

Review

Bench-to-bedside review: Metabolism and nutrition

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Critical Care 2008, **12**:222 (doi:10.1186/cc6945)**Abstract**

Acute kidney injury (AKI) develops mostly in the context of critical illness and multiple organ failure, characterized by alterations in substrate use, insulin resistance, and hypercatabolism. Optimal nutritional support of intensive care unit patients remains a matter of debate, mainly because of a lack of adequately designed clinical trials. Most guidelines are based on expert opinion rather than on solid evidence and are not fundamentally different for critically ill patients with or without AKI. In patients with a functional gastrointestinal tract, enteral nutrition is preferred over parenteral nutrition. The optimal timing of parenteral nutrition in those patients who cannot be fed enterally remains controversial. All nutritional regimens should include tight glycemic control. The recommended energy intake is 20 to 30 kcal/kg per day with a protein intake of 1.2 to 1.5 g/kg per day. Higher protein intakes have been suggested in patients with AKI on continuous renal replacement therapy (CRRT). However, the inadequate design of the trials does not allow firm conclusions. Nutritional support during CRRT should take into account the extracorporeal losses of glucose, amino acids, and micronutrients. Immunonutrients are the subject of intensive investigation but have not been evaluated specifically in patients with AKI. We suggest a protocolized nutritional strategy delivering enteral nutrition whenever possible and providing at least the daily requirements of trace elements and vitamins.

Introduction

Patients with acute kidney injury (AKI) have a high prevalence of malnutrition, a condition that is associated with morbidity and mortality [1]. AKI develops mostly in the context of critical illness and multiple organ failure, which are associated with major changes in substrate metabolism and body composition, overwhelming the alterations induced by AKI itself. Key effectors of these changes are inflammatory mediators and neuroendocrine alterations. The development of AKI further adds fluid overload, azotemia, acidosis, and electrolyte disturbances. In addition, AKI is associated with increased inflammation and oxidative stress [2]. The most severe cases of AKI require renal replacement therapy (RRT), with continuous treatments (continuous renal replacement therapy, CRRT) being the modality of choice in most intensive care

units (ICUs) [3]. These extracorporeal treatments facilitate nutritional support but may, on the other hand, induce derangements of nutrient balances. The rationale for nutrition during critical illness is mainly to attenuate the catabolism and the loss of lean body mass in the hypermetabolic critically ill patient. However, the concept of improving clinical outcome by improving energy and nitrogen balance is still being challenged [4]. The purposes of this paper were to review the metabolic alterations underlying critical illness and AKI, to discuss nutritional and metabolic support in these patients, and to address the nutritional implications of CRRT. The reader is also referred to several other reviews on this subject [5-10].

Metabolic alterations in critical illness and acute kidney injury

Critical illness is generally recognized as a hypermetabolic state, with energy expenditure (EE) being proportional to the amount of stress [11,12]. Although active solute transport in a functioning kidney is an energy-consuming process, the presence of AKI by itself (in the absence of critical illness) does not seem to affect resting EE (REE) [13]. EE in AKI patients is therefore determined mainly by the underlying condition. Studies in chronic kidney disease yield conflicting results varying between increased [14,15], normal [16], or even decreased REE [17].

A characteristic of critical illness is the so-called 'diabetes of stress' with hyperglycemia and insulin resistance. Hepatic gluconeogenesis (from amino acids and lactate) increases mainly due to the action of catabolic hormones such as glucagon, epinephrine, and cortisol. In addition, the normal suppressive action of exogenous glucose and insulin on hepatic gluconeogenesis is decreased. Peripheral glucose utilization in insulin-dependent tissues (muscle and fat) is also decreased [18,19]. Since most patients with AKI also have an underlying critical illness, it is not surprising that the same

AKI = acute kidney injury; CO₂ = carbon dioxide; CRRT = continuous renal replacement therapy; EE = energy expenditure; EN = enteral nutrition; ESPEN = European Society for Enteral and Parenteral Nutrition; ICU = intensive care unit; MOD = multiple organ dysfunction; PN = parenteral nutrition; RCT = randomized controlled trial; REE = resting energy expenditure; RRT = renal replacement therapy.

