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Review

Metabolic and nutritional aspects in continuous renal replacement therapy

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ABSTRACT

Nutrition is one of the foundations for supporting and treating critically ill patients. Nutritional support provides calories, protein, electrolytes, vitamins, and trace elements via the enteral or parenteral route. Acute kidney injury (AKI) is a common and devastating problem in critically ill patients and has significant metabolic and nutritional consequences. Moreover, renal replacement therapy (RRT), whatever the modality used, also profoundly impacts metabolism. RRT and of the extracorporeal circuit impede 'effect the evaluation of a patient's energy requirements by clinicians. Substrates added and removed within the extracorporeal treatment are not always taken into consideration, making treatment even more challenging. Furthermore, evidence on nutritional support during continuous renal replacement therapy (CRRT) is scarce, and there are no clinical guidelines for nutrition adaptations during CRRT in critically ill patients. Most recommendations are based on expert opinions. This review discusses the complex interaction between nutritional support and CRRT and presents some milestones for nutritional support in critically ill patients on CRRT.

Introduction

The incidence of acute kidney injury (AKI), a common and devastating complication in critically ill patients, has increased in recent decades. Moreover, AKI treated with renal replacement therapy (RRT) has more than doubled over almost 20 years.[1,2] Consequently, continuous renal replacement therapy (CRRT) has become the modality of choice in critically ill patients, especially hemodynamically unstable patients.[3]

Metabolic and Nutritional Changes in AKI

Nutrition is an essential part of the treatment of critically ill patients; these patients, in general, are at increased risk of malnutrition. AKI profoundly impacts metabolism. The kidneys are instrumental in homeostasis, regulating and maintaining water balance, acid-base balance, and electrolyte concentrations. The kidneys also participate in metabolic processes such as gluconeogenesis and insulin excretion.[4] In AKI, disturbances in carbohydrates and lipid metabolism occur. For example, lipoprotein lipase activity is impaired, and triglycerides accumulate in the bloodstream.[5] However, AKI itself does not cause a significant change in energy metabolism; a study assessing resting energy expenditure (REE) by indirect calorimetry (IC) in mechanically ventilated patients found no difference between patients with and without AKI.[6] Targeting nutritional needs of critically ill patients poses a significant challenge, and data are scarce. Most data that provide the foundations for current guidelines are from observational studies in different patient populations, and there are no randomized control trials (RCTs) addressing critically ill patients on CRRT.

CRRT and Nutrition

CRRT is increasingly used in intensive care units (ICUs). Compared with intermittent hemodialysis, CRRT is better tolerated hemodynamically, and permits better control of fluid balance.[7–9] CRRT has both direct and indirect effects on nutrition. The commencement of CRRT and the subsequent improvement in fluid balance control enable physicians to be more comfortable with supplying nutrition (volume). Maintaining neutral or negative fluid balance can also improve intestinal absorption and motility by reducing intestinal edema.[10] CRRT clearance is not specific to uremic toxins; low molecular weight substances, some of which are essential, are also cleared through CRRT. Macronutrients, such as small proteins and peptides, and mi-

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cronutrients, such as amino acids, glucose, trace elements, and water-soluble vitamins, are cleared from the patient's blood into the effluent.[5,11–16]

CRRT can provide a significant source of non-nutritional calories, with amounts changing according to the solutions used and type of anticoagulation. However, it is crucial to avoid overfeeding in critically ill patients because this is associated with an increased risk of infections, higher carbon dioxide levels (which can delay weaning from mechanical ventilation), and increased mortality.[17–20] Underfeeding is also associated with prolonged ICU stay and an increased risk of infections and death.[21] Therefore, providing the correct caloric needs is essential to achieve a positive outcome in critically ill patients. However, despite these observations, there is no substantial evidence that increasing caloric intake improves outcomes.[21–23]

Among all interventions used to treat critically ill patients, CRRT is the one that has the most significant effect on nutrition in general and considers energy balance in particular.[24] Data on the effect of CRRT on metabolism and nutritional requirements are limited. Furthermore, CRRT performance has different modalities, dose prescriptions, and types of fluids (citrate, dialyzate, and replacement). Consequently, it is impossible to generalize to all CRRT modes based on the limited studies and different approaches to the topic.

Dosing of Energy Requirements

Energy requirements of critically ill patients are based on prior nutritional status, the current metabolic stress inflicted by the severity of illness, and the treatment given, with emphasis on CRRT. Unfortunately, most ICU patients do not receive the recommended amounts of calories and protein.[21] Therefore, the REE must be determined to target caloric needs in critically ill patients. Many estimation formulas based on anthropometric variables have been suggested to calculate REE, and some of these predictive formulas have a correction coefficient for CRRT. However, all these formulas have been proven to be inaccurate and unreliable, especially when applied to individual patients with unstable renal function.[16,25–27] Comparison of the estimation formulas with IC – the gold standard for estimating caloric needs[28] – in two observational trials in critically ill patients revealed that the precision level was low, and overestimation and underestimation were common.[29,30]

Additionally, most of the estimation formulas incorporate patient weight. Critically ill patients with severe AKI have significant fluid shifts owing to fluid resuscitation, intravenous drugs, and fluid removal once CRRT is started. Therefore, determining dry weight in critically ill patients with AKI requiring CRRT may be imprecise.

