Critical Care

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The kidney: the critical organ system for guiding nutrition therapy in the ICU-patient?

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Abstract

Most randomized controlled studies on nutrition in intensive care patients did not yield conclusive results or were neutral or negative concerning the primary endpoints but also in most secondary endpoints. However, there is a consistent observation that in several of these studies there was a negative effect of the nutrition intervention on the kidneys in one of the study arms. During the early phase and in unstable periods during further course of disease an inadequate clinical nutrition can damage the kidneys, can elicit or aggravate acute kidney injury and/ or increase requirements of renal replacement therapy (RRT). This relates to total energy intake, glucose intake/hyperglycemia and protein/ amino acid intake at various stages of renal dysfunction. The kidney could present a critical organ system for guiding nutrition therapy, a close monitoring of kidney function should be observed and nutrition therapy may need to be adapted accordingly. The long-held dogma of performing full nutrition and accept an otherwise not necessary RRT is definitely to be refuted.

Keywords Nutrition, Critically ill, Kidney function, Acute kidney injury, Individual adaptation

Introduction

The major large randomized controlled studies (RCTs) on nutrition in intensive care patients in recent years unfortunately, have not been able to show any beneficial effects of various nutritional interventions, were neutral or negative concerning the primary endpoint. What is further noteworthy, however, and previously not analysed is the fact that in several of these studies there were consistent negative effects on the kidneys or in patients with ongoing acute kidney injury (AKI) in one of the study arms (Table 1).

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These renal complications either were not reported or were not observed in all available RCTs on nutrition in critically ill patients. This discrepancy may at least in part be based on differences in the start of nutrition (in the unstable early acute phase or later on, due to time losses in randomization and inclusion), in the starting dose and the speed in the build-up of nutrition therapy.

These observations underscore the fact that inappropriate clinical nutrition may damage the kidneys, induce injury in the presence of normal renal function, worsen AKI in presence of an ongoing injury and increase an otherwise not necessary need for renal replacement therapy (RRT). This is particularly relevant in the early acute phase of disease and in unstable periods during the further course in the ICU and relates to various aspects of nutrition, the energy intake, as well as glucose/ insulin and amino acid or protein intake respectively.

Evolving kidney injury and an increased RRT requirement exert fundamental consequences for the further course of disease, the evolution of complications and impairment of short- and long-term outcome in critically ill patients [1]. Thus, close monitoring of kidney function

Table 1 Randomized-controlled nutrition studies in critically ill patients reporting a difference in renal secondary endpoints (for specifics see text)

Study/ Akronym/ Pub-Year First author	Main rationale of the study	Reported renal outcome (secondary endpoint)
PermiT Study 2015 Arabi YM [2]	Early permissive underfeeding vs. full nutrition	Higher rate of AKI requiring RRT in full nutrition
Intensive Insulin therapy 2001/ 2008, secondary analysis Schetz M. [13]	Normoglycemia vs. liberal glucose control	Higher rate of AKI during hyperglycemia
TGC-Fast Trial 2023 Gunst J. [15]	Normoglycemia vs. liberal glucose control without parenteral nutrition	Higher rate of AKI and RRT-requirement during hyperglycemia
Nephroprotective Trial 2015 Secondary analysis Zhu R. [28]	High vs. low amino acid intake and renal function	Lower risk of AKI, need of RRT and mortality if no baseline renal injury with high dose amino acids
REDOXS-Trial 2013/ 2015 Secondary analysis Heyland DR. [32]	High dose glutamine vs. placebo	Higher mortality of AKI-2–3 not requiring RRT with high dose glutamine
EFFORT *Protein* Trial 2023 Heyland DR. [33]	High vs. low protein intake	Higher mortality of AKI not requiring RRT with high protein intake
EPaNIC Study, 2011/2013 Secondary analysis Gunst J. [37]	Early vs. late parenteral nutrition	Higher rate of AKI and longer requirement of RRT in early parenteral nutrition

in the acute phase or during unstable periods of disease and adaptation of nutrition therapy accordingly are mandatory in the metabolic care of the critically ill to avoid renal side effects and associated complications thereof.

