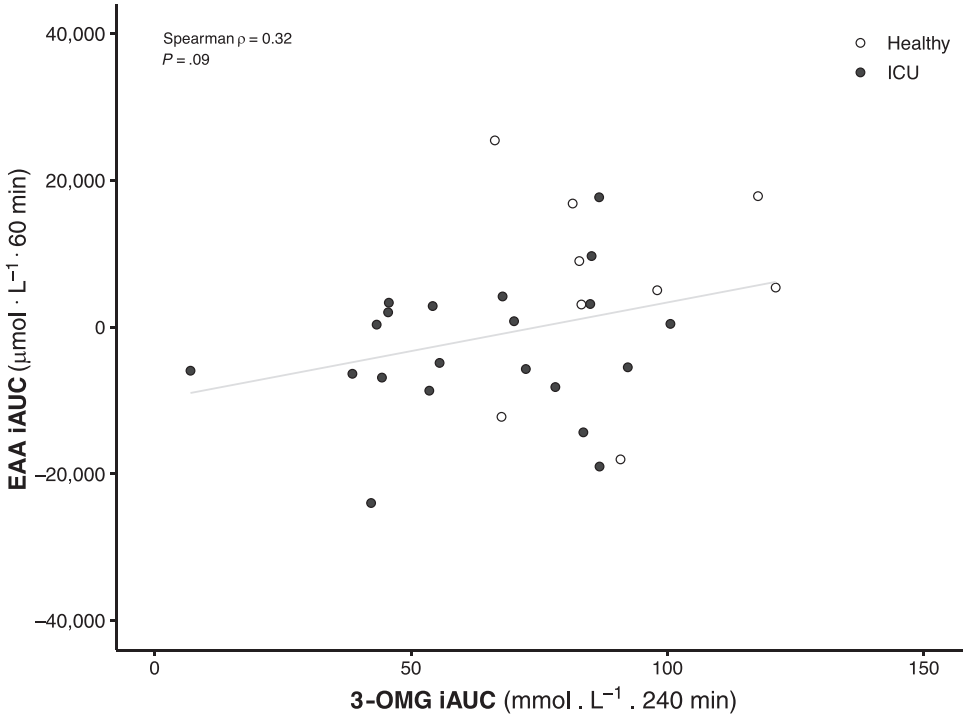

FIGURE 2 Correlation between early essential amino acid (EAA) response and 3-O-methyl-d-glucose (3-OMG) uptake. Filled circles represent intensive care unit (ICU) patients, and empty circles represent the healthy controls. Correlation was tested using Spearman correlation coefficient. iAUC, incremental area under the curve

use of free amino acid tracers precludes the contribution of digestion. Future comparison between protein and amino acid uptake could aid in delineating the relevance of maldigestion to protein malabsorption.

In the current study, we did not see a rise in EAA concentrations during a short-term period following a single postpyloric bolus feed. Increasing continuous provision of enteral protein for longer periods during ICU stay is able to increase total amino acid concentrations.[34] Similarly, increasing enteral protein supply appears to increase short-term protein balance in ICU patients.[33] Parenteral infusion of amino acids, which directly bypasses gut and liver, results in a sustainable increase of amino acid concentrations and whole-body protein balance within 3 hours.[35] These data suggest that impaired protein uptake can be partially overcome by increasing protein dose or altering the route of protein provision. It is therefore all the more relevant to correctly identify patients at risk for impaired protein uptake to modify nutrition therapy accordingly.

In addition to 3-OMG uptake and EAA response as a marker of small-intestinal function, we investigated the postprandial FGF19 response as a potential alternative marker of small-intestinal function. FGF19 is an endocrine gut hormone that is released by the terminal ileum after intestinal bile salt uptake in response to enteral but not parenteral nutrition.[36,37] We have recently shown that the normal postprandial response of FGF19 is blunted in critically ill patients and hypothesized that the impaired response could be used as a novel marker for small-intestinal function in this patient group.[20] However, we observed only a minimal postprandial elevation of bile salts, which was much lower than previously reported.[20,36] Consequently, no significant or relevant FGF19 response was evident in either the ICU or healthy control group. The postprandial sampling period in the current study was longer than in our previous study, making it unlikely that delayed intestinal transit time is the underlying cause of a blunted FGF19 response. The lack of response in the healthy control group suggests that the currently used mixed-meal bolus did not elicit sufficient gallbladder contraction, as it had a much lower fat content that the meal used in our previous study.[20]

There are both strengths and limitations to the current study. An important strength is the standardized nutrient stimulus, including the use of a postpyloric feeding tube, which negates possible confounding effects of delayed gastric emptying.[38] Although this also allowed us to investigate the relation of postprandial FGF19 response to small-intestinal function, the nutrient bolus in our study was insufficient to induce a clear plasma elevation in either the healthy or ICU group. A main limitation of the study is that we are unable to delineate the exact mechanism of impaired uptake of EAA. Other limitations include the limited sample size, especially for the healthy control group, and the use of different sampling sites between the groups. ICU patients had arterial samples taken from the radial artery, whereas venous samples from the antecubital vein were collected in the healthy control group. We cannot exclude that these different sites could result in small differences in amino acid concentrations.[39] However, it is unlikely that this affected the individual responses as analyzed here, and if it did, it would likely result in a less pronounced effect in the healthy control group.