The superiority of IC over different estimation formulas was confirmed in the TICACOS study.[31] Furthermore, IC is the recommended tool in European and US guidelines for nutritional support in critically ill patients.[32,33] IC is a non-invasive method that estimates REE via the Weir equation, with assessment based on oxygen consumption and carbon dioxide production from exhaled air.[34] The importance of using IC to determine REE was demonstrated in a study evaluating 124 critically ill patients with AKI; 62% of the patients were found to be hypermetabolic and 14% hypometabolic.[35]

The use of IC on critically ill patients on CRRT has been questioned, and even considered contraindicated by some experts, owing to possible interferences. First, IC has not been validated during CRRT.[36] During the CRRT procedure, carbon dioxide is removed; hence, using the measured carbon dioxide in the Weir equation could lead to an underestimation of REE.[37,38] Several other limitations, at least in theory, preclude the use of IC during CRRT. Briefly, exposure of patient's blood to the extracorporeal circuit and the membranes of filters induces immunological activation and heat loss – a concept termed "dialytrauma" – which should augment the metabolic rate and increase REE.[39,40] Several studies have examined these predicted limitations, but there were no significant changes in REE.[36,41,42] These findings may be explained by a number of factors. First, membranes currently used in filters are bio-compatible and do not induce a robust immunologic response.[43,44] Second, heat loss is partially countered by using heating devices.[45] In addition, compensatory mechanisms are shut down in critically ill patients using sedation and muscle relaxants; hence, REE is even decreasing in these patients.[46,47] The unpredictable nature of the balance between energy intake and expenditure makes generalizability challenging, and estimation using predictive equations may lead to large errors. Measurement of REE using IC is therefore advocated.[32] However, considering the dynamic patient status and the continuous nature of CRRT, it is the authors' opinion that REE measurements in such patients should be performed repeatedly to account for the potentially rapid and large energy changes.

IC use during CRRT has been validated by measuring REE in patients before and during CRRT.[41,48] In an in vitro study evaluating the rate of VCO_2 removal – defined as the amount of carbon dioxide produced and exhaled from the body per time unit – it was estimated that there is only a 4% drop in REE, an acceptable margin of error.[49] An observational study investigated 42 mechanically ventilated critically ill patients with AKI; six of them were on CRRT. There was no difference in measured IC between patients with AKI and patients with AKI on CRRT.[29] The MECCIAS trial[42] investigated the impact of CRRT on IC and demonstrated that carbon dioxide alterations due to CRRT are clinically not significant; therefore, no correction factor of REE is needed. The investigators concluded that IC must be used to determine nutritional targets during CRRT.[42] Some authors suggest measuring during downtime intervals in CRRT, reducing the procedure effect. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines[50] recommend using calorimetry in patients on CRRT.

When targeting nutritional goals, non-nutritional calories must be considered.[51,52] The most common source of non-nutritional calories in critically ill patients on CRRT are propofol and the buffer used for the CRRT procedure, which is predominantly citrate. If non-nutritional calories are not considered, there is an increased risk of overfeeding. When using 10% propofol, each 1 mL is equal to 1.1 kcal, while the calories of each buffer solution depends on the composition and concentrations. The glucose composition of CRRT fluids (replacement or dialyzate) can significantly affect caloric gain or loss. Dextrose concentration in different CRRT fluids ranges from 0 mg/dL to 110 mg/dL. Glucose-free fluids can lead to glucose losses, and hence caloric loss.[53]

The buffer used in CRRT solutions has changed over time. Acetate was quite common in the past but is no longer used owing to adverse hemodynamic effects. Lactate, another possible source of non-nutritional calories, is found in some CRRT solutions as a buffer. Studies comparing lactate to bicarbonate have found faster lactate clearance, better correction of acidosis, and improved hemodynamic tolerance when bicarbonate is used.[54,55] Therefore, Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[56] recommend using bicarbonate as the buffer of choice.

Currently, citrate is the gold standard for extracorporeal circuit anticoagulation in CRRT. Compared with unfractionated heparin, citrate is associated with a lower risk of bleeding and better extracorporeal circuit survival,[57,58] making it a safer alternative to unfractionated heparin. However, citrate anticoagulation does have some potential side effects.[59–61] Additional advantages of citrate include the reported reduction in oxidative stress and the inflammatory state with less activation of the complement system, with one study showing decreased mortality in young surgical patients with multi-organ dysfunction.[62–64]

When regional citrate anticoagulation (RCA) is used, citrate itself influences metabolism. Each 1 mmol of citrate, a rich source of both bicarbonate and calories, is metabolized to 3 mmol of bicarbonate in the liver. Citrate load during CRRT depends on several factors, such as blood flow rate and hemofiltration rate, and it is partially removed by convection and dialysis processes. The citrate that enters the patient's blood is predominantly metabolized by the liver, but the kidneys and skeletal muscles also contribute to its metabolism. Citrate, an intermediate metabolite, enters the Krebs cycle and has several metabolic regulatory functions in glycolysis, proteolysis, and lipolysis. Citrate may also affect insulin resistance.[65,66] In addition, citrate may be a significant source of calories. Each gram of citrate that is metabolized yields 2.5 kcal. When using RCA in CRRT, depending on the specific citrate solution, the caloric gain can be substantial, reaching 1434 kcal/day.[67] Another study reported a marked caloric gain – 512 kcal/day – in 10 critically ill patients on CRRT using RCA, with approximately half of the calories from glucose (295 kcal/day) and half from citrate (218 kcal/day).[27] Failure to account for this source of calories may result in significant overfeeding. Selecting specific modalities can also limit caloric gain from citrate. For example, if hemodialysis is combined into the modality, citrate is lost to the effluent by diffusion, which decreases entry of citrate into the patient's bloodstream and limits caloric gain to 100–300 kcal/day.[59,60]