picture is seen in AKI patients [20]. In normal conditions, the kidney plays an important role in glucose homeostasis, contributing to 15% to 25% of glucose release in the postabsorptive state (mainly gluconeogenesis from lactate and glutamine) and 10% to 20% of glucose uptake [21,22]. Whether the loss of kidney function by itself contributes to the altered carbohydrate metabolism in AKI is not clear. Endotoxin injection in mice provoked a downregulation of the GLUT-2 and SGLT-2 transporters responsible for glucose reabsorption in the convoluted segment of the proximal renal tubule. These pathophysiological changes—if applicable to humans—may further complicate glucose homeostasis during AKI [23].

The most striking metabolic feature of critical illness is protein catabolism and net negative nitrogen balance. The increased protein synthesis is unable to compensate for the higher proteolysis. Major mediators are the previously mentioned catabolic hormones and cytokines and the reduced anabolic influence of growth hormone, insulin, and testosterone [18,19]. In the acute phase, this catabolic response may be beneficial, providing amino acids for hepatic gluconeogenesis (supplying substrate for vital tissues such as the brain and immune cells) and for synthesis of proteins involved in immune function and in the acute-phase response. However, the sustained hypercatabolism in the chronic phase of critical illness results in a substantial loss of lean body mass and in muscle weakness and decreased immune function. In patients with advanced chronic renal failure, acidosis promotes proteolysis by activating the ubiquitin-proteasome pathway and branched-chain keto acid dehydrogenase [24]. Whether this contributes significantly to the catabolism of AKI patients has not been determined. In patients with AKI, (normalized) protein catabolic rates between 1.3 and 1.8 g/kg per day have been noted [25-27]. Protein catabolism will also accelerate the increases of serum potassium and phosphorus that are seen in renal dysfunction.

Changes in lipid metabolism in critically ill patients are ill characterized. The increased catecholamine, growth hormone, and cortisol levels in stress states stimulate lipolysis in peripheral adipose stores. The released free fatty acids are incompletely oxidized (hyperglycemia/hyperinsulinemia exerting an inhibitory effect on lipid oxidation), the remaining being re-esterified and resulting in increased hepatic triglyceride production and secretion in very-low-density lipoproteins [18]. Whether triglyceride levels are increased depends on the efficacy of lipoprotein lipase-mediated lipolysis and tissue uptake of remnant particles which is impaired in severe stress situations [28]. Increased triglyceride levels, an impaired lipoprotein-lipase activity, and reduced clearance of exogenous lipids have also been described in AKI patient populations [29].

Nutritional and metabolic support in critical illness and acute kidney injury

Although there are no large randomized controlled trials (RCTs) investigating the effect of nutritional support versus

starvation in this setting, most ICU patients receive nutritional support in an attempt to counteract the catabolic state. The timing, route, and ideal composition of ICU nutritional support remain a matter of discussion and even official guidelines and consensus statements are not always consistent [30-35]. This is also the case for meta-analyses and systematic reviews [36-39] and is due mainly to the absence of adequately powered randomized trials, the inadequate design of available clinical studies, and the heterogeneity of the patients.

The traditional ICU doctrine is that enteral nutrition (EN) is always better than parenteral nutrition (PN) because 'it keeps the intestinal mucosa active and reduces bacterial translocation' [33-35]. Compared with standard care, EN indeed may reduce mortality [38]. However, meta-analyses comparing EN with PN did not establish a difference in mortality and the lower incidence of infectious complications with EN may be explained largely by the higher incidence of hyperglycemia in patients receiving PN [36,39]. On the other hand, enteral feeding is likely to be cheaper [40-43] and critically ill patients therefore should be fed according to the functional status of their gastrointestinal tractus.

