CHAPTER 73

Impact of Renal Replacement Therapy on Metabolism and Nutrient Requirements in the Critically Ill Patient

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OBJECTIVES

This chapter will:

1. Explain the impact of several modalities of renal replacement therapy on metabolism and nutrient balances.
2. Describe the effect of extracorporeal circuits and different types of anticoagulation on the inflammatory state of the patient.
3. Teach how to minimize these side effects and adapt nutrition therapy to compensate therapy-associated changes in nutrient requirements.

Renal replacement therapy (RRT) modalities are following a primary metabolic aim, that is, the alleviation of the manifold consequences of uremic intoxication. Nevertheless, all types of RRT, intermittent and continuous treatment modalities, are associated with a broad spectrum of additional, mostly untoward effects on metabolism and nutrient balances that often are neglected.[1,2]

Knowledge of the additional effects of extracorporeal treatment modalities on metabolism and nutrient balances is relevant in the care of critically ill patients because they can be associated with serious complications and have fundamental implications for designing nutritional programs for patients.[3,4] (The specific alterations of metabolism and the nutrition of patients with acute kidney injury [AKI] are covered in Chapter 78.)

Please Note: All modalities of renal replacement therapy are associated with clinically relevant losses of nutrients and electrolytes, which have to be regarded in the care of these patients.

INTERMITTENT RENAL REPLACEMENT THERAPY, INTERMITTENT HEMODIALYSIS, HEMODIAFILTRATION, AND SLOW-EFFICIENCY EXTENDED HEMODIALYSIS

Intermittent RRT modalities (iRRT) continue to present standard treatment modalities in the care of patients with AKI. Also in the ICU these modalities are preferred in stable AKI patients and during the rehabilitation phase of the critical illness.

During the last decade also "semicontinuous" modalities with prolonged treatment periods at low blood flow rates, such as slow-efficiency extended hemodialysis (SLED) (also called extended daily dialysis, or EDD, e.g., the GENIUS machine) are used increasingly in the intensive care unit (ICU).

Metabolic Effects of Hemodialysis Modalities

All iRRTs obviously are not specific types of therapy that eliminate uremic toxins only from the bloodstream, but also all other substances that are water soluble and have a low molecular weight (Box 73.1). Thus iRRT modalities are associated with relevant losses of various nutrients and electrolytes.

Amino acids with a mean molecular weight of about 145 D are eliminated effectively during hemodialysis (HD).[5] Amino acid loss is affected by the type of membrane used, the treatment modality (HD vs. hemodiafiltration [HDF]), and blood flow. However, a general rule is to assume a loss

BOX 73.1

Metabolic Side Effects of Intermittent Hemodialysis, Slow-Efficiency Extended Hemodialysis, and Hemodiafiltration

Loss of water-soluble molecules:
- Amino acids
- Water-soluble vitamins
- L-carnitine, etc.

Electrolyte derangements (hypophosphatemia)
Induction of an inflammatory reaction/ release of cytokines (IL-1ß,TNF-α, etc.)
Activation of protein catabolism
- Loss of amino acids
- Loss of proteins and blood
- Inflammatory state
- Increased formation of reactive oxygen species

of about 2 g/hr of treatment, which may be increased by about 30% with the use of modern high-flux membranes.[6,7] Furthermore, the loss of about 4 g amino acids, which is associated with the elimination of small peptides must be added. During SLED an amino acid loss of about 1 g/hr of treatment has been reported.[8–10]

Depending on the transmembrane pressure and the use of membranes with higher molecular cutoffs (and especially with "super-flux" membranes), a relevant elimination of albumin can occur. Filter clotting and the obligatory residual blood remaining in the extracorporeal circuit after termination of intermittent hemodialysis (iHD) treatment can result in additional losses of proteins (and blood).