Conversely, if a patient is receiving heparin anticoagulation and replacement or dialyzate solutions are dextrose-free, then the patient can experience a negative energy balance due to CRRT.[46] In between these two edges, of highly positive to negative energy balance, working with sodium citrate 18 mmol/L anticoagulation, which contains neither lactate nor glucose, and using replacement and dialyzate solutions with dextrose 100 mg/dL, patient exposure to non-nutritional calories is milder, characterized by a range of 200–500 kcal/day. Stevenson et al.[53] developed an equation predicting total calories removed based on the different CRRT prescriptions; however, the equation does not account for the use of glucose-containing fluids. The net balance of glucose gain, or loss, also depends on the patient's blood glucose levels. A high pre-filter blood glucose level will lead to an increase in the amount of glucose filtered and lost to the effluent.

An equation for estimating citrate caloric load during continuous veno-venous hemodiafiltration (CVVHDF) is shown in (Figure 1.)[68]

Several citrate solutions are commercially available, with different citrate concentrations and compositions. Some citrate solutions contain lactate and dextrose, while others contain only sodium. The variety of compositions and concentrations causes vast differences in their caloric value (Table 1). The balance between a patient's blood glucose level and CRRT fluid dextrose concentration is the primary determinant of caloric balance.

In summary, the net energy balance is markedly influenced by the CRRT prescription. The energy balance ranges from large non-nutritional caloric gains when the regimen includes specific RCA protocols and glucose-containing fluids to caloric losses when not using citrate anticoagulation or when glucose-free fluids are employed. Therefore, local individual CRRT practices must be considered when targeting caloric needs in a critically ill patient on CRRT to avoid overfeeding or malnutrition.

Protein Loss and Requirements

Critically ill patients, especially those on CRRT, are subject to extreme metabolic stress and are in a catabolic state. From the time of insult, leading to critical illness, during the first hours of critical illness, the body consumes its energy from the glycogen stored in the liver and muscle. Once depleted, an alternative energy source must be used.[24] Degradation of muscle proteins into their amino acid building blocks, which can enter the gluconeogenesis pathway to be converted into glucose, provides an alternative energy source. Critical illness also impairs the process of protein synthesis. The combination of both, consumption and degradation of proteins, lead to a negative nitrogen balance. Proteins are constructed from amino acids, which are classified as either essential or non-essential based on the capability of the human body to synthesize them. However, when RRT is started, the high rate of amino acid loss causes some of the non-essential amino acids to become essential, as metabolism cannot keep pace with the losses.[50] During this catabolic state, amino acid losses can peak at 1.3–1.8 g/kg/day. However, once this state is complicated with AKI, amino acid losses through RRT can be even higher, up to 15 g/day.[14,24] Therefore, providing an increased supply of protein and amino acids during the nutritional intervention can counterbalance and even match the nitrogen losses, but it can neither reverse the catabolic process nor enhance it.[24]

Table 1
Non-nutritional calories in CRRT.

Substance	Caloric value (kcal/g)	Solution
Citrate	3	ACD-A, TSC, and citrate 12 mmol or 18 mmol
Glucose	3.4	ACD-A, dialyzate, and replacement
Lactate	3.62	Buffer in different solutions

ACD-A: Anticoagulant citrate dextrose A; CRRT: Continuous renal replacement therapy; TSC: Trisodium citrate.

$$\text{Citrate calories entering blood stream}_{\text{min}} = \left[\left(\frac{\text{FR}}{1000}\right) \times \text{Citrate dose}_{\text{mmol/L}}\right] \times \left[1 - \left(\frac{\text{FF}}{100}\right)\right] \times 0.59$$

Figure 1. Estimation of citrate caloric load during CVVHDF. CVVHDF: Continuous veno-venous hemodiafiltration; FF: Filtration fraction (%); FRL: Flow rate (mL/min).

Calculating the protein catabolic rate for hospitalized patients on RRT is essential. Assessment of the degree of catabolism and evaluation of protein intake should measure nitrogen balance. The degree of catabolism – a derivative of the severity of critical illness – dictates the required amounts of proteins/amino acids to avoid a negative nitrogen balance. Failure to achieve that target is associated with increased mortality.[24] Critically ill patients with AKI on CRRT that achieved a positive nitrogen balance had better hospital outcomes.[69] A recent retrospective cohort study involving 350 critically ill mechanically ventilated patients on CRRT demonstrated that early high protein provision – before day 4 and ≥1.2 g/kg/day – was significantly associated with lower hospital and ICU mortality.[70]

There are logistical and technical challenges in calculating nitrogen balance in a critically ill patient, particularly once on RRT. Different formulas are used to calculate nitrogen balance, but none have been validated during RRT. Despite these barriers, evaluating the protein catabolic rate is crucial and highly recommended. Urea in urine estimates nitrogen balance by measuring nitrogen losses in urine, stool, and teguments. However, the mechanisms underlying the correlation of the effluent removal rate of urea with the effluent removal of proteins, amino acids, and other molecules related to the nitrogen balance have yet to be elucidated.