Feeding of critically ill patients should be started early [33-35]. Early nutrition is defined as the initiation of nutritional therapy within 48 hours of either hospital admission or surgery [34,44]. A meta-analysis of early versus late EN showed reduced infectious complications and length of hospital stay with early EN, but no effect on noninfectious complications or mortality [45]. However, enterally fed critically ill patients often do not meet their nutritional targets, especially in the first days of ICU stay [46,47]. Adequate early nutrition is easier with the parenteral route and most of the mortality benefits of PN were indeed established in comparison with late EN [37,48], suggesting that PN should be given to patients in whom EN cannot be initiated within 24 hours of ICU admission [49]. The optimal timing for PN to be initiated is still debated [44,50]. The clinical impact of early versus late PN in addition to EN in critically ill patients is actually being studied in our center (EPaNIC [Impact of Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients] trial [51]).

The optimal amount of calories to provide to critically ill patients is unclear. Overfeeding should be avoided in order to prevent hyperglycemia, excess lipid deposition, azotemia, excess carbon dioxide (CO₂) production with difficult weaning from the respirator, and infectious complications [52-54]. Although not based on solid evidence, recent recommendations suggest a nonprotein energy supply of 25 to 30 kcal/kg per day in men and 20 to 25 kcal/kg per day in women, with the lowest values being used in the early phase and in patients older than 60 years [31,34]. The proposed proportions of nonprotein energy supply are 60% to 70% of carbohydrate and 30% to 40% of fat. Whether caloric intake, adjusted to measured EE, improves outcome remains to be

proven. The gold standard for measuring EE in critically ill patients is indirect calorimetry. It appears to perform better than predictive equations with added stress factors [55,56]. However, the use of indirect calorimetry in critically ill patients also has theoretical and practical limitations. Results may become unreliable due to variations in ventilator settings, air leaks, high FiO_2 (fraction of inspired oxygen), acid-base disturbances, intermittent feeding, diet-induced thermogenesis, absence of a quiet thermoneutral environment, pain, agitation, and so on [57-59]. Its use during CRRT is discussed below.

The results from two recent trials incited renewed interest in hypocaloric feeding, combining normal protein with reduced caloric supply. An RCT showed fewer infectious complications and reduced ICU stay with less aggressive (and markedly hypocaloric) early EN, suggesting that the clinician should weigh the complications of full-target early EN against its benefits [60]. An observational trial, evaluating the consistency of current feeding regimens with existing guidelines, found that caloric intake of between 33% and 66% of the target was associated with better survival [61]. The rationale for hypocaloric feeding is to provide nutrition without exacerbating the stress response. It is, however, evident that this needs to be validated in an adequately powered RCT [62]. The rationale against hypocaloric feeding is that patients receiving less than their REE will inevitably develop negative energy balances [63]. Two observational trials observed an association between a worse clinical outcome and a negative cumulative energy balance [64] or a caloric intake of below 25% of American College of Chest Physicians recommended targets [65].

Nutritional support often results in an aggravation of hyperglycemia, an effect that is more pronounced with PN than with EN [66]. Multiple observational trials in different types of critically ill patients have shown an association between hyperglycemia and morbidity and/or mortality. A cause-and-effect relationship was confirmed in two large prospective randomized clinical trials that have shown an improved morbidity and mortality with tight glycemic control with insulin infusion in fed critically ill patients [67,68]. This treatment strategy also reduced the incidence of AKI [69]. Prevention of glucose toxicity in tissues not depending on insulin for glucose uptake is the proposed underlying mechanism [70,71]. Other metabolic effects were an improved lipid profile [72] and reduced insulin resistance [73]. The beneficial effect of intensive insulin therapy was not confirmed by a recent prospective randomized trial in patients with severe sepsis. However, this study was stopped prematurely because of a high rate of hypoglycemia and therefore was tenfold underpowered [74]. Any nutritional protocol in ICU patients with or without AKI should therefore include tight glycemic control.

