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Micronutrient and amino acid losses in acute renal replacement therapy

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Abstract

Purpose of review

A wide range of renal replacement therapies is now available to support patients with acute kidney injury. These treatments utilize diffusion, convection or a combination of these mechanisms to remove metabolic waste products from the bloodstream. It is inevitable that physiologically important substances including micronutrients will also be removed. Here we review current knowledge of the extent of micronutrient loss, how it varies between treatment modalities and its clinical significance.

Recent findings

Very few studies have specifically investigated micronutrient loss in renal replacement therapy for acute kidney injury. Recent data suggest that trace elements and amino acids are lost during intermittent dialysis, hybrid therapies such as sustained low efficiency diafiltration and continuous therapies. Extent of micronutrient loss appears to vary with treatment type, with continuous convection based treatments probably causing greatest losses.

Summary

Patients with acute kidney injury are at high risk of disease related malnutrition. The use of renal replacement therapy, while often essential for life support, results in loss of micronutrients into the filtrate or dialysate. Losses are probably greater with continuous convective treatments, but it is not yet known whether these losses are clinically significant or whether their replacement would improve patient outcomes.

Key Words

Acute kidney injury, renal replacement therapy, haemofiltration, sustained low efficiency diafiltration, SLEDf, micronutrients

Introduction

Renal replacement therapy (RRT) is required as a supportive treatment in the management of patients with severe acute kidney injury (AKI). A range of RRT modalities is available, each able to remove metabolic waste products and correct acid-base abnormalities. In oliguric patients, RRT is also important in achieving fluid balance. RRT modalities vary in two basic parameters: (i) duration of treatment, from intermittent to continuous and (ii) mechanism of solute clearance: diffusion, convection or a combination of the two. The goal of RRT is to remove unwanted molecules from blood, but of course diffusion and convection will also remove physiologically important molecules such as micronutrients. The extent of such losses will depend on the physical properties of the molecule in question and the clearance mechanism of the RRT modality. Despite this potential negative aspect of RRT, there has been remarkably little research in the area. This is of particular concern given the high risk of malnutrition in patients with AKI and critical illness.

Acute Kidney Injury

AKI is characterized by an abrupt decline in kidney function over hours or days, resulting in retention of metabolic waste products and dysregulation of fluid, electrolyte and acid-base homeostasis. AKI is a common complication of critical illness and is associated with high mortality rate and increased length of hospital stay for survivors. AKI is also associated with other adverse patient outcomes, such as development or worsening of chronic kidney disease (CKD) and progression to end stage renal disease (ESRD). AKI is a syndrome rather than a diagnosis in itself. It can be caused by a wide

variety of conditions, but most fall into one of the following categories: (i) renal ischaemia (including hypovolaemia, haemorrhage and hypotension), (ii) sepsis, (iii) nephrotoxins. There is now reasonable international consensus on the definition of AKI based on increase in serum creatinine or fall in urine output over specified time. Three similar classification systems have been published over the past 10 years: RIFLE, AKIN and KDIGO (see [1]* for a recent discussion of AKI definition).

Malnutrition in AKI and critical illness

There is a high prevalence of disease related malnutrition (DRM) in critically ill patients with AKI, which has been identified as an independent predictor of mortality in this group [2]. Risk of DRM is high because of (i) reduced intake (due to anorexia, malabsorption and reliance on enteral or parenteral prescription), (ii) metabolic changes, particularly increased catabolism and (iii) increased losses (gastrointestinal, other bodily fluids and losses from RRT). There are far more published studies of nutritional status in ICU patients than specifically of patients with AKI requiring RRT, though the latter subgroup will share most nutritional risk factors of the former as well as having others specific to RRT. A recent comprehensive review of nutrition in critical illness was provided by Casaer and Van den Berghe [3]**.