Nevertheless, there is a reliable calculation based on urea removal. Several factors must be considered for calculating nitrogen balance in a critically ill patient on CRRT. For nitrogen load, all intake from enteral and parenteral nutrition is considered, and for nitrogen loss, all pathways are considered, including residual urine, effluent fluid, and insensible loss, mainly in the stool. Nitrogen loss into effluent can either be calculated by measuring the concentration and total volume or by a rough estimation of amino acid loss into effluent. The latter depends on ultrafiltration flow rate; for 1 L/h, approximately 1.5 g nitrogen/day is lost, and for 2 L/h approximately 2 g nitrogen/day is lost. These values are added to urinary excretion of urea nitrogen plus 4 g nitrogen/day for insensible loss.[71,72] Considering the above is essential for translating research into recommended protein dosing in CRRT patients.

It is estimated that during CRRT, amino acid losses are around 15–20 g/day and protein losses are around 5–10 g/day. Loss of amino acids in the CRRT procedure is unavoidable and abundant owing to their relatively low molecular weight causing them to be readily filtered from the blood into the effluent.[13,24,72,73] Consequently, total nitrogen loss in CRRT patients may be up to 25 g/day, thus worsening the nitrogen balance.[14,17] Patients on RRT may therefore require higher protein supplementation due to the negative influence of RRT on protein and nitrogen balance.[5,74] Protein supplementation up to 2.5 g/kg/day led to an almost positive or slightly positive nitrogen balance.[17,71] AKI patients on CRRT receiving a higher dose of dietary protein supplementation of 2.5 g/kg/day were compared with patients receiving 1.2 g/kg/day dietary protein supplementation (both groups received equal amounts of calories), and those receiving the higher dose of protein achieved a positive nitrogen balance (53.6% *vs.* 36.7%, P <0.05). The higher dose of dietary protein supplementation led to increased blood urea nitrogen production and required an increased CRRT dose.[14,15]

Estimates of protein and amino acid losses are mainly derived from earlier studies.[18,72,75,76] Most of these studies lacked randomization and did not assess nitrogen balance, and it is possible that with the progress in CRRT technology, dose delivery, and newer filter membranes, actual amino acid losses are even higher. The choice of RRT modality, dose, and filter membrane properties will affect the amounts of amino acids/proteins lost. Currently, available RRT modalities have increased efficiency, allowing higher blood flow rates and increased effluent removal; therefore, the actual amino acid losses of patients on CRRT are much greater than those reported in earlier studies.[12,75,77] RRT that is continuous or intermittent; convection, diffusion, or both; the dose of treatment; the blood flow rate; replacement fluid rate; dialysis fluid rate; and fluid removal may have various effects on amino acid losses during RRT.[73] Removal rate also depends on the plasma concentration of amino acids and hence the route of nutrition – enteral *vs.* parenteral.[78,79]

Future research must consider all of the above points to convert amino acid and protein loss into protein dosing in CRRT patients. A recent study by Stapel et al.[79] evaluated amino acid loss during continuous veno-venous hemofiltration (CVVH) in critically ill patients. Patients have prescribed a blood flow rate of 180 mL/min and a pre-dilution flow of 2400 mL/h. The estimated amino acid loss was 13.4 g/day, corresponding to a protein loss of approximately 11.2 g/day. Filter membrane properties influence amino acid removal. Maxvold et al.[72] demonstrated a 30–40% higher amino acid clearance with a convection method (CVVH) than with a diffusion method (CVVHD). Bellomo et al.[14] studied the effect of combined CVVHDF and high (2.5 g/kg/day) parenteral amino acid supplementation on nitrogen balance. The study showed that high protein intake increases the serum concentration of most amino acids, achieving a slightly negative overall nitrogen balance in highly catabolic patients while allowing adequate azotemic control.

Scheinkestel et al.[69] tried to establish optimal protein delivery during total parenteral nutrition in critically ill, ventilated, anuric patients on CRRT while measuring amino acid losses across the hemofilter. Protein intake of <2.5 g/ kg/day caused a reduction in blood levels of 14–57% of the measured amino acids below the normal range. Amino acid balance became more positive as protein input increased to 2.5 g/kg/day. The study also demonstrated that amino acid losses were dependent on their blood concentration and that a protein intake of 2.5 g/kg/day optimizes nitrogen balance and corrects amino acid deficiencies. In another study by the same group, contin-

uous hemodialysis combined with parenteral nutrition led to a 17% loss of the amino acids administered to the patients. Other studies have also demonstrated the connection between amino acid blood concentration and amino acid loss in effluent.[12,25,75] This means that the amount of protein and amino acids supplied and the route and possibly infusion rate may play a role in their removal rate. According to the published data, the high amino acid dose, up to 2.5 g/kg/day, is not associated with an increment in blood urea nitrogen levels. A positive nitrogen balance in AKI with critical illness is associated with increased patient survival.[71]