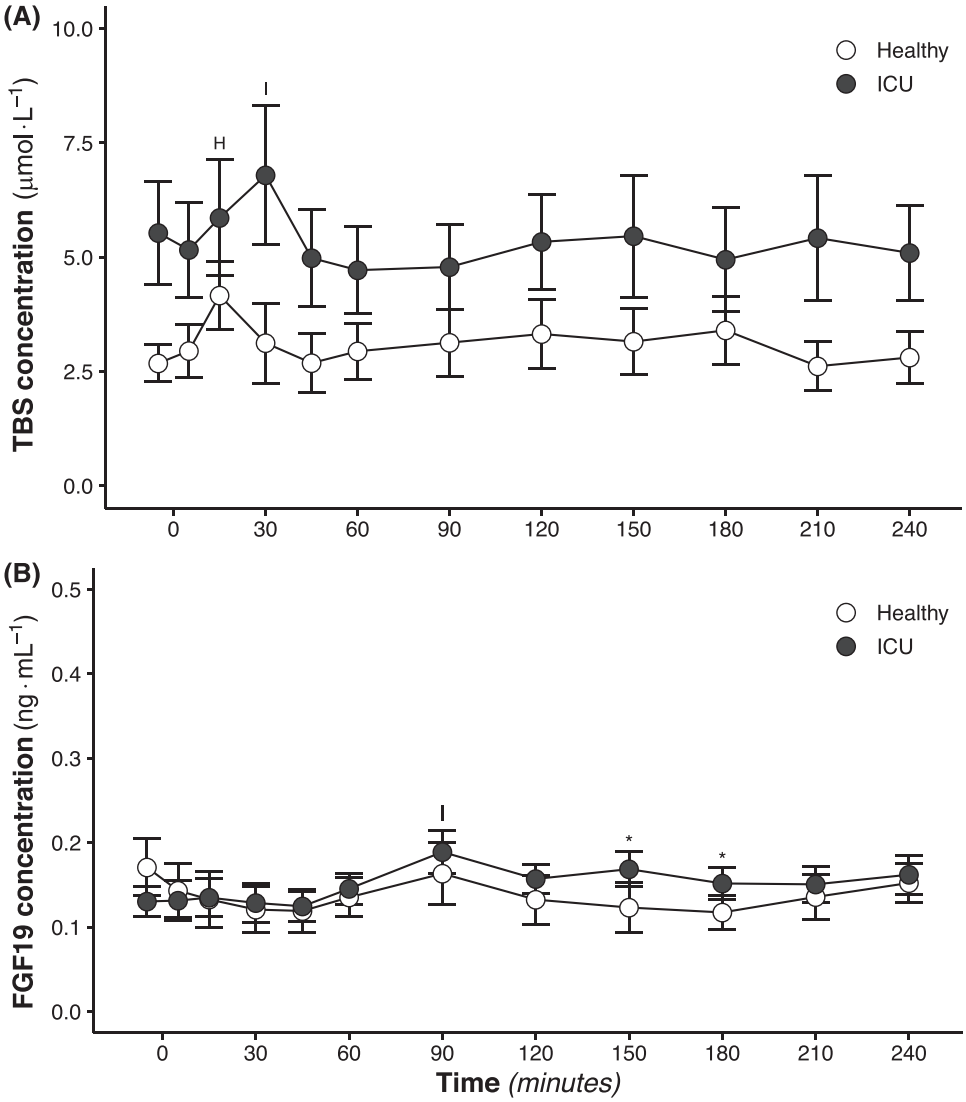

FIGURE 3 Postprandial total bile salt (TBS) (A) and fibroblast growth factor 19 (FGF19) (B) concentrations over time. Data are presented as mean ± SE. "H" or "I" marks significant changes from baseline for the healthy group (H) or intensive care unit (ICU) group (I), respectively, derived from the linear mixed-effects model. Significant differences between groups are marked with *($P < .05$)

CONCLUSION

In conclusion, our study shows that the postprandial increase of EAA is impaired during critical illness, which was not associated with small-intestinal function assessed by 3-OMG uptake. These data suggest that governing mechanisms are likely to differ between macronutrients. Future studies should aim to delineate putative mechanisms of protein malabsorption, including maldigestion of dietary protein into free amino acids, reduced intestinal absorption of digested protein, and increased splanchnic metabolism by the gut and liver.

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CONFLICT OF INTEREST

None declared.

FUNDING INFORMATION

None declared.

AUTHOR CONTRIBUTIONS

Rob J. J. van Gassel, Marcel C. G. van de Poll, Frank G. Schaap, Mark Plummer, Adam Deane, and Steven W. M. Olde Damink equally contributed to the conception and design of the research; Rob J. J. van Gassel, Mark Plummer, and Adam Deane contributed to the acquisition and analysis of the data; Rob J. J. van Gassel, Marcel C. G. van de Poll, Frank G. Schaap, Mark Plummer, Adam Deane, and Steven W. M. Olde Damink contributed to the interpretation of the data; Rob J. J. van Gassel drafted the manuscript. All authors critically revised the

manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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SUPPORTING INFORMATION

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