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Continuing Medical Education (CME)

Specific nutritional problems in acute kidney injury, treated with non-dialysis and dialytic modalities

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Abstract

Patients who develop AKI, especially in the intensive care unit (ICU), are at risk of protein–energy malnutrition, which is a major negative prognostic factor in this clinical condition. Despite the lack of evidence from controlled trials of its effect on outcome, nutritional support by the enteral (preferentially) and/or parenteral route appears clinically indicated in most cases of ICU-acquired AKI, independently of the actual nutritional status of the patient, in order to prevent deterioration in the nutritional state with all its known complications. Extrapolating from data in other conditions, it seems intrinsically unlikely that starvation of a catabolic patient is more beneficial than appropriate nutritional support by an expert team with the skills to avoid the potential complications of the enteral and parenteral nutrition methodologies. By the same token, it is ethically impossible to conduct a trial in which the control group undergoes prolonged starvation. The primary goals of nutritional support in AKI, which represents a well-known inflammatory and pro-oxidative condition, are the same as those for other critically ill patients with normal renal function, i.e. to ensure the delivery of adequate nutrition, to prevent protein–energy wasting with its attendant metabolic complications, to promote wound healing and tissue repair, to support immune system function, to accelerate recovery and to reduce mortality. Patients with AKI on RRT should receive a basic intake of at least 1.5 g/kg/day of protein with an additional 0.2 g/kg/day to compensate for amino acid/protein loss during RRT, especially when daily treatments and/or high efficiecy modalities are used. Energy intake should consist of no more than 30 kcal non-protein calories or $1.3 \times$ BEE (Basal Energy Expenditure) calculated by the Harris–Benedict equation, with ∼30–35% from lipid, as lipid emulsions. For nutritional support, the enteral route is preferred, although it often needs to be supplemented through the parenteral route in order to meet nutritional requirements.

Keywords: acute kidney injury; catabolism; dialysis; enteral nutrition; parenteral nutrition

Introduction

Acute kidney injury (AKI) is a complex and heterogeneous syndrome occurring in different clinical settings, especially in the intensive care unit (ICU) [1,2]. Its development is now considered an independent risk factor for increased morbidity and mortality [3].

Many definitions have been utilized in the past for the syndrome, making the comparison of studies and populations difficult; thus, an unifying and simplified definition has been recently proposed by a consensus of experts, the Acute Kidney Injury Network (AKIN), accounting for the relevant prognostic impact of even relatively slight increases in serum creatinine levels. On these bases, AKI can be defined as an abrupt (within 48 h) reduction in kidney function with an absolute increase in serum creatinine of either ≥ 0.3 mg/dl (≥ 0.25 μmol/l) or a percentage increase of $\geq 50\%$ or a reduction urine output (≤ 0.5 ml/kg/h for > 6 h) [4]. A grading system for AKI severity stratification in three stages has been also developed [4].

The incidence of AKI is increasing [5], with frequencies of 3–10% observed among hospitalized patients [6], which can rise up to 10–30% in those admitted to the ICU [7]. Up to 5% of the patients with AKI in the ICU usually undergo renal replacement therapy (RRT) [8], the most common indications being azotaemia, hypercatabolism, volume overload refractory to diuretic therapy, electrolyte abnormalities (in particular hyperkalaemia), uraemic complications (such as altered sensorium, pericarditis, bleeding diathesis), severe acidosis, severe acute intoxications, etc. [7].

In the ICU, AKI usually develops in the context of multiple organ failure. Nutrition should be aimed at counteracting and attenuating the negative effects on lean body mass of both catabolism and hypermetabolism associated with critical illness. Thus, adequate nutritional support is considered a key element of overall therapeutic strategy of the syndrome [9]; moreover, it should be carefully integrated with RRT when requested, taking into account both the peculiar metabolic derangements/complications of the

acute uraemic state and the effects of RRT itself on nutrient balance [9–13].

Nutritional status in AKI

Owing to the presence of many interfering factors, such as acute illness, alterations in body water distribution, external fluid balance derangements, etc., the evaluation of nutritional status can be difficult in critically ill patients, especially if AKI is present, and traditional methods in this clinical setting have shown limited sensitivity and specificity [14].