It is important to emphasize that increasing the dose of proteins or amino acids is not equivalent to increasing the amount of energy. Rugeles et al.[80] studied high-protein-hypocaloric *vs.* normal-caloric enteral nutrition in critically ill patients, and found that reducing energy supply from 25 kcal/kg/day to 15 kcal/kg/day at a protein dose of 1.7 g/kg/day was not associated with worse outcomes and even improved glucose control by lowering insulin requirements. The optimal prescription dose of proteins in critically ill patients on CRRT remains to be established. An increase in protein delivery is logical due to the increased loss of amino acids during CRRT. Other studies suggest that protein delivery >1.5 g/kg/day can positively impact this survival.[15,17,75] However, the optimal protein supplementation in critically ill patients with AKI on RRT is still unclear.[12]

In current daily practice, it is not achievable to perform a nitrogen balance daily, nor can specific amino acid losses be determined[73], and therefore practical recommendations are needed. In critically ill patients undergoing CRRT procedures, an increase in protein supplementation should be considered during nutritional interventions. Those patients have increased loss of amino acids with the ultrafiltrate, and thus increased protein supplementation to values exceeding 1.5 g/kg/day can benefit prognosis.[25] The ESPEN guidelines[32] recommend protein delivery in critically ill patients at a dose of 1.5 g/kg/day, and when CRRT is commenced, the dose should be increased to 1.7 g/kg/day. The ASPEN guidelines[33] recommend protein delivery in critically ill patients on CRRT at a dose of 2.0–2.5 g/kg/day. According to the available data reviewed here, supplementation of 2.0–2.5 g/kg amino acids as recommended can be used without increasing blood urea nitrogen or increasing amino acids loss (more than the acceptable amount by filtration).[32,33]

All these recommendations are based on body weight, which presents a problem. Critically ill patients with AKI, especially if anuric, gain fluids and hence weight. Conversely, once RRT is started with fluid removal, weight decreases. Therefore, using weight to calculate protein requirements may be biased in those situations. In a recent study on critically ill patients with AKI, before and after starting RRT, it was found that there is an increased risk of under- or overfeeding when nutrient needs are estimated instead of measured. The energy/protein requirements should be achieved progressively and after 48 h (after the acute phase of catabolism) to avoid overfeeding.[29]

One amino acid that deserves special attention is glutamine, a disease-specific nutrient. Glutamine is the most abundant amino acid and the principal carrier of nitrogen in the body, and it plays an essential role in immune function. In critically ill patients, a low concentration of glutamine in the blood is associated with increased mortality rates. Glutamine is predominantly synthesized in the skeletal muscles. During the catabolic phase of critical illness, muscle mass decreases, and hence glutamine synthesis decreases. Furthermore, glutamine is lost in the effluent, with the loss estimated at 1.2 g/day.[50] Novak et al.[81] published a meta-analysis, mainly composed of early and underpowered studies, demonstrating that glutamine supplementation can reduce the incidence of infections, shorten hospital stays, and decrease mortality rates. Three large RCTs that followed – the SIGNET study,[82] the REDOX study,[83,84] and the MetaPlus study[85] – failed to show any benefit with glutamine supplementations, and the latter two studies even indicating a harmful effect, with higher mortality rates in critically ill patients with multi-organ failure, mainly AKI. However, those latter two studies did use higher doses than the usually recommended doses. Accordingly, current guidelines do not recommend glutamine supplementation in critically ill patients suffering from multi-organ failure.

Further studies on protein supplementation in patients receiving CRRT are needed. A distinction should be made between studies on amino acid loss in effluent with contemporary CRRT modalities and studies evaluating the effect of protein supplementation on clinical outcomes in patients receiving CRRT. Multiple factors lead to an increase in critical illness catabolism in patients with AKI on RRT, and the most prominent of these factors is amino acid losses in ultrafiltrate and dialyzate. As discussed here, several parameters influence the rate of amino acids loss, including timing, administration route (i.e., parenteral or enteral), and protein target; all the above should be combined into a broader approach to assess amino acids loss and protein requirements. Therefore, evaluating variables of convection (CVVH), diffusion (CVVHD), or the ratio of convection/diffusion (CVVHDF), amino acid intake, rate of parenteral administration of amino acid, and route of amino acid administration are justified.

Lipids

Lipids are an alternative energy source to avoid carbohydrate overload in enteral and parenteral nutrition. Lipids are the source of essential fatty acids and allow the delivery of fat-soluble vitamins (vitamins A, D, E, and K). Most formulas in use contain lipids mainly in triglycerides form with different fatty acid chains (medium, long, or very-long-chain).[86,87] Few data are available on lipid metabolism in patients with AKI. Approximately 40% of critically ill patients with AKI are malnourished.[88] In a *post hoc* analysis by Hellerman et al.[89] the IC of critically ill patients with AKI (13 on CRRT) was measured and the results suggested that these patients are underfed in both carbohydrate and lipid needs. AKI induces derangements in lipid metabolism and is associated with increased low-density lipoprotein triglyceride content, changing lipolysis, and reduced hepatic lipase activity.[32] Changes in lipid metabolism rapidly develop after AKI, and impaired fat elimination is evident at 48–96 h.