Energy intake

The PermIT study was one of the first large RCTs to examine an early "isocaloric" diet (covering the calculated energy expenditure) with early "permissive malnutrition" with the same protein intake in intensive care patients [2]. Nutritional goals were not achieved in both groups (46% vs 71%). There was no difference in the primary endpoint, 90-day mortality and most secondary endpoints. However, the rate of AKI requiring RRT (AKI-RRT) was significantly increased in the group with higher energy intake.

A meta-analysis focusing on the question of "higher versus low energy intake" identified 5 studies reporting renal endpoints and came to the conclusion that a lower energy intake in intensive care patients is associated with a reduced the risk of developing AKI-RRT [3]. Whether this advantage is only limited to the early acute phase of disease could not be answered in this analysis.

These results were not confirmed in all studies., to mention two of them. In the TARGET trial comparing an energy dense (1.5 kcal/ml) with a standard enteral diet (1.0 kcal/ml) in intensive care patients [4]. Delivered were 23.1. vs. 15.6 kcal/kg actual body weight; there was not difference in the need of RRT. This however, was not a study on the early phase of illness, the build-up was adapted individually within a time frame of 7 days.

The Nutrera-3 Study also compared a higher (22.0 kcal/kg/BW/day) versus a lower (7.4 kcal/kg/BW/ day) energy intake, this time in ventilated intensive care patient with shock [5]. The 90-day mortality was not different, but there was reduction in the time to be discharged from the ICU (both primary endpoints). In the lower energy group, there were fewer gastrointestinal complications, a lower rate of liver dysfunction and interestingly, a faster decrease in organ failure score (SOFA) but the need for RRT was similar between groups.

One can only speculate about the causes of a potential negative impact of high energy intake on the kidneys. In earlier times of "hyperalimentation", when very high energy intake rates were recommended, in addition to hepatomegaly, nephromegaly was observed. To what extent this metabolic overload can also to fatty infiltration of the kidneys ("fatty kidney"?) and lead to renal damage remains to be shown [6].

To summarize this point, a high energy intake during the early acute phase of disease when endogenous substrates are released besides causing various other serious side effect and complications potentially can also induce renal injury [7].

Caloric restriction prior to a renal insult is a preconditioning measure that protects the kidney in animal experiments [8] and potentially also in humans [9]. However, this concerns the period of time before renal injury and does not reflect the metabolic situation and the nutritional management of the intensive care patient.

Glucose and insulin

A much-debated point regarding the kidney and nutrition therapy in general is the importance of hyperglycemia. Numerous experimental studies have shown that hyperglycemia impairs endothelial structure and function, promotes inflammation, and can increase but also trigger renal damage [10, 11]. In the first large RCT on

"intensive insulin therapy", the rate of AKI-RRT was reduced by lowering blood sugar concentration [12]. This renoprotective effect was confirmed in a secondary analysis of two RCTs from the same working group [13].

However, this beneficial effect could not be proven in all follow-up studies. The NICE-Sugar study found no difference in the evolution of AKI or the need for RRT [14]. Nevertheless, the difference in blood sugar concentration between the intervention group (around 120 mg/dl) and the control group (around 145 mg/dl) in this trial was so small that an important effect could hardly be expected.

A recent other study on intensive insulin therapy to achieve normoglycemia in critically ill patients, the TGC-Fast Trial, included 9230 patients without early parenteral nutrition (PE) and assigned to a tight (blood glucose 80–110 mg/dl, 4608 patients) and liberal glucose group (insulin therapy to maintain blood glucose between < 215 mg/dl and > 180 mg/dl; 4622 patients) [15].

The actually achieved mean blood sugar concentration in the liberal group was around 140 mg/dl, versus 107 mg/dl in the tight glucose control group so that, as in the aforementioned NICE Sugar study the difference between groups was low and again no pronounced effects were to be expected. The primary endpoint (length of ICU stay, and 90-day mortality as safety endpoint) and most secondary endpoints were not different. However, there was a clear trend toward a lower 90-day mortality for neurological/neurosurgical diagnosis in normoglycemic patients. The most interesting aspect was the observation that the rate of AKI and the need for RRT was significantly reduced in the lower glycemia group.

Although the importance of reducing hyperglycemia as an element of an "AKI bundle" in the prevention of renal dysfunction has recently been challenged [16], all relevant national and international societies have made a strong recommendation in lowering blood sugar in acute care patients < 180 mg/dl (10 mmol/l) [17]. Since the blood sugar concentration fluctuates throughout the day, some groups recommend a target value of 150 mg/dl in order to remain safely below 180 mg/dl over time [18].

Because the blood sugar concentrations were not very different between the groups in various trials, the question arises what actually is responsible for a renoprotective effect, the lowering of blood sugar or rather the higher insulin infusion. In a follow-up analysis of the data from the first RCT on intensive insulin therapy, it was suggested that the beneficial effects in terms of reducing mortality, critical illness polyneuropathy, infections and inflammation were associated with the reduction of blood sugar levels, the reduced rate of AKI however was rather related with higher insulin infusion [19]. However, a secondary analysis of the first two Leuven RCTs and an animal study by the same working group showed that glucose lowering and not insulin infusion protected the kidney against damage [20, 21].

Nevertheless, PN certainly requires a slightly higher insulin dose to achieve the desired reduction in blood sugar. If enteral nutrition is not possible there may be nothing wrong with starting PN given the common practice of a start at a low dose and a slowly increase in an individually adapted nutrition therapy [22].

In summary, both a reduction of glucose load and/or avoiding hyperglycemia rather than a higher insulin dose may help to avoid kidney injury during nutrition therapy.

Protein or amino acid intake

The most controversial point concerns the optimal level of protein or amino acid intake in relation to kidney function. Possible effects can be either protective or inert, but also harmful and these completely different effects may depend—and this is a crucial point—on the stages of AKI.

In healthy but not in injured kidneys, a high protein or amino acid intake leads to an increase in renal perfusion and glomerular filtration, which is referred to as renal reserve capacity [23]. Whether this physiological reaction can be exploited to prevent or treat AKI is the subject of extensive discussion. A first small pilot study in 14 patients only showed that nutrition with an amino acid intake of 150 g/day compared to 75 g/day in intensive care patients increased blood urea concentrations but led to a mitigated increase in serum creatinine, an increase in diuresis and a reduction in the need for diuretics [24].

A larger Australian RCT evaluated a similar intervention (supplement of up to 100 g amino acids i.v. or standard care (NephroProtective Trial) [25]. Groups unfortunately were unbalanced with the amino acid group being sicker and having a higher rate of kidney dysfunction at baseline. The primary outcome, the duration of renal function was not different but estimated glomerular filtration rate (eGFR) and diuresis were significantly better with the higher amino acid administration in the first few days. In the amino acid group there was a trend to a higher need in RRT (9.56 vs. 5.5%, $p = 0.062$).

An isolated infusion of amino acids immediately after heart surgery (total 100 g of amino acids/ day until discharge of the ICU), resulted in a significant improvement in eGFR, increased urine output and a shorter duration of AKI [26]. Also in this study there was a trend for a higher need of RRT, not significant because of the low number of events.

These results were confirmed in a recent large RCT, the PROTECTION study in which 2 g/kg/day of amino acids or placebo were infused for three days [27]. The risk of developing of stage of AKI-1 and especially AKI-3 was significantly reduced in the amino acid group but the

need of RRT was not affected. One has to stress that this is an isolated intervention independent of nutrition therapy in perioperative patients with baseline normal renal function in whom renal reserve capacity can be recruited by an increased amino acid infusion.

Particularly important in the context of nutrition is a secondary analysis of the aforementioned Nephro-Protective study [28]. In this analysis the effect of an increased amino acid administration associated with nutrition therapy in critically ill patients was separately compared in patients with normal baseline kidney function and those with impaired kidney function or a high risk of functional impairment. In patients with initially normal kidney function, this intervention was associated with an increased eGFR and remarkably, also with an improved 90-day survival rate, but this was not the case in patients with impaired kidney function.