To better characterize the condition of lean body mass wasting and fat mass depletion occurring in AKI, the term 'protein–energy wasting' (PEW) has been recently proposed, along with the recommendation to use four categories of diagnostic criteria: biochemical (such as albumin or prealbumin), body weight loss, decreased muscle mass and low energy and protein intakes [15]; however, further studies are needed, in order to validate the concept of a multidimensional approach to nutritional status evaluation in AKI.

Anyway, PEW seems to be a frequent problem in AKI: as a matter of fact, severe malnutrition, as defined by the Subjective Global Assessment (SGA), can be observed in ∼40% of patients with AKI in the ICU [16]. Many factors are likely to contribute PEW in these patients, including inadequate nutritional support, preexisting poor nutritional status, superimposed catabolic illnesses (sepsis, trauma, surgery, chemotherapy, etc.), acidosis, blood losses, nutrient losses during extracorporeal circulation, etc. [9–13,15,16]; moreover, a key role is thought to be played by specific derangements in metabolic and hormonal pathways, leading to lean body mass catabolism.

Nutritional status is a major prognostic factor in the patients with AKI [14,17]. Severe PEW severely impairs patient's outcome, whether defined in term of length of hospital stay, increased risk of complications (sepsis, bleeding, arrhythmia, respiratory failure, etc.) or increased in-hospital mortality [14]; moreover, in the same study, severe malnutrition was an independent predictor of in-hospital mortality, along with other well-known complications and co-morbidities of AKI [14]. Thus, it is likely that optimizing nutritional status, and preventing nutritional status deterioration, could improve patient outcome.

Goals of nutritional support in AKI

The coexistence of poor nutrient intakes and high catabolic rates is likely to put the patients in negative calorie and nitrogen balance and to worsen nutritional status, therefore exposing them to the negative outcomes associated with severe PEW. Thus, as in other critically ill patients, starvation is not a sensible or ethical option in AKI, and this very fact easily accounts for the lack of/and the difficulty in performing controlled trials of nutritional intervention. The recently defined goals of nutritional support in AKI [12,13] are by large quite similar to those typically indicated for other catabolic critically ill patients (Table 1). It should be

Table 1. Goals of nutritional support in AKI

To prevent protein–energy wasting
To preserve lean body mass and nutritional status
To avoid further metabolic derangements
To avoid complications
To improve wound healing
To support immune function
To minimize inflammation
To improved antioxidant activity and endothelial function
To reduce mortality

taken into account that attaining a positive nitrogen balance with gain in lean mass could be less than realistic in ICU patients with AKI; in this clinical condition, all that can be achieved by nutritional support is to minimize muscle wasting and to preserve as much lean mass as possible. Regain of lean mass with positive nitrogen balance must await convalescence when catabolic stimuli, such as inflammatory and mediators and hormones, have resolved and a combination of food and physical activity can stimulate muscle regeneration.

Metabolic alterations in AKI

AKI is associated with major changes in substrate metabolism and body composition. Both the presence of critical illness and the loss of the kidney homeostatic/metabolic function are the main factors accounting for these relevant metabolic and hormonal derangements [18,19]. AKI in fact is associated with specific changes in protein, carbohydrate and lipid metabolism, combining together to cause a general disruption of the 'internal milieu': catabolism of skeletal muscle proteins with increased amino acid turnover and negative nitrogen balance, hyperglycaemia and insulin resistance, altered lipid metabolism, water, electrolyte and acid–base metabolism unbalances [19].

The kidneys are an important site of gluconeogenesis and insulin metabolism, thus participating in glucose homeostasis [20]. It follows that the loss of this homeostatic component may further aggravate glucose metabolism derangements associated with critical illness, through dysregulated inflammation, increased oxidative stress and worsening insulin resistance [1].