The CRRT procedure, in all its modalities, does not significantly affect lipid metabolism and derangements because the high molecular weight and lipophilic properties of the lipids make their clearance in the hemodialyzer membranes negligible. However, the high molecular weight of the lipids may result in them blocking the hemofilter capillaries. This impact

of lipids on dialyzer survival time may be lower when local citrate-based anticoagulation is applied.[90] L-carnitine is an amino acid derivative that is essential for fatty acid mobilization into the mitochondria. L-carnitine depletion occurs in critically ill patients and is increasingly lost during CRRT, which may lead to lipid accumulation. Several studies have demonstrated the beneficial effects of L-carnitine supplementation on lipid metabolism during CRRT. An alternative way to overcome this lipid accumulation might be by supplying medium-short triglycerides, which do not require the presence of L-carnitine for their metabolism.[90] However, there are no studies supporting this hypothesis. Moreover, there is no gradient when comparing lipid concentrations pre-filter *vs.* postfilter, implying the absence of membrane adsorption.[91,92]

The leading cause of lipid abnormalities is reduced hepatic lipase activity and lipolysis. Consequently, triglyceride contents in lipoprotein increase while the high-density lipoprotein cholesterol fraction reduces. In addition to lipolysis reduction, there is an impairment in fat clearance after lipid administration. These changes in lipid metabolism are characterized by hypertriglyceridemia, especially in patients fed parenterally, and with low cholesterol levels.[25] Therefore, triglyceride blood concentrations should be monitored in patients with AKI undergoing CRRT. The degree of hypocholesterolemia appears to correlate with the severity of critical illness, morbidity, and mortality. It has also been suggested that critically ill patients with AKI oxidize considerably more lipids as compared with carbohydrates than would be expected.[89]

The ASPEN guidelines[33] suggest optimal carbohydrate and lipid-calorie combinations in hospitalized patients with AKI needing medical nutrition. The ratio of lipids and carbohydrates may be adjusted to increase lipid intake and reduce carbohydrate provision based on actual substrate utilization assessed by IC.

Other than the nutritional caloric source, some polyunsaturated fatty acids (PUFAs) have an immunological effect. Omega-3 and omega-6 PUFAs are of particular interest; the first is associated with anti-inflammatory effects, while the latter is associated with pro-inflammatory effects. Several studies have confirmed better outcomes, such as improved hemodynamics, with omega-3-enriched lipid emulsions.[93,94] Therefore, ESPEN recommends intravenous lipid emulsions containing omega-3 PUFAs for critically ill patients due to the anti-inflammatory and immune-modulating effects of these molecules. These recommendations do not exclude patients with AKI,[32] although no RCT is currently available to support the recommendation of the use of intravenous lipid emulsions containing omega-3 PUFAs for patients with AKI.

Currently, there are insufficient data to recommend alternation in fat administration for critically ill patients on CRRT, except in cases of hypertriglyceridemia that require a change in the prescription of nutrition.

Micronutrients

Micronutrients (trace elements, vitamins, and electrolytes) are essential substances that participate in many metabolic pathways and contribute to immune system reactions, antioxidant activity, and wound healing. Critical illness influences the level of many of these substances, with reduced concentrations detected in most critically ill patients. The redistribution in micronutrients is due to cellular shifts, changes in absorption and excretion, increased utilization, and alterations in protein binding. When CRRT is added to the equation, the complexity increases.[95–97] Essential dietary components, such as micronutrients (trace elements and water-soluble vitamins), are lost during CRRT, due to removal or adsorption. Furthermore, the solutions used in CRRT – dialyzate and replacement fluids – are "contaminated" with trace elements in different amounts.[98] There are no recommendations to correct low levels of different micronutrients during critical illness. The optimal dose of micronutrient supplementation has not yet been determined in critically ill patients as it is a controversial subject.[95,99] In addition, data regarding micronutrient concentrations in critically ill patients during CRRT are limited, with wide variation in RRT modality, dose, and duration. Moreover, although there is additional loss of micronutrients in CRRT, there are no data to recommend increasing supplementation beyond what is found in regular nutrition prescriptions.[100,101] However, failing to compensate for what is lost might increase the risk of deficiencies.[102]

Trace Elements

The loss of trace elements into effluent is known and proven. An in vitro study evaluated the loss of trace elements during CRRT by measuring trace elements in bovine plasma and ultrafiltrate and calculating sieving coefficients. Copper, chromium, manganese, selenium, and zinc were all detected in the effluent. The different trace elements exhibited different degrees of loss; the highest loss was for selenium and copper, causing a significant negative balance. This suggests the need for supplementation of these two elements.[103]

Borman et al.[98] examined eight trace elements (chromium, copper, manganese, cobalt, zinc, rubidium, molybdenum, and selenium) in 31 patients on CRRT. Both plasma and effluent samples were taken at time zero before CRRT and 36 h after starting CRRT. The results were also compared with a control group of healthy volunteers. Plasma levels of selenium and rubidium were significantly reduced when compared with the control group, with a marked loss of effluent. However, the levels of chromium, cobalt, and molybdenum were increased in the study group. According to those results, selenium supplementation must be considered for critically ill patients on CRRT.