Proteins are administered in an attempt to improve protein synthesis and nitrogen balance. Although negative nitrogen

balances are associated with worse outcome, there are no randomized studies comparing different protein or nitrogen intakes with regard to clinical outcomes in ICU patients. Although the ideal amount is still debated [4], a protein intake of between 1.2 and 1.5 g/kg per day (0.16 to 0.24 g nitrogen/kg per day) is usually recommended [19,30,75]. Because many nonessential amino acids are not readily synthesized or increasingly used in critically ill patients, the combination of essential and nonessential amino acids is supposed to be superior.

Role of specific components

Glutamine

Glutamine is the most abundant amino acid in the body and is an important fuel for cells of the immune system. In stress situations, its serum and intracellular concentrations decrease and it becomes a 'conditionally' essential amino acid. Although not all clinical trials show a beneficial effect [76], the available guidelines recommend enteral glutamine supplementation in trauma and burn patients and high-dose parenteral supplementation in general ICU patients receiving total PN [33-35].

Antioxidant micronutrients

Micronutrients (vitamins and trace elements) play a key role in metabolism, immune function, and antioxidant processes. They are deficient in critically ill patients and should be supplemented, although the precise requirements have not been determined. In particular, the antioxidants selenium, zinc, vitamin E, and vitamin C have shown promising effects on infectious complications and/or mortality in ICU patients [77-80]. With the exception of vitamin C, levels of antioxidant vitamins and trace elements are not different in the presence of AKI [81]. Recommended vitamin C intake in AKI varies between 30 to 50 mg/day [82] and 100 mg [6]. Theoretically, the presence of AKI might even increase the potential role of antioxidants. When compared with a group of matched critically ill patients, AKI patients have increased oxidative stress, reflected by lower plasma protein thiol content and higher plasma carbonyl content [2]. A smaller study also confirmed that multiple organ dysfunction (MOD) with AKI resulted in more oxidative stress and a stronger depletion of the antioxidative system than MOD alone [81].

Immunonutrients

Nutrients with an immune-modulating effect, including glutamine, arginine, nucleotides, and omega-3 fatty acids, have been the subject of intensive investigation [83]. Data on immunonutrition in AKI are scarce and the number of patients suffering from AKI on inclusion is not reported in most studies. Arginine is a precursor of nitric oxide synthesis and may be detrimental in critically ill patients with an ongoing inflammatory response [84,85]. Meta-analysis aggregating the results of three RCTs of enteral supplementation of omega-3 fatty acids (fish oil) in patients with acute respiratory distress syndrome demonstrated that enteral formula

enriched with fish oils significantly reduces mortality and ventilator days and tended to reduce ICU length of stay [85]. A role for exogenous omega-3 fatty acids in human renal protection is, at this moment, purely speculative [86].

Others have evaluated cocktails of several immunonutrients. A large RCT ($n = 597$ patients) comparing enteral immunonutrition (containing glutamine, arginine, nucleotides, and omega-3 fatty acids) with standard EN in critically ill patients showed no difference in clinical outcome [87], which was confirmed by a recent meta-analysis [85]. Another clinical trial evaluated an enteral pharmaconutrient cocktail in 55 septic patients, the majority of whom were on CRRT. The primary outcome parameter, the change in sequential organ failure score, improved with the pharmaconutrient, whereas mortality and ICU and hospital lengths of stay were not affected [88].

Recommendations for nutrition during acute kidney injury in the intensive care unit