Plasma levels of some micronutrients are affected by the systemic inflammatory response syndrome (SIRS). In many cases the plasma or serum level of a micronutrient will not represent the overall body status of that substance because of redistribution between body compartments. Selenium, for example, is a trace element important in the

body's response to the oxidative stress of critical illness, essential to the functioning of the antioxidant glutathione peroxidase. Plasma selenium levels have been demonstrated to be low in critically ill patients and are reported to correlate with increased mortality. Ghashut et al [4] investigated the effect of systemic inflammation on plasma selenium and zinc levels and demonstrated that their levels were each independently associated with CRP and albumin. They concluded that low plasma levels do not necessarily reflect true deficiency in the context of SIRS, but that deficiency can be inferred in the presence of normal CRP and serum albumin. Stefanowicz et al [5]* also concluded that plasma concentrations of selenium, zinc and copper were primarily influenced by systemic inflammation rather than a reflection of nutritional status. They measured plasma and erythrocyte levels of these trace elements in 125 patients admitted to ICU with SIRS. Iglesias et al [6]* studied 173 children admitted to ICU and also noted that both malnutrition and elevated CRP were associated with low plasma selenium, providing further caution about interpretation of plasma selenium levels.

In some cases, activity of trace element-dependent enzymes may offer a more accurate means of determining tissue trace element status. Combs reviewed biomarkers of selenium status in considerable detail and discussed markers of intake, retention, tissue levels and function [7]*. Activity of the glutathione peroxidases GPX1 (in erythrocytes) and GPX3 (extracellular) may reflect selenium tissue status but interpretation of results is again complex because of genetic variation in enzyme activity. Furthermore, assaying enzyme activity is likely to be of use only in states of selenium deficiency, rather than being able to stratify higher levels of tissue selenium. Biomarkers of copper status are probably even less adequate. Danzeisen et al reviewed this subject in 2007 [8]. It was

known then that plasma copper does not reflect copper status, nor do cuproproteins such as ceruloplasmin (which may reflect severe depletion but does not stratify adequate or excessive levels). The cuproenzymes superoxide dismutase (SOD) 1 and 3 have proved to be poor biomarkers of copper status but the copper chaperone for SOD (CCS) has some advantages. Further discussion of biomarkers of micronutrient status is beyond the scope of this review but there is a parallel between these and novel AKI biomarkers. There has been considerable clinical and commercial interest in each of these fields over the past 10 years, with numerous candidate biomarkers but none fulfilling its early promise so far.

Similarly, urinary levels of micronutrients do not seem to provide reliable information about overall status of a given micronutrient. In some cases urinary levels reflect recent intake but in many cases not even that, because of numerous confounding factors affecting urinary excretion. For example, Fukuwatari and Shibata demonstrated that, for 8 out of 9 water soluble vitamins that they tested, 24-hour urinary excretion correlated with intake [9]. Knowledge of urinary excretion of micronutrients in health and disease-related malnutrition is important when considering whether losses from other routes, including RRT, are likely to be excessive and clinically relevant.

Renal Replacement Therapy in AKI

In modern renal and intensive care units, a wide range of RRT types is available for supporting patients with AKI, varying in duration of therapy and mechanism of solute removal. The two most commonly used techniques lie at opposite ends of the spectra

for both duration and clearance mechanism. Intermittent haemodialysis (IHD) is a diffusion-based treatment where blood and dialysate flow countercurrent at relatively high pump speeds, separated by a semipermeable membrane, usually in the form of thousands of synthetic capillaries within the dialyser. It is used for a few hours daily or on alternate days. Continuous veno-venous haemofiltration (CVVH) is convection based, with solutes being removed with filtrate as a consequence of pressure being applied across the capillary membrane within the haemofilter. Physiologically appropriate replacement fluid is required, in view of the relatively large volume of filtrate lost. In principle, the process continues without interruption for >24 hours. RRT techniques are now available which cover most of the possible permutations of duration and clearance mechanism including 'hybrid' treatments such as sustained low efficiency diafiltration (SLEDf), which is used typically for 8-12 hours daily and utilizes both diffusion and convection. It is essentially slow dialysis (i.e. slow blood and dialysate pump speeds) with an element of filtration in addition.

There is ongoing debate about which RRT modality is best, but in terms of hard outcomes such as mortality and renal recovery after AKI, there is not yet any convincing evidence that any one modality is superior. A recent review of RRT in AKI by Ronco et al addresses some of the options and controversies [10]*. In practice, choice of RRT modality is usually influenced by local facilities and experience. IHD is used predominantly in renal units and continuous RRT (CRRT) methods such as CVVH predominantly in intensive care units. CRRT is usually favoured in the presence of hypotension or haemodynamic compromise. A recent survey of RRT use in general adult ICUs in the United Kingdom demonstrated highly variable practice, reflecting the

lack of evidence to support RRT prescription for AKI [11]. Peritoneal dialysis (PD) is rarely used to treat AKI in developed countries where extracorporeal RRT methods are widely available, but is sometimes used in children and occasionally in adults where there are significant problems with vascular access or haemodynamic stability.

Micronutrient loss in CRRT

Diffusion based RRT (dialysis) in general is more efficient at clearing small molecules, whereas larger molecules are removed by convective treatments, up to a point, depending on pore size of the haemofilter membrane and solute size. For example, hyperkalaemia is treated more efficiently with IHD than CVVH because potassium is a small cation and diffuses down a concentration gradient (from blood to dialysate) quickly. In contrast, some inflammatory mediators such as cytokines are more likely to be removed by CVVH, but would be too large for effective removal by diffusion. The same principles apply when considering loss of micronutrients during RRT. In practice, losses are more difficult to predict because of the wide range of RRT modalities now available and the complex interaction of associated variables such as pore size and thickness of the dialysis (or haemofilter) membrane, pump speed for blood and dialysate, proportion of plasma water removed (filtrate). Diffusion based treatments will also involve a degree of convection if fluid is removed during the treatment, so it is difficult to compare pure diffusion with pure convection in a clinical study.

Very few published studies have quantified micronutrient losses in RRT for AKI and all, so far, have involved low numbers of patients. Few have compared micronutrient losses

between RRT modalities or investigated losses in newer hybrid treatments such as SLEDf. In general, nutritional status of patients with CKD including ESRD has been studied far more extensively than nutritional status of patients with AKI. The same applies to studies of micronutrient loss in RRT, with far more data available for ESRD. These data may be of some use in formulating hypotheses for losses in RRT for AKI, but should be treated with caution. AKI and ESRD are very different conditions, with different metabolic profiles and nutritional problems; ideally they should be studied independently. Amino acid losses from CRRT in patients admitted to ICU have been investigated occasionally in small studies over the past 25 years. The interest relates to concerns about negative nitrogen balance in critically ill patients, as a contributing factor to malnutrition. Btaiche et al [12] reviewed 8 small studies conducted between 1991 and 2003 involving different types of CRRT (3 studies included the outdated technique of continuous arterio-venous haemofiltration, CAVH). Most of the studies included fewer than 10 patients, but they did demonstrate that all types of amino acid were cleared in the filtrate, that losses correlate with serum amino acid levels and with clinical condition (e.g. greater losses with cardiogenic shock). CVVH resulted in 30-40% greater losses than continuous veno-venous haemodialysis (CVVHD, diffusion-based, with very low blood and dialysate pump speeds). More recently, Umber et al [13] quantified amino acid losses in 5 critically ill patients treated with sustained low efficiency dialysis (SLED, a diffusion-based treatment). They reported amino acid losses comparable to those previously reported for CVVH, with a median loss of 15.7g per treatment.

Such small and dated studies need to be interpreted with caution, but the results appear generally consistent with preliminary data from a relatively large study from our group in Nottingham. We have completed recruitment of 72 patients requiring RRT for AKI and investigated losses of amino acids, trace elements and B-vitamins. We compared losses between 3 types of RRT: CVVH, SLEDf and IHD i.e. a continuous convective treatment, an intermediate-duration convective and diffusion-based treatment and an intermittent diffusion-based treatment, respectively. Data have been published only in abstract form so far but demonstrate significant losses of amino acids and trace elements, greatest in CVVH [14]*. We are not aware of any other recent adequately sized studies that have investigated losses of trace elements or water soluble vitamins in RRT for AKI. Kosmadakis et al [15]* published a detailed review of vitamins in dialysis for ESRD, including discussion of roles, requirements and losses from treatment. Shaban et al [16] have also recently reviewed measurement of vitamins and trace elements in ESRD; Filler and Felder [17] reviewed trace elements in the context of children requiring chronic dialysis and recommended regular assessment of 9 different trace elements, though the evidence to support this is currently sparse and the population reviewed is very different from critically ill adults with AKI.

Replacement of micronutrients

Demonstrating deficiency of micronutrients in patients with AKI is clearly not the same as demonstrating a clinical benefit from supplementation. Indeed many micronutrients are potentially toxic in excess or in certain circumstances e.g. plasma catalytic iron (i.e. circulating iron not bound to transferrin or other proteins) levels appear to be associated with increased risk of AKI, RRT and mortality in patients admitted to ICU

[18]*. Whether this association is causative is not clear. Glutamine supplementation has been a controversial subject in intensive care medicine for several years. It has been considered a 'conditionally essential' amino acid in critically ill patients, on the basis that, with muscle wasting, glutamine production might not meet increased requirements for important roles such as immune cell functioning. Low glutamine levels have been associated with poor outcome in critical illness, but well-designed randomized controlled trials have not shown any benefit of glutamine supplementation [19, 20]. In fact the REDOXs study [20] suggested that early high dose (parenteral and enteral) glutamine supplementation was harmful. A post-hoc analysis revealed that 28 day mortality was significantly higher only in the subgroup of patients receiving glutamine supplementation who had baseline renal impairment but did not receive RRT [21]*. The inclusion of a relatively large proportion of patients with renal impairment in this study contrasted with most of the previous studies investigating glutamine supplementation in critical illness and might explain in part the different results. The parenteral glutamine supplement used in this study was the synthetic dipeptide L-alanyl-L-glutamine, which the manufacturers suggest should not be used where GFR is less than 25 mL/min, because of the possibility of aggravation of uraemia. A recent review of the subject concluded that supra-physiological doses of glutamine should not be given to critically ill patients with multi-organ failure including low GFR [22]. It remains unclear how glutamine supplementation should be used optimally, in terms of timing, dosing and patient subgroups.

Various other non-renal ICU based studies have failed to demonstrate benefit of micronutrient supplementation. Landucci et al [23] undertook a systematic review of 9

RCTs investigating selenium supplementation in critically ill adults and suggested a possible albeit rather unconvincing beneficial effect on 28 day mortality. Despite lack of data to support routine micronutrient supplementation, macro- and micronutrients are often routinely administered intravenously in the acute phase of critical illness on the basis that the benefits, such as reducing risk of refeeding syndrome, are likely to outweigh the risks. For those patients with AKI requiring RRT, it is not known whether additional micronutrient supplementation to compensate for RRT losses improves outcomes. It is routine practice to prescribe regular supplements of water soluble vitamins to patients with ESRD receiving regular haemodialysis, but even in this more extensively studied group, there is little evidence of improvement in hard outcomes such as mortality [24, 25*].

Conclusion

Patients with severe AKI requiring RRT have a high risk of disease related malnutrition. True deficiency is difficult to assess in the case of many micronutrients because blood levels may not represent overall body status. There is evidence that micronutrients are lost in effluent (dialysate or filtrate), which might be anticipated from knowledge of the physical properties of the molecules and the mechanisms of their clearance. These losses have been quantified to some extent in a few small studies, mostly involving CVVH. One ongoing relatively large study is seeking to compare micronutrient losses between 3 commonly used RRT modalities. It is likely that certain micronutrients might be lost during RRT by adsorbing to the haemofilter rather than by filtration, but this mechanism has not been studied adequately to date. Two far more important questions remain unanswered: (i) do these micronutrient losses result in clinically significant

consequences and (ii) would replacement of calculated losses, perhaps tailored to individual patients and RRT modalities, result in improved outcomes? Large well designed clinical trials will be required to answer these questions. Considering the high risks of mortality and morbidity associated with severe AKI, and the huge costs to the health service [26]** it is surprising that nutrition research in AKI has attracted so little interest to date.

Key points

- Renal replacement therapy is a route of micronutrient loss in patients with acute kidney injury
- The extent of micronutrient losses varies with the type of RRT
- It is not yet clear if these losses are clinically significant and whether they should be accounted for when calculating a patient's nutritional requirements

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