This discrepancy between the possible protective effects of an increased protein or amino acid intake in an undamaged kidney and an aggravation of injury in a previously damaged kidney was referred to by RA Zager as the "amino acid paradox" and was demonstrated in animal experiments already several decades ago [29]. In a porcine model of septic shock an amino acid infusion actually decreased renal blood flow and GFR [30].

These untoward renal effects of a high protein or amino acid intake in critically ill patients with baseline kidney dysfunction were confirmed in two large RCTs. In the REDOXS study (a hardly physiologic high) glutamine administration of 0.73 g/kg/day independent from nutrition therapy was compared with placebo [31]. Hospital and 6-month mortality were significantly increased in the glutamine group. A secondary analysis of this study showed that the administration of this single amino acid in such a high dose led to a significant increase in mortality in those patients who had pre-existing kidney dysfunction (OR 95% CI 3.8 (1.9–9.0) [32].

In a recent large RCT, the EFFORT *protein* study a very high, again hardly physiologic protein intake of 2.2 g/kg/day given independent from energy intake was compared with a protein dose currently recommended by European Guidelines (1.2 g/kg/day) [17, 33]. Actually, provision of 1.6 vs. 0.9 g/kg/day were achieved only. Neither the primary endpoint (hospital discharge alive) nor the secondary endpoint (60-day mortality) was different between groups. However, an increased mortality was found in patients with AKI at baseline and those patients with a high organ failure score (SOFA score > 9).

In a post hoc analysis of this study these effects of high protein intake in patients with baseline AKI were reported in more detail [34]. Combining AKI patients with AKI stages 1–3, mortality was increased by 40%, even with the actually achieved protein intake of 1.6 g/kg/day. If the patients were already on a kidney replacement modality (AKI-RRT), no effect on survival was seen.

A further obvious reason why in addition to potential specific toxic effects exerted by protein intake on the kidneys is the increase in urea production during exaggerated amino acid/protein intakes and thus, augmentation of the need of RRT in critically ill patients. This is due to a reduced urea clearance and also augmented urea formation because of the inability to suppress endogenous proteolysis by exogenous substrates, the anabolic resistance in the acute disease states. This was seen in several investigations and also found in the much-cited EPaNIC study from 2011, which compared PN started early versus later [35]. There was a significant difference of being discharged earlier life from the ICU and also from hospital, but no differences in mortality. In a large number secondary endpoints there was a reduced rate of infections, of cholestasis, a trend towards a lower incidence of AKI ($p < 0.06$) and a reduced duration of RRT in the late PN-group [35, 36].

A secondary analysis of this study demonstrated that in the first two weeks 63% of the parenterally supplied amino acids actually, are not utilized anabolically, but are broken down into urea (anabolic resistance) [37]. This increased amount of urea production required an otherwise not necessary RRT, which had to be started earlier or had to be carried out over a longer period of time. Similarly, in the EAT-ICU study comparing immediate full nutrition ("early goal directed nutrition") with standard of care a non-significant trend towards a higher need for RRT was observed and this in spite of the fact, that protein intake was reduced in patients with kidney dysfunction (urea > 20 mml/l) [38].

A secondary analysis of the REDOXS study suggested an association of an increased urea-to-creatinine ratio induced by the higher nitrogen load is associated with an increased risk of death [39]. Similarly, a further secondary analysis of the EFFORT *protein* study (RE-EFFORT) showed that a twofold rise in serum urea was associated with an increased mortality at 30 days [40]. Thus, in contrast to earlier assumptions that toxicity of urea is rather low, a large range of potential direct and indirect toxicities of urea have been described recently [41].

To summarize this point, it must be stated that the optimal protein or amino acid intake depends on the stage of renal injury. In the case of normal kidney function and possibly also in the risk stage AKI-1, a higher intake could potentially even have a protective effect, although the current evidence certainly, does not allow a general recommendation. In contrast, in the damage stages AKI-2 and AKI-3, a lower intake must be observed to avoid aggravation of renal injury [36].

Thus, in the early acute phase of disease a high but also a "normal" protein intake is associated with a broad pattern of untoward side effects beyond suppressing autophagy [7, 42]. Since this is an ongoing discussion, there are currently no clear recommendations on the optimal dose of protein in these unstable stages of critical illness (maximum 0.3 to 0.6 g/kg/day?). In stable AKI patients on RRT in accordance with international recommendations a higher protein intake can be given to compensate for therapy-associated amino acid losses although solid evidence is lacking (1.2 to max. 1.5 g/kg/day) [43].

Clinical implications

AKI is a crucial organ dysfunction in the critically ill patient, about 60% of ICU patients will experience AKI, in about 50% of these patients AKI is developing during the stay at the ICU [44]. AKI at all stages has a fundamental effect on the further course of disease, the evolution of complications, the short- and long-term outcome [45]. Mortality in patients with AKI requiring RRT remains to be excessively high (>60% in most studies). Metabolic factors can play a major role in prevention of renal injury but as the analysis of the studies discussed here has illustrated also in eliciting or aggravating renal injury and increasing requirement of RRT with all the evolving negative consequences thereof.

When the kidneys are healthy and/ or at risk, it is all about prevention, whereby a wide variety of metabolic / nutritional factors should be taken into account [46, 47]. In AKI- stages 2 and AKI-3 without RRT, the aim is to mitigate and not to aggravate this damage by excessive nutrition therapy (energy intake, protein intake, glucose intake/hyperglycemia). When kidney replacement therapy has become necessary, then it is a matter of ensuring sufficient nutrition and compensating for therapy-related losses and adapting for increased intake of energy substrates, such as propofol or citrate [43].

There is no "nutrition for AKI", we have to take into account the different stages of AKI, which require completely different nutritional approaches, as detailed recently [46, 47]. The for decades long-held dogma of maintaining a full diet at all stages of kidney dysfunction and accepting RRT if necessary is definitely to be refuted. Moreover, in the meanwhile, the complex side effects of extracorporeal kidney replacement modalities have been described extensively [48]. Initiation of an otherwise not necessary RRT due to a wrongly guided nutrition therapy will have a broad pattern of detrimental consequences on the further course of disease and outcome.

An early build-up of full nutrition during the acute phase of critical illness when mobilization of endogenous substrates (glucose, amino acids, fatty acids) is increased is associated with a broad range of serious negative side effects in addition to suppressing autophagy and ketogenesis [49, 50]. The start of nutrition at a low dose and an individually adapted increase of intake is generally accepted practice nowadays [51, 52].

Unfortunately, we have no really good indicators for this highly individualized build-up of nutrition [53]. Certainly, we have to consider the hemodynamic situation (vasopressor requirement, blood lactate concentration), the gastrointestinal tolerance (in the case of enteral nutrition) but unfortunately, very few metabolic factors such as insulin requirements and plasma phosphate concentrations. As our analysis underscores, this individual adaptation of the build-up of nutrition may need to integrate also the renal situation. In an unstable patient with rising creatinine, a full ("isocaloric") nutrition should be avoided. This however, concerns not only in the early acute phase but—a rarely addressed point—also recurrent unstable periods during the further course of disease.

To this end a close monitoring of kidney function in the acute phase and during unstable situations in the further stay is mandatory and nutrition may need to be adapted accordingly. Monitoring of renal function must encompass alterations of serum creatinine, the kinetics of plasma urea concentrations during nutrition therapy and urinary output. In this context, biomarkers might have the potential to differentiate reversible kidney dysfunction from ongoing tubular injury but appropriate studies are still lacking.

Conclusion

Overzealous nutrition support during the acute phase but also during unstable phases in the further course of critical illness can damage the kidneys, cause AKI or increase ongoing renal injury and may necessitate an otherwise not required RRT with all its well-documented serious side effects. The several decades old dogma of performing full nutrition and accept an otherwise not necessary RRT is definitely to be refuted. The kidney is an extremely sensitive organ system that should be crucial for guiding clinical nutrition in critically ill patients. A close monitoring of kidney function during unstable situations and adaptation of nutrition accordingly should be mandatory, the concept of a "kidney tolerance" principle may be observed in the individualized nutrition therapy of the critically ill patient.-

Availability of data

The datasets generated and/or analysed is extracted from existing studies.

Competing interest
The authors declare no competing interests.

Consent for publication
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