In ICU patients with AKI, the recommendations for nutritional support are largely the same as for other ICU patients [6,9,82]. We provide an overview of the nutritional strategy during AKI with references to the available evidence (Table 1). Introduction of a nutritional management protocol improved nutrition delivery and clinical outcome in two nonrandomised trials [89,90]. Standardization of PN is suggested by recent guidelines of the American Society for Parenteral and Enteral Nutrition [91]. The European Society for Enteral and Parenteral Nutrition (ESPEN) recommends 0.6 to 0.8 g protein/kg per day in case of conservative therapy, 1 to 1.5 g/kg per day with extracorporeal treatment, and a maximum of 1.7 g/kg per day in 'hypercatabolism' [82]. Possible restrictions to adequate nutrition in AKI are fluid overload (requiring more concentrated solutions), electrolyte disturbances (requiring electrolyte-free solutions), and the increased urea generation associated with a large amount of protein intake. Older and largely underpowered studies showed controversial effects of the addition of amino acids to glucose on mortality and renal recovery [92-94]. Most recent studies on nutritional support in AKI patients have been performed during CRRT and will be discussed in the next section. EN in AKI is, in general, safe, although increased gastric residual volumes have been described in comparison with non-AKI ICU patients [95]. The ability to provide EN is associated with improved outcome [96]. No clinical trials have specifically addressed the effect of immunonutrition in AKI patients.

Nutritional support during continuous renal replacement therapy

CRRT allows unrestricted nutritional support, reaching nutritional targets without the risk of fluid overload and excessive urea levels. The effect of CRRT on EE and protein catabolic rate is probably small and not clinically relevant. A small observational study found no change in REE before and after the start of CRRT [97]. CRRT frequently induces hypo-

thermia, the degree of which correlates with the ultrafiltration rate [98]. This hypothermia represents thermal energy loss [99] but also reduces REE, especially if not associated with shivering [98,100]. Studies by Gutierrez and colleagues in the early 1990s suggested that blood-membrane contact during RRT may induce a protein catabolic effect, an effect that was seen only with cuprophane membrane and not with synthetic membranes [101] and was not reduced by the addition of glucose to the dialysate [102]. Compared with intermittent hemodialysis, the use of CRRT simplifies the calculation of protein catabolic rate [27].

Several studies have evaluated nutritional support during CRRT in AKI patients. Unfortunately, neither of these used clinically relevant outcomes. Fiaccadori and colleagues [103] used a crossover design to compare the combination of 1.5 g protein/kg per day with 30 or 40 kcal/kg per day. The higher energy provision did not improve nitrogen balance, protein catabolism, and urea generation rate but resulted in increased metabolic complications, including hypertriglyceridemia and hyperglycemia [103]. In an observational study using regression techniques, Macias and colleagues [26] showed that high-protein intakes, required to achieve nitrogen balance, may increase protein catabolism, especially if combined with high caloric intake. The authors therefore suggest an energy intake of 25 to 35 kcal/kg per day with a protein intake of 1.5 to 1.8 g/kg per day. Other authors have suggested higher protein intake. An early observational study showed that higher protein input (up to 2.5 g/kg per day) results in a less negative nitrogen balance, but at the expense of higher azotemia and CRRT requirement [104]. The same authors showed positive nitrogen balances in 35% of the patients with protein intakes of 2.5 g/kg per day [105]. Scheinkestel and colleagues [106] randomly assigned CRRT patients to 2 g protein/kg per day or escalating doses (1.5, 2.0, and 2.5 g/kg per day), energy intake being isocaloric in both groups. Protein intake correlated with nitrogen balance, and nitrogen balance correlated with survival, but, surprisingly, protein intake did not correlate with survival. In addition, in contrast to what the title suggests, this is not a randomized trial comparing high- versus low-protein intake [106]. More research, using adequate design and endpoints, is therefore needed before larger protein loads can be recommended in AKI patients on CRRT. The problem is that we do not know the metabolic fate of the administered amino acids that may be used for synthesis of 'beneficial' proteins but that may also be burnt or even join the inflammatory mediator pool.

Nutritional support during CRRT should take into account the extracorporeal losses of nutrients. Most clinical studies on glucose dynamics during CRRT were performed in the early 1990s, often with arteriovenous techniques and low effluent rates in patients receiving PN [107-110]. The net loss or gain of glucose induced by CRRT depends on the balance between glucose losses in the ultrafiltrate and/or effluent

Table 1**Nutritional strategy in patients with acute kidney injury in the Department of Intensive Care Medicine, University Hospital Leuven**

		Reference(s)
Protocolized prescription for artificial nutrition	Caloric target: 24, 30, and 36 kcal/kg protein included, based on age, gender, and corrected ideal body weight. Target and energy provisions of previous day shown in Patient Data Management System. Energy from sources other than PN is included.	[31,34,89,90]
'Early' EN	EN is initiated within 36 hours from admission unless (a) formal contraindication (for example, high gastrointestinal fistula, intestinal ischemia, and high-dose vasopressor) or (b) the patient is starting to eat.	[32,34,45,96]
Progressive increase of EN dose during hospitalization	Day 2: 200 to 500 kcal Day 3: 700 to 900 kcal Day 4: 1,100 to 1,300 kcal Day 5: 1,500 to 1,700 kcal	[60]
PN: according to randomization in ongoing EPaNIC trial	Early PN: within 48 hours of initiation of standard PN to complement EN up to 100% of caloric target, unless patient is starting to eat. Late PN: no PN during the first week after admission on the ICU.	[44,50] [51]
Standardized formulations	Commercially available ready-to-use EN and PN preparations.	[91]
Composition of EN and PN	60% to 70% dextrose, 30% to 40% lipids. Lipids less than 1 g lipids/kg body weight per day. Proteins: 0.8 to 1.2 g/kg body weight per day. No adaptation for acute renal failure and/or CRRT. Use of glucose-containing replacement fluid (physiological concentration) in CRRT.	[4,10,19]
Parenteral lipid restriction	If plasma triglycerides are greater than 300 mg/dL. Lipid-free PN is administered and lipids are added once weekly. Glucose administration in binary PN should not exceed 5 g/kg per day.	[10,29]
Volume and electrolyte restriction	In case of fluid overload, renal replacement therapy will be started rather than PN or EN volume reduced. Concentrated EN is used only during prolonged critical illness with intermittent hemodialysis. Electrolyte-free standard formulations are used on indication.	[6]
Strict glycemic control	All patients in the ICU receive insulin targeted at blood glucose levels of 80 to 110 mg/dL.	[67,68]
Vitamins and trace elements	All patients requiring nutritional support receive recommended daily allowances of parenteral trace elements and vitamins until they receive more than 1,600 kcal standard enteral formulation. During severe hepatic failure, doses of manganese and copper are reduced to once weekly.	[85,123,125] [127]
Immunonutrition	No routine use of enteral or parenteral immunonutrients.	[85]
Frequent monitoring of electrolytes and lactate	Potassium, bicarbonate, and lactate every 4 hours. Sodium, chlorine, magnesium, and phosphorous every 24 hours.	[82,115]

CRRT, continuous renal replacement therapy; EN, enteral nutrition; ICU, intensive care unit; PN, parenteral nutrition.

dialysate and the glucose administered via the replacement fluid or dialysate. Extracorporeal losses can be compensated by the use of physiological levels of glucose in the replacement fluid or dialysate, the ideal level probably being the target level suggested by the randomized trials on tight glycemic control [67,68]. Supraphysiological levels may result in hyperglycemia and should be avoided. 'Modern' CRRT, using higher effluent rates, will accentuate extracorporeal glucose losses that, on the other hand, can be

reduced by tight glycemic control. Assuming a glucose-free replacement fluid, a blood glucose level of 100 mg/dL with a filtration or dialysate flow rate of 2.5 L/hour will result in a daily extracorporeal glucose loss of 60 g or 240 kcal/day, whereas a blood level of 150 mg/dL results in a loss of 90 g or 360 kcal/day.

The metabolic effects of infusing lactate or citrate should also be taken into account [111]. If entirely oxidized, 1 mmol of

lactate can provide 0.32 kcal [112]. Assuming a lactate level of 30 mmol/L in the replacement fluid with a flow rate of 2 L/hour, this would result in a potential energy provision of 460 kcal. Continuous veno-venous hemofiltration, especially if performed with bicarbonate in the replacement fluid, appears to be a risk factor for hypoglycemia [113]. Whether this reflects the higher illness severity of patients receiving bicarbonate instead of lactate or the ability of lactate to serve as a substrate for gluconeogenesis remains to be determined. Compared with bicarbonate, the use of lactate as a buffer in continuous veno-venous hemodiafiltration has indeed been shown to result in higher blood glucose levels and higher glucose turnover [114]. Lactate- or bicarbonate-buffered replacement fluids each induce specific changes in sodium, chloride, magnesium, and phosphate mass balances [115]. The significant extracorporeal phosphate losses may aggravate refeeding hypophosphatemia. Frequent electrolyte monitoring is therefore required [82].

Theoretically, CRRT might also influence metabolic monitoring by inducing extracorporeal loss or gain of CO₂. The net effect depends on the pH of the patient, the use of bicarbonate versus nonbicarbonate buffers, and how fast nonbicarbonate buffers are metabolized to bicarbonate and CO₂. Since the changes induced by CRRT are much smaller and slower than with intermittent hemodialysis, the impact is probably minimal. In addition, changes in VCO₂ (rate of elimination of CO₂) result in much smaller errors in the measurement of EE than changes in VO₂ (oxygen uptake) of the same magnitude [57].

An additional catabolic factor is the extracorporeal loss of amino acids, which appears to correlate directly with the serum amino acid concentration and the effluent rate [116,117]. Sieving coefficients approach 1 except for glutamine that is less efficiently eliminated [117,118]. In trauma patients on continuous hemodiafiltration, daily amino acid losses of between 10 and 15 g have been reported [116]. Others found extracorporeal losses reaching 4.5% to 20% of the daily substitution [105,118-120]. In two studies, glutamine represented 16% and 33% of the total losses, respectively [116,119]. Despite the described losses, the serum amino acid profile does not seem to be affected, suggesting that the losses are small compared with the daily turnover [116,117]. Again, these studies were performed more than 10 years ago and used lower effluent rates than are currently recommended.

Since most lipids circulate as lipoproteins or are bound to albumin, extracorporeal losses are not to be expected. Indeed, only trace quantities of cholesterol and triglycerides have been found in the ultrafiltrate [121].

Water-soluble vitamins and trace elements may be lost during CRRT. Earlier studies are probably less reliable because of the use of less sensitive assays. Markedly different losses of

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selenium have been reported, varying from 'much less than' to 'more than twice' the recommended daily intake [122-125]. Losses of zinc are generally small [122,125,126] and even positive zinc balances (due to the presence of zinc in the replacement solution) have been described [123]. Losses of thiamine may amount to 1.5 times the recommended intake [123], whereas the clinical significance of vitamin C losses remains unclear [122]. The ESPEN guideline states that extracorporeal losses should be supplemented but excessive supplementation may result in toxicity and therefore micronutrient status should be monitored [82].

Conclusion

AKI and critical illness are characterized by a catabolic state, insulin resistance, and altered carbohydrate and glucose metabolism. These changes are provoked by counter-regulatory hormones, acidosis, and cytokines. The contribution of AKI by itself remains difficult to establish. The losses of macronutrients and micronutrients during CRRT further complicate this picture. The optimal nutritional support strategy for patients with AKI requiring CRRT remains a matter of controversy. It should aim at attenuating tissue wasting and reducing the risk for nutrition-related side effects. The heterogeneity of the patients, the complexity of the disease process, and the inadequate design of the available trials preclude firm conclusions. The available recommendations are based more on expert opinion than on solid evidence. In general, the guidelines of general ICU patients can be followed, with modifications for the extracorporeal nutrient losses. Nutrition probably should be protocolized, aimed at EN whenever possible and providing at least the daily requirements of trace elements and vitamins. Augmented doses of energy, carbohydrates, lipids, and proteins as well as pharmacological doses of immunonutrients should be avoided except in the context of adequately powered RCTs until evidence is available. Any nutritional regimen and any future trial on nutrition in critical illness or AKI should be combined with tight glycemic control.

Competing interests

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