A recent study by Ostermann et al.[95] measured plasma levels of vitamins B1, B6, B12, C, and D, folate, selenium, zinc, copper, and iron in critically ill patients with severe AKI on CRRT. The concentrations of micronutrients were also measured in the effluent. All trace elements, vitamin C, and folate, were detected in the effluent fluid. The plasma concentrations of zinc, iron, selenium, vitamin D, and vitamin C were below the reference range, but this finding was in both CRRT and non-CRRT patients with AKI.

Klein et al.[104] examined the balance of manganese, selenium, boron, silicon, and nickel in CRRT patients. Except for selenium, all other trace elements were detected in dialyzate fluids. The authors demonstrated a negative balance for selenium but raised concerns about manganese and nickel's positive balance.

Berger et al.[105] measured the concentration of several trace elements in the plasma, replacement fluids, and effluent of 11 patients on CRRT. Baseline plasma concentrations of selenium and zinc were below normal levels. Trace elements, especially zinc, were detectable in replacement fluids and effluents. There was a significant negative balance between selenium, copper, and thiamine, while the zinc balance was slightly positive.

The same group also described a case report where a patient on prolonged CRRT developed severe deficiencies of copper and selenium, leading to life-threatening bradycardia and severe hypertriglyceridemia, respectively. Therefore, monitoring copper is recommended in patients on CRRT for prolonged periods, and copper supplementation, approximately 3 mg/dL, is suggested to prevent deficiency.[106]

These studies indicate that trace elements are filtered and cleared during the process of CRRT, but other factors influence trace element levels as well, such as contamination of the dialyzate and replacement fluids, and the inflammatory state of the patient.[107] Clearance is also different for different trace elements; while a negative balance was predominantly reported for selenium and copper, some studies showed a positive balance for zinc and manganese.

It is generally agreed that micronutrient loss, especially selenium, needs to be compensated with increasing supplementation beyond what is provided in standard nutritional formulas.[10,105–107] Some researchers suggest trace elements must be doubled or even tripled and given intravenously to enterally fed patients to compensate for effluent loss during CRRT.[16]

Vitamins

Water-soluble vitamins are lost into effluent during CRRT. Consequently, some vitamins are lost during CRRT in amounts more significant than those found in different multivitamin preparations, which increases the risk of a vitamin deficiency developing.

In a study on 55 critically ill patients with severe AKI, treated with CRRT for up to 6 days, serial plasma and effluent concentrations of many micronutrients were measured. Losses of vitamin C and trace elements were high as expected, consistent with the literature. However, unexpectedly, other water-soluble vitamins – vitamins B1, B6, and B12 – were not detected in the effluent. This finding may be explained by dilution in the effluent, adsorption in the CRRT circuit and filter, or conversion to other metabolites not recognized by the measuring techniques.[100,108] Supporting the concept of loss, reduced levels of several water-soluble vitamins, including B1, B6, and folic acid, were found in blood of patients on CRRT, compatible with vitamin deficiency.

Regarding Vitamin C, the literature is inconclusive. One study reported 93 mg/day of vitamin C lost to affluent, slightly above the 90 mg/day daily recommended dose,[97] Hence, a 100 mg/day vitamin C dosage has been suggested for patients on CRRT. In a study evaluating the loss and supplementation of vitamin C in critically ill patients, it was estimated that patients lost approximately 1.68 g/day of vitamin C during CRRT; however, the patients in this study did receive mega doses of vitamin C.[109] Based on this study and others, a review published on vitamin C stated that patients on CRRT need 2 g/day of vitamin C to maintain a normal range.[110]

As described above, although micronutrients are small molecular weight substances, they have different sieving coefficients due to other characteristics and hence different clearance rates.

Another study evaluating the loss of micronutrients during CRRT measured folic acid and vitamin B12, but there were no clinically significant losses of these vitamins.[111] The study also evaluated the impact of different blood flow and dialyzate flow rates on the loss of micronutrients, and found no correlation. A different study found that significant amounts of folic acid are lost during CRRT.[112]

Significant losses of vitamin B1 into effluent during CRRT – more than twice the amount found in parenteral nutrition prescriptions – were found by Berger et al.[105] (approximately 4 mg/24 h). This rate of vitamin B1 loss would cause depletion in 1 week of CRRT treatment.

A study evaluating the concept of dialytrauma found that the removal rate of vitamin B6 was negligible compared with the recommended daily intake. However, after 3 days of CRRT, the levels of vitamin B6 in the blood of patients were below the normal range. A possible explanation is that the lower levels of vitamin B6 are connected to disease severity. Therefore, increasing the supplementation of vitamin B6 seems logical.[112]

Lipid-soluble vitamins are not removed from the effluent during CRRT. Despite this, some experts recommend supplementation of vitamins E (10 IU/day) and K (4 mg/week).[24] In critically ill patients, levels of vitamins A and E are low, and vitamin D metabolism is impaired, but when considering the effect of CRRT, several studies did not detect these three vitamins in the effluent fluid.[108,111]

Although data are limited, some suggest doubling the dose of vitamins supplied during CRRT.[16] The ESPEN guidelines[32] recommend the following supplementation for B complex vitamins: B1 100 mg/day, B2 2 mg/day, B3 20 mg/day, B5 10 mg/day, B6 100 mg/day, B7 200 μg/day, folic acid 1 mg/day, and B12 4 μg/day. In addition, these guidelines recommend that vitamin C be supplemented at 250 mg/day, and that vitamin A dosing be reduced to compensate for deficient retinol degradation during AKI. The same guidelines also recommend doses for some trace elements: selenium 100 μg/day, zinc 50 mg/day, and copper 5 mg/day.