As a matter of fact, in experimental models of AKI, the acute loss of renal function is associated with accumulation of oxidation and nitration free products in the plasma [21]. Patients with AKI have unbalanced pro- and anti-inflammatory responses, with raised levels of both pro- and anti-inflammatory cytokines, which is independent of the presence of sepsis; these changes are significantly associated with an increased risk of death [22]. Finally, oxidative stress-related gene polymorphisms, associated with higher levels of nitrogen oxidative species, also predict an adverse outcome in this clinical condition [23].

Insulin resistance is common in patients with AKI and the severity of hyperglycaemia correlated with mortality [20]; this association remains significant even after adjustments for age, sex, race, previous diabetes status, severity of

Table 2. Factors involved in the pathogenesis of protein catabolism in AKI

Inadequate supply of nutrients
Uraemic toxins
Endocrine factors
   Defective response to insulin (insulin resistance)
   Increased secretion of catabolic hormones (glucagon,
     catecholamines, glucocorticoids, etc.)
   Resistance to and/or decreased/suppressed secretion of
     growth/anabolic factors
Critical illness/acute phase reaction/systemic inflammatory response
   (cytokines)
Metabolic acidosis
Proteases (ubiquitine–proteasome system, etc.)
Loss of nutritional substrates by renal replacement therapy

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illness, plasma cortisol levels, severity of AKI and nutritional status.

Even though it is intuitive that tight glycaemic control could improve some of the metabolic changes in critically ill patients with AKI, no data are currently available showing that tight glycaemic control with insulin, particularly during nutritional support, has the same positive effects on mortality and morbidity reported in the case of surgical or medical critically ill patients [24–26]. Moreover, hypoglycaemia could be more frequently observed during intensive insulin therapy in AKI: kidney failure requiring dialysis was in fact an independent risk factor for the development of hypoglycaemia [24], probably because 30% of insulin catabolism occurs in the kidney [24].

Protein metabolism is altered in experimental models of uncomplicated AKI [19]: catabolism is increased [27], protein degradation/release from skeletal muscle is increased early, along with depressed protein synthesis [28–30], transport and intracellular concentrations of amino acids in the skeletal muscle are altered [31], amino acid extraction from plasma, hepatic gluconeogenesis and urea production are increased, while the synthesis of protein, apart from visceral and acute phase proteins, is inhibited [9,18] and finally urea synthesis is upregulated in experimental AKI, probably as a result of changes in gene expression [32].

In clinical conditions, AKI is not always associated with increased catabolism, and in critically ill patients with AKI, when present, protein catabolic state is often multifactorial (Table 2). Whatever the pathogenetic factors are, in most cases this catabolic state cannot be simply counteracted by artificial nutrition, although this may attenuate the net rate of body tissue loss [18].

In human AKI, both plasma and intracellular components of the amino acid pool are altered, and tissue utilization of exogenously infused amino acids is impaired; in fact, amino acid oxidation is stimulated, but amino acid transport into muscle is reduced [18,33,34]. Serum amino acid concentrations such as phenylalanine, methionine, taurine and cysteine are elevated, whereas serum valine and leucine are decreased; finally, several non-essential amino acids (e.g. tyrosine, arginine) become conditionally essential and phenylalanine conversion to tyrosine becomes inadequate [18,33,34]. Plasma concentration of glutamine is low in patients with AKI [35].

Plasma levels of triglycerides and very low-density lipoprotein (VLDL) levels are increased in patients with AKI, while those of total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) are decreased [36]. Impaired lypolysis is the most important cause of plasma lipid changes [37], the activity of both peripheral lipoprotein lipase and hepatic tryglceride lipase being reduced by ∼50% in AKI [36–38]; moreover, lipoprotein lipase activity is inhibited if acidosis coexists [39].

Fat clearance following parenteral administration of lipids is reduced in AKI. Metabolism of commercially available fat emulsions is similar to that of endogenous VLDL; thus, in AKI clearance of lipid emulsions is slowed, especially when the administration rate is high [36]. In spite of the reduced rate of clearance of exogenous lipid particles from plasma, fatty acid oxidation is preserved in AKI, and lipids are a key energy substrate in AKI, as suggested by the low respiratory quotient measured in this clinical setting [40].