During iHD relevant amounts of water-soluble vitamins are eliminated.[11,12] As has been shown for vitamin C, in addition to diffusive losses during iHDF, convective losses contribute to the elimination of vitamins.[13]

This is especially relevant for ICU patients with preexisting malnutrition and reduced vitamin stores. Thiamine presents a crucial factor in energy metabolism, and iHD-induced losses can cause serious and even life-threatening complications, such as lactic acidosis and neurologic injury (see below, Metabolic Effects of Continuous Renal Replacement Therapy Modalities).[14,15] Carnitine also is eliminated during iHD, the relevance of which has not been assessed in acutely ill patients with AKI.

Most dialysate solutions for HD are designed for the therapy of chronic iHD patients and thus are phosphate free. Patients with AKI are at risk of developing hypophosphatemia, and this is augmented during iHD. Patients with AKI who develop hypophosphatemia during iHD may develop serious complications, such as weaning failure, and have a worse prognosis.[16]

Metabolic side effects during HD, however, are caused not only by the loss of various substances. Originally shown in investigations with sham HD treatments, the extracorporeal HD circuit induces—depending on the biocompatibility of the membrane used—an activation of protein catabolism.[17,18] This is mediated mainly by the induction of an inflammatory reaction and the release of inflammatory mediators. This activation of protein catabolism persists several hours after termination of HD treatment. Intracellular mRNA of cytokines in skeletal muscle is upregulated also for several hours.[19] Thus, iHD therapy induces an inflammatory reaction and is a catabolic event.[18,20]

In addition, it was demonstrated that during iHD there is an increased formation of reactive oxygen species (ROS).[21] This is caused not only by the losses of nutritive antioxidants, such as vitamin C, but also by generation of ROS by the bioincompatibility of the extracorporeal circuit and the interaction of blood and artificial surfaces and in the bubble trap.[22]

In critically ill patients with AKI a profound depression of the antioxidant system is present, which is implicated as a leading mechanism in the pathophysiology of tissue injury and organ dysfunction.[23] iHD can contribute to this pro-oxidative state. The loss/increased metabolic use of antioxidants increases nutrition requirements of antioxidative compounds.[13]

Taken together, many of the untoward side effects of iHD are present also when using modern, more biocompatible membranes and tubing systems and can be attributed to the obligatory phenomena of bioincompatibility. iHD induces an inflammatory reaction, which, together with the hemodynamic stress induced by iHD and its consequences for microcirculation, is associated with the induction of protein catabolism and the cardiopulmonary side effects and potential tissue injury. Last, this increases the risk of developing infections by impairment of immunocompetence. Whether anticoagulation with heparin may contribute to this pattern of side effects and whether this potentially can be mitigated by the use of citrate anticoagulation remains to be shown (below, Metabolic Effects of Continuous Renal Replacement Therapy Modalities).[24]

Therapeutic Implications

The most important implication of this broad spectrum of side effects of iHD concerns nutrition therapy. Therapy-associated losses have to be considered when designing a nutrition program and be compensated by an increased intake.

Amino acid intake should be increased by 0.2 g/kgBW.[3] The intake of water-soluble vitamins should be increased to twice the recommended daily allowance (RDA) (i.e., 2 ampoules of a multivitamin preparation/day).[25]

Plasma phosphate must be monitored during therapy, and phosphate must be substituted as required. In patients not on nutrition support, intradialytic parenteral nutrition may be considered to improve nutrition state. Intradialytic nutrition can reverse the catabolic event hemodialysis into an anabolic situation.[26]

However, also from a metabolic perspective, the practice of iHD has to be adapted to the ICU patient, to minimize hemodynamic instability and hemodynamic microcirculatory stress and to improve biocompatibility (potentially also by the modification of anticoagulation).

METABOLIC EFFECTS OF CONTINUOUS RENAL REPLACEMENT THERAPY MODALITIES

In critically ill, hemodynamically unstable, ventilated ICU patients in whom it is difficult to maintain a desired fluid balance, continuous renal replacement therapy (CRRT) usually is employed. Because of the continuous mode of therapy and the currently recommended dose of therapy (dialysate/filtration volumes), these modalities exert a profound effect on metabolism and nutrient balances and are prone to the development of metabolic side effects and serious complications[1] (Box 73.2).