All studies reported levels of micronutrients in patient blood and loss of micronutrients into the effluent fluid, but no studies addressed the clinical context. Therefore, it remains unknown whether supplementation of micronutrients aiming to increase blood levels to the normal range will have a clinical significance.[10,105,113]

All current recommendations and guidelines are based on expert opinion, and there is a controversy about the optimal dosage. Study findings are inconsistent. According to current data, a consensus exists that additional monitoring with blood assays in patients on prolonged courses of CRRT is warranted.[73]

Conclusions

Providing adequate nutritional support for critically ill patients is complex. Adding AKI metabolic disturbances and RRT multiple modalities is challenging. Nutritional needs differ significantly between patients with AKI. The RRT, including all

Table 2
Summary of different recommendations for nutritional support in CRRT.

Reference	Energy	Fats	Protein/amino acids	Micronutrients	Water-soluble vitamins	Fat-soluble vitamins
McClave et al. [33]	Consider non-nutritional calories Beware of overfeeding	Monitor triglyceride level	2.0–2.5 g/kg/IBW/day	Monitor	Monitor	No recommendations
Singer et al. [32]	IC Consider non-nutritional calories Beware of overfeeding	Monitor triglyceride level	1.5–1.7 g/kg/day	Monitored and supplemented, especially selenium, zinc, and copper	Monitored and supplemented especially vitamin C, folate, and thiamine	E: 10 IU K: 4 mg/week A: Decrease the amount
Onichimowski et al. [24]	Catabolic phase: 20–25 kal/kg/IBW/day Anabolic phase: 25–35 kal/kg/IBW/day	0.7–1.5 kal/kg/IBW	1.7–2.0 g/kg/IBW/day	A doubled dose of commercial preparations for PN, additional intravenous substitution for EN	B1: 100 mg/day B2: 2 mg/day B3: 20 mg/day B5: 10 mg/day B6: 100 mg/day B7: 200 μg/day B9: 1 mg/day B12: 4 μg/day C: 250 mg/day A doubled dose of commercial preparations for PN, additional intravenous substitution for EN	E: 10 IU K: 4 mg/week A: Without supplementation In practice, the dose of commercial multivitamin preparations may be doubled
Honoré et al. [16]	IC 25–35 kal/kg/IBW/day Carbohydrates 60–70% Lipids 30–40%	Monitor triglyceride level	1.5–1.8 g/kg/IBW/day	Selenium: + 100 μg/day Zinc: 50 mg/day Copper: 5 mg/day A triple dose of intravenous trace elements-containing solutions	B1: 100 mg/day B2: 2 mg/day B3: 20 mg/day B5: 10 mg/day B6: 100 mg/day B7: 200 mg/day B9: 1 mg/day B12: 4 μg/day C: 250 mg/day	E: 10 IU K: 4 mg/week A: Reduce supplementation
Ostermann et al. [71]	IC 25–30 kal/kg/day	No recommendations	>1.5 g/kg/day	Selenium: 50–70 μg/day Zinc: 5–10 mg/day Chromium: 0.01 mg/day Manganese: 0.5 mg/day Copper: 1–2 mg/day A double or triple dose of intravenous trace elements-containing solutions	B1: 100–200 mg/day B2: 2 mg/day B3: 20 mg/day B5: 10 mg/day B6: 50–100 mg/day B7: 200 mg/day B9: 1 mg/day B12: 4 μg/day C: 0.5–6.0 g/day	No recommendations

CRRT: Continuous renal replacement therapy; EN: Enteral nutrition; IBW: Ideal body weight; IC: Indirect calorimetry; PN: Parenteral nutrition.

modalities, has an enormous impact on body metabolism and nutrition. Since the clearance of RRT is not specific, loss of some aspects of nutrition (such as amino acids, peptides, proteins, trace elements, and vitamins) and gain of other aspects of nutrition (such as dextrose and non-nutritional calories like citrate and lactate) take place and both must be considered when prescribing nutritional support.

There is currently no evidence to recommend when to initiate nutrition in patients with AKI undergoing CRRT. This patient population does require meticulous nutritional support when CRRT is started. If nutrition has not already commenced and the patient is hemodynamically and respiratory stable, we suggest initiating feeding as soon as CRRT is started.

Evidence-based data are scarce and lacking on this subject. The optimal nutritional support, the amount of energy and proteins needed to be supplied, and the role of micronutrient additives in improving patient outcomes remain unclear. Some recommendations have been made, which are predominantly based on expert data.Table 2 summarizes some of these recommendations. Additional studies are needed to further explore this subject and provide better nutritional care for patients on CRRT.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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