Nutrient requirements in AKI

Carbohydrates, proteins, lipids

As generally observed in the critically ill [41,42], also in patients with AKI energy expenditure seems to depend more on the severity of the underlying disease, pre-existing nutritional status and acute/chronic comorbidities, than on the presence of the syndrome itself [12,13,43,44]; energy expenditure measured by indirect calorimetry rarely exceeds 1.3 times the basal energy expenditure (BEE) calculated by the Harris–Benedict equation, corresponding to 20–25 non-protein kcal/kg/day [12,13].

The optimal protein intake of AKI patients is ill defined: as protein catabolic rate (PCR) in this clinical condition varies from 1.4 to 1.8 g/kg/day [34], an intake of at least 0.25 g of nitrogen/day is required to achieve less negative or nearly positive nitrogen balance. Evidence from RCTs concerning advantages of very high protein intakes in critically ill patients with AKI is lacking. With 2.5 g/kg/day of protein and 35 kcal/kg/day of energy, only one-third of patients achieved a positive nitrogen balance [45]; in a cross-over study on AKI patients receiving an isocaloric regimen—in most cases through EN—nitrogen balance was positively related to protein intake, with a positive nitrogen balance being more likely to be obtained with intakes >2 g/kg/day (0.3 g nitrogen/kg/day) [46]. However, in many patients with AKI, hypercatabolism cannot simply be overcome by increasing protein or amino acid intake much above 0.25–0.3 g nitrogen/kg/day, even when energy intake is optimal. It is likely that above this level of nitrogen intake any further increase contributes nothing to protein synthesis, simply increasing urea production. Both EEA and NEAA are recommended in AKI, since a higher provision of EEA only does not appear to be advantageous [12,13]. No data are currently available for other specific amino acids, e.g. glutamine.

Nutritional support is able to significantly increase amino acid levels in AKI patients [35,47].

Protein and amino acid losses through the extracorporeal circulation of RRT can be quantified as ∼0.2 g amino acids/l of ultrafiltrate (up to 10–15 g amino acids per day), and 5–10 g/day of protein [12,13,35,48]; in order

to compensate for these losses, especially when high-flux filters and/or highly efficient modalities (such as CRRT or SLED) are used, the protein intake should be increased by ∼0.2 g/kg/day.

For relatively non-catabolic AKI patients with the milder nonoliguric forms of the syndrome not needing RRT and who are likely to regain renal function in a few days (drug toxicity, contrast nephropathy, etc.), lower protein intakes (up to 0.8 g/kg/day) will suffice for short periods of time, combined with adequate calorie intakes (30 kcal/kg/day) [12,13,18].

The optimal energy to nitrogen ratio has not been clearly defined in patients with AKI. In an observational study of patients on CRRT, less negative or weakly positive nitrogen balance values were predicted by linear regression analysis models when protein intakes of 1.5 g/kg BW/day were provided in parallel with non-protein energy intakes of ∼25 kcal/kg BW/day; simply increasing the calorie to nitrogen ratio in this study was not invariably associated with better nitrogen balance [49]. With a protein intake of 1.5 g/kg/day, an increase in energy provision up to 40 kcal/g/day did not improve nitrogen balance compared with lower energy intakes (30 kcal/kg/day); instead, more severe metabolic complications (hypertriglyceridaemia, hyperglycaemia) ensued [50].

Lipids should represent ∼30–35% of total nonprotein energy supply [12,13]. In the case of parenteral nutrition, this can be obtained by giving the patient 0.8–1.2 g/kg/day of lipid from 10 to 30% lipid emulsions or as a part of the commercially available three-in-one total nutrient admixtures. Lipids should be infused over 18–24 h, and serum tryglicerides should be monitored, stopping lipid administration when tryglicerides exceed 400 mg/dl. Even though the use of parenteral MCT may result theoretically in lower serum triglyceride levels because of faster oxidation rate, pharmacokinetic studies failed to show any clear advantages, in terms of plasma clearance of trygliceride, of the mixed MCT/LCT lipid formulas compared with LCT only emulsions [36]. Lipid losses through the filters do not occur during haemodialysis or haemofiltration.

Trace elements, vitamins and electrolytes

Levels of trace elements (essential micronutrients with regulatory, immunologic and antioxidant functions) can be lower than normal in AKI [9,50–53]. This can be due to many factors: acute phase reaction/critical illness, leading to variable protein binding, redistribution of elements between plasma and tissues, acute losses of biological fluids, dilution, varying concentrations of trace elements in dialysis/haemofiltration fluids, effects of enteral or parenteral nutrition fluid, analytical problems, etc. Moreover, RRT fluids (dialysis fluid or sterile solutions for fluid replacement in the case of haemofiltration) may have variable content of trace elements, at concentrations often difficult to detect; finally, the effects of RRT on the removal of mainly protein-bound trace elements are far from being clearly defined. Data from *in vitro* studies indicate that selenium, chromium, copper and zinc can be removed from plasma by convective/diffusive RRTs [54]. In the clinical setting, CVVH is associated with reduced plasma selenium and zinc

but high chromium levels; there was a little loss of the former two elements in the ultrafiltrate, whereas considerable losses of chromium and copper were observed [51]. Zinc was detected in effluent fluid in CVVHDF, but zinc balance was nonetheless positive, owing to the zinc content of PN and replacement fluid solutions, and its presence as a contaminant of the anticoagulant solution (trisodium citrate). These sources when combined exceeded the losses due to CRRT [53,55]. In contrast, the association of convection and diffusion in CVVHDF was associated with selenium losses [55], regardless of the buffer solution used, resulting in a daily negative balance equivalent to twice the daily intake from standard formula parenteral nutrition fluids [53]. Thus, patients with AKI are at risk of trace element depletion; however, the precise requirements have not been clearly defined.

In ICU patients with AKI, plasma levels of water-soluble vitamins, such as vitamin C, thiamine and folic acid, may be lower than normal [51,56], due mainly to the losses occurring through the extracorporeal circuit: in CVVH vitamin C losses can reach up to 600 µmol/day, i.e. 100 mg/day, and folate losses up to 600 nmol/day [51–56]; in CVVHDF thiamine losses may amount more than 1.5 times the daily provision of the vitamin from standard total parenteral nutrition solutions [53]. While in experimental AKI, plasma retinol levels are increased, in clinical conditions serum levels of vitamin A and vitamin E can be decreased [12,13,18]; the risk of hypervitaminosis A and vitamin A-related toxicity seems to be increased in paediatric patients with AKI receiving artificial nutrition, especially parenteral nutrition [57]. The activation of vitamin D_3 is impaired in AKI [12,13,18].

Recommended vitamin C administration in patients with AKI is 50–100 mg/day; higher intakes (up to 150–200 mg) may be needed when continuous modalities of RRT are used. No supplementation of fat-soluble vitamins is usually necessary in AKI.

Derangements in fluid, electrolyte and acid–base equilibrium, such as hypo- and hypernatraemia, hyperkalaemia, hyperphosphataemia, metabolic acidosis, etc., commonly occur in critically ill patients with AKI. Intensive (daily) RRT can readily correct these abnormalities by appropriate regulation of the composition of haemodialysis/haemofiltration fluids and of the intensity of RRT. The highly efficient modalities of RRT often induce hypophosphataemia and hypomagnesaemia, abnormalities that can be prevented by adequate electrolyte supplementation.

Effects of nutritional support on patient outcome in AKI

Due to the heterogeneity/complexity of the syndrome, and to major methodological flaws in the available studies, the advantages of nutritional support in AKI remain controversial, especially in highly catabolic patients, and nor are there clear indications about the optimal timing of artificial nutrition. Studies published during the 1980s analysed the effect of parenteral nutrition on mortality, but they are largely underpowered. In one retrospective study [58], parenteral nutrition was associated with better outcome, while in the other three prospective studies [59–61] no survival advantage was demonstrated. However, such

studies were methodologically flawed also by due to suboptimal selection of patients, population heterogeneity, lack of stratification for severity of illness, nutritional status, RRT dose received, use of historical controls, quantitative and qualitative inadequacy of caloric and nitrogen intake, etc. In a prospective trial assessing calorie and protein needs of critically ill anuric patients requiring CRRT, nitrogen balance was positively related to protein intake and more likely to be attained with protein intakes of >2 g/kg/day [46]. Similar data were obtained in a group of patients with milder forms of nonoliguric AKI [62].

Negative nitrogen balance has been associated with worse ICU and hospital outcomes in AKI patients receiving mixed nutritional support (enteral plus parenteral) [46]; in the same study, the use of the enteral route had a statistically significant advantage in terms of outcome. Enteral nutrition was also associated with a positive outcome in a large observational cohort of AKI patients in the ICU [3].

There is sparse and indirect evidence suggesting that amino acids might favour the recovery of renal function. Intravenously or enterally administered amino acids increase renal plasma flow and glomerular filtration rate in animals and in normal subjects [62,63], and GFR can improve moderately following an amino acid load in chronic renal failure [64,65]. However, the information available on the possible beneficial effects of amino acids in patients with AKI is scarce. In one experimental study, enteral nutrition (EN) was superior to parenteral in this respect [66]. A positive effect of a high amino acid parenteral regimen on renal function in terms of diuresis preservation and water balance has been suggested recently in patients with nonoliguric forms of AKI [67].

Indications for nutritional support and route of feeding in AKI

The indications for nutritional support in AKI are not quite different from those established for the other critically ill patients [41]. In the same way, also in this clinical setting the route of feeding depends more on gastrointestinal tract (GI) function than on the presence of the syndrome itself. Thus, in AKI the enteral route should be the first choice for nutritional support if the GI tract is functioning, while parenteral nutrition should be reserved when GI tract cannot be used, or when EN appears inadequate to reach nutrient intake goals [68].

Renal failure can impair gastrointestinal motility [15]. Apart from AKI itself, other factors commonly present in critically ill patients are known to impair GI function, e.g. medications such as sedatives, opiates or catecholamines; hyperglycaemia; electrolyte disorders; mechanical ventilation, etc. Finally, AKI is a well-defined risk factor for upper-gastrointestinal bleeding [69]; it is uncertain whether enteral nutrition has any protective effects on this risk.

Enteral nutrition is safe and effective in AKI, even though data are scanty. No evidence was found that AKI is associated with a consistent increase of gastrointestinal, mechanical or metabolic complications during enteral nutrition in an observational study on 182 patients with AKI, receiving either a standard formula or a disease-specific formula for patients with renal failure on haemodialysis [68]. High gastric residual volumes were the most frequent side effect. Underdelivery of targeted energy intakes due to enteral nutrition-related complications was rarely observed. Although standard enteral formulae are adequate for the majority of critically ill patients with AKI, the use of disease-specific (renal) formulae designed for patients with chronic renal failure may afford some advantage, due to their high energy (2 kcal/ml) and protein content (70 g/l) and low electrolyte levels [68]; however, even with the most suitable disease-specific enteral formulae, parenteral supplementation of amino acids is likely to be required in order to meet the targeted nitrogen requirement.

In patients with AKI in the ICU, the combination of enteral and parenteral feeding allows successful nutritional support in most cases [46]: thus, the two routes of nutritional support are to be considered complementary and not mutually exclusive [12,13].

Standard formulae for parenteral nutrition (amino acids solutions and commercial three-in-one nutrient admixtures) containing both essential and non-essential are to be preferred in AKI on RRT. In some patients, three-in-one nutrient admixtures without electrolytes (i.e. without sodium, potassium, etc.) are now commercially available, and can be used with caution and careful monitoring or customized according to patient needs. Whether immune enhancing diets should be given to AKI patients remains unsettled.

For short time periods, peripheral PN can be used in AKI patients, according to fluid restriction needs and calorie/protein goals. Due to the need of fluid restriction and the high osmolarity of more concentrated commercial three-in-one admixtures, parenteral nutrition in AKI patients, especially those in the ICU, must be infused in a central vein [12,13].

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