BOX 73.2

Metabolic Side Effects of Continuous Renal Replacement Therapies

Loss of heat (= loss of energy)
(excessive) intake of substrates (= of energy)
(lactate, citrate, glucose)
Loss of nutrients
(amino acids, vitamins, trace elements, L-carnitine, etc.)
Loss of electrolytes (phosphate, potassium, magnesium)
Elimination of peptides/ proteins
(albumin, hormones, mediators)
Metabolic consequences of bioincompatibility
(Induction of an inflammatory reaction; activation of mediator-cascades, stimulation of protein catabolism)

Heat Loss

Modern machines for CRRT have integrated heating systems by which the temperature of substitution fluid /dialysate can be adapted as required and heat balance can be modified. But also the use of those modern systems for CRRT is associated with heat loss, depending on the dose of therapy and filtration volume.[27] Thus, during CRRT, body temperature is usually reduced.

This therapy-induced hypothermia can be desired (in the case of high fever, multiple organ dysfunction syndrome [MODS], and hemodynamic instability) and induce beneficial effects (i.e., reduction of oxygen consumption, improvement of hemodynamics, reduction of protein catabolism, mitigation of inflammation and tissue injury). However, this hypothermia potentially also can induce untoward effects, such as a disturbance of immunocompetence and increase in infections and impairment of wound healing.

Glucose Balance

Substitution fluids/dialysates for CRRT should have a glucose concentration of 100 to 180 mg/dL to maintain a zero glucose balance.[28,29]

The use of glucose-free substitution fluids cannot, as sometimes erroneously assumed, improve metabolic glucose control in ICU patients who exhibit insulin resistance. The glucose eliminated from the body (depending on the filtration volume, up to 40 to 80 g/day) in this situation must be considered when calculating energy requirements and substituted by an increased intake with nutrition.

Solutions with a high glucose concentration, as solutions designed for peritoneal dialysis, which are used in some countries, should not used for CRRT. The use of these solutions is associated with an excessive intake of glucose.[29] Furthermore, the mode of anticoagulation (use of anticoagulant citrate dextrane [ACD] for citrate anticoagulation 25 g/l glucose) can affect glucose balance during CRRT.[30]

Lactate, Acetate, and Citrate Intake

Acetate-based substitution fluids should no longer be used for CRRT because of the well-described negative side effects of acetate in ICU patients and, especially, its hemodynamic consequences (i.e., vasodilation, impairment of myocardial contractility).[31]

Many substitution fluids for CRRT contain as organic anion L-lactate. This certainly is an acceptable practice for many patients. Clinicians must be aware of the fact that, depending on the infusion/filtration volume, the use of these solutions is associated with a high infusion of L-lactate and thus increased energy intake.

This lactate uptake during CRRT can become relevant in two clinical contexts: (1) when metabolism of lactate is massively impaired, such as in liver failure or sepsis, or (2) in those situations in which endogenous lactate formation is augmented, such as in hemodynamic shock or septic shock. In these conditions the use of lactate-containing solutions can increase plasma lactate concentrations and should be avoided.

Many institutions prefer lactate-free substitution fluids based on bicarbonate. These solutions can contribute to an improvement of hemodynamic stability during CRRT.[32]

Anticoagulation using citrate for CRRT has become standard in many ICUs, either by using concentrated citrate solutions or by addition of citrate to the substitution fluid (serving as organic anion and anticoagulant).[33] The metabolic use of citrate is not impaired in renal failure.[34]

Energy intake associated with citrate is dependent on the type of citrate anticoagulation and the solutions used and by the ratio of infusion/filtration, because a considerable part of citrate (and citrate calcium complex) is eliminated during therapy. The energy gain from citrate can account for about 400 kcal/day.[30] When citrate anticoagulation is performed when using lactate-containing substitution fluids, this additional energy intake can add up to more than 1200 kcal/day. This combination should be avoided for CRRT.[35]

Electrolyte Derangements

Please Note: Patients on CRRT are at an increased risk of developing electrolyte derangements. In addition to the concise observation of fluid balance, CRRT requires a close monitoring of plasma electrolyte concentrations and electrolyte balance.

The high fluid turnover associated with modern CRRTs and the continuous mode of therapy increase the risk of inducing derangements of electrolyte balance. Even in clinical studies on RRT the rate of electrolyte derangements is unacceptably high.[36,37] Thus CRRT require a tight monitoring of plasma concentrations of electrolytes. In many patients additional infusions of phosphate, potassium, and magnesium may become necessary.

During CRRT plasma water is filtered, which has a sodium concentration of approximately 146 to 150 mmol/L and thus is higher than in plasma or whole blood. With the use of most available substitution fluids a negative sodium balance is achieved, and this can contribute to hyponatremia, an electrolyte derangement that often is present in ICU patients.[38]

Phosphate elimination during CRRT can cause hypophosphatemia and intracellular phosphate depletion, which are associated with many potentially life-threatening complications. Among these, prolonged mechanical ventilation, difficulties in the weaning, increase in infections, and an impaired prognosis of critically ill patients have been reported.[39,40] Initiation of nutrition support can increase the risk of inducing hypophosphatemia ("refeeding syndrome").[41,42]

Until recently most substitution/dialysate fluids for CRRT have been phosphate free. To prevent the evolution of hypophosphatemia, phosphate has to be substituted in most patients. This can be achieved either by separate phosphate infusions, or preferentially by adding phosphate

to the substation fluids (about 1 mmol/L). Recently, several phosphate-containing substitution fluids have become available, which will reduce the risks of phosphate depletion during CRRT.[43]

Citrate as anticoagulant is complexing not only calcium but also magnesium. Several available substitution fluids are magnesium free, and thus magnesium has to be supplemented in many patients.[44] Some institutions use concentrated calcium plus magnesium for antagonizing citrate in the venous line during citrate anticoagulation.

The potassium concentration of various substitution fluids is inadequate to maintain stable plasma concentration and potassium has to be supplemented as required.

Please Note: Hypophosphatemia evolving during CRRT is a dangerous complication and must be regarded as a type of malpractice! Monitoring of electrolytes is an essential component in the care of CRRT patients.

Loss of Nutrients

Depending on the molecular weight, protein binding and plasma concentration of substances CRRT are associated with the loss of various nutrients. Depending on the mode and duration of therapy, the dose employed and the type of membranes used the losses reported in various studies are highly variable.

Because of the low molecular weight (mean MW, approximately 145 D) and the water solubility free amino acids (AA) are eliminated during CRRT. Because the sieving coefficient for amino acids is approximately 1, losses during postdilution hemofiltration correspond to the mean plasma concentration of amino acids (about 0.25 g/L) multiplied with the filtration volume.[3] Depending on the dose of therapy/filtration volume, this loss can account for 8 g to 16 g AA/day.[45,46] Continuous hemodialysis and continuous hemodiafiltration are associated with an amino acids loss of comparable magnitude.[46,47]

Glutamine is the amino acid with the highest plasma concentration. Because of electrochemical properties glutamine losses are even higher than expected from the plasma concentration (sieving coefficient > 1) and can account for up to 5 g/day.[48,49]

Nutrition therapy provided during CRRT does not increase amino acid losses substantially. Endogenous clearance of amino acids is approximately 100 times higher than the exogenous clearance.[3] However, when excessive amounts of amino acids are infused (recommended by some groups up to 2.5 g AA/kg/day), plasma concentrations of amino acids will rise and thus also the elimination of amino acids is increased.

During CRRT water-soluble vitamins also are eliminated effectively from the body. Specifically, this has been demonstrated for vitamin C, folic acid, and vitamins B_1 and B_6.[50,51] For example, thiamine deficiency can be induced during CRRT, with associated derangements of energy metabolism, lactic acidosis, and severe neurologic impairment.[14] Thiamine deficiency mostly remains unnoticed but certainly presents the most important, potentially life-threatening micronutrient deficiency state in critically ill patients.[15]

Regarding the loss of trace elements, it has been shown that selenium is eliminated during CRRT in relevant amounts (>50 μg/day, i.e., two times the RDA).[52,53] There is no generally accepted consensus on the optimal selenium supplementation in ICU patients with AKI. In consideration of the therapy-associated losses, an intake of 300 to 600 μg/day during the first treatment days seems to be a reasonable approach. Reports on elimination of other trace elements, such as zinc, copper, and chromium, are conflicting.[54]

Elimination of Peptides and Short-Chain Proteins ("Mediators")

Convective transport during hemofiltration is characterized by an identical clearance of all molecules up to a molecular size, which is determined by the pore size of the filtration membrane. This "cutoff" of modern synthetic membranes is about 15 to 25 kD. Membranes with a higher cutoff of about 50 kD to eliminate larger molecules have been tested in patients with sepsis.

Thus, compared with hemodialysis (= diffusion) during hemofiltration (= convection) also molecules with higher molecular size, "middle molecules," can be extracted from the circulation. This convective elimination potentially extends also to cytokines, "mediators," or other molecules involved in the pathology of sepsis and MODS, respectively ("bad guys"), and to other short-chain (potentially beneficial) peptides, such as hormones and immunomodulatory substances ("good guys").[55,56]

For assessment of physiologic relevance of the amount of a peptide eliminated, clinicians must consider the whole body pool, the endogenous turnover, and the elimination half-life of the molecule. Even when a hormone or a "mediator" is eliminated with a sieving coefficient of approximately 1.0 (for most peptides much below 1), this is not associated with any alterations in plasma concentrations or consequences for the course of disease because of the high endogenous turnover and short half-life.

Examples are the hormones catecholamines and insulin, which have a high elimination in the extracorporeal circuit, but this has no impact on hemodynamic stability or glucose tolerance during treatment.[57]

Most available studies could not demonstrate any relevant impact of hemofiltration on plasma concentrations of cytokines. But even if high-volume hemofiltration may have small effects on plasma levels, no relevant impact on the course of disease and prognosis in critically ill patients has been demonstrated.[58,59] However, high filtration volumes may increase the risk of inducing electrolyte derangements and an inappropriate dosing of antibiotics, which are also eliminated during CRRT.[59]

Because of the rather flat cutoff characteristics of modern membranes, there is a loss of molecules with higher molecular weight, such as albumin. Depending on the mode of therapy, the membrane used, and transmembrane pressure employed, this albumin loss can account for up to 20 g/day.[60]

Adsorption of Proteins (Mediators), Drugs, and Endotoxin

Elimination of various substances and drugs during CRRT is caused not only by diffusion/convection but also by adsorption of proteins (hormones, cytokines, complement factors), of drugs (especially antibiotics), and potentially of endotoxin to the extracorporeal surfaces.[56,61]

Adsorption in the extracorporeal circuit is a temporally limited phenomenon. Artificial surfaces are rather rapidly saturated, and adsorption decreases within a time frame of 2 to 6 hours.[56] After a short dip, plasma levels of a given molecule are rising again after a few hours.

If adsorptive properties should be take profit of (for which there is no evidence for a beneficial effect when using

conventional CRRT membranes), this would mean that the filters would have to be exchanged regularly. Specific adsorber cartridges with a much higher elimination capacity than conventional CRRT membranes have been designed and are tested in clinical studies.

Activation of Protein Catabolism During Continuous Renal Replacement Therapy

Protein catabolism during RRT is not only caused by the loss of amino acids (proteins and other nutrients). As discussed above for iHD, any extracorporeal circuit with protracted contact of blood components and the artificial surfaces induces obligatory phenomena of bioincompatibility, which can be summarized as an inflammatory reaction.[62]

This aspect of inflammation has not been evaluated systematically in CRRT. Even when modern synthetic membranes used for CRRT have a high biocompatibility, CRRT still is associated with an activation of various plasmatic cascades systems, such as of coagulation and complement system, and also of various blood cells (thrombocytes, PMNs, monocytes) and thus induce a "low-grade " inflammation. In a randomized controlled study comparing CRRT versus no CRRT, an increase in inflammatory markers has been observed in those patients allocated to hemofiltration.[63]

Implications for Nutrition Support

Considering energy intake, heat balance, glucose, lactate, and citrate intake must be considered. Total energy supply should not exceed the current recommendations for critically ill patients of 20 to 25 (maximum 30) kcal/kg/day.

During nutrition support of patients on CRRT protein/amino acid intake should be increased by approximately 0.2 g /kg/day to compensate therapy-induced losses. Currently, an intake of 1.5 to 1.7 g protein / AA /kg/day is recommended at least by ESPEN.[25] Higher intakes of up to 2.5 g/kg/day, as recently suggested in the ASPEN guidelines, have no proven benefits.[64]

To achieve this protein target the admixture of a protein supplement to the enteral diet during enteral nutrition solution or a separate parenteral infusion of amino acids may become necessary.

Because of the high therapy-associated losses during CRRT, the provision of the double amounts of the RDA of water-soluble vitamins should be provided during CRRT.[25] Usually, two ampoules of a commercially available multivitamin preparation should be added to the nutrition solution. A higher intake of selenium (300 µg/day) should be considered (see earlier in the chapter).

Metabolic Effects Peritoneal Dialysis

Unfortunately, peritoneal dialysis (PD) is much underused in critically ill patients. Especially in elderly patients, in those with multiple comorbidities, and in patients with congestive heart failure or liver insufficiency, PD can offer fundamental advantages.[65]

Concerning potential metabolic side effects, certainly PD is associated with a lower inflammatory response and also lower losses of nutrients. Moreover, these losses can have considerable variations depending on the state of the peritoneum (inflammation), dwell time, and the rate of peritoneal fluid exchanges. However, metabolic side effects of PD are clinically relevant and should be considered during metabolic care and nutritional support of the patients.

BOX 73.3

Metabolic Side Effects of Peritoneal Dialysis

Glucose uptake
Loss of proteins
(increased during peritonitis)
Loss of protein bound molecules
(trace elements, lipid-soluble vitamins)
Loss of amino acids
Loss of other water-soluble molecules
(water-soluble vitamins, etc.)

To achieve the required fluid elimination and target fluid balance, solutions with high glucose concentrations are used during PD. In ICU patients with impaired glucose tolerance, this can induce hyperglycemia and an increase in insulin requirements.[66] Depending on the glucose concentration of peritoneal fluid, the dwell time, and the rate of fluid exchanges, this can account for the uptake of 200 to 400 kcal/day.[67]

The losses of water-soluble substances, such as amino acids or water-soluble vitamins are much lower than during iHD or CRRT. In the case of amino acids this accounts for 2 to 4 g/day.

However, PD is associated with a much higher loss of albumin and other proteins, within a range of 5 to 12 g/day.[67] This loss of "protein-bound" amino acids can increase considerably in the presence of peritoneal inflammation.[66] In addition, many protein-bound nutrients, such as trace elements and fat-soluble vitamins, are eliminated at a higher rate in PD as compared with iHD/CRRT (Box 73.3).

Implications for Nutrition Support

For calculating energy intake, peritoneal glucose uptake must be considered. When solutions with high glucose concentrations are used (3.6%), an energy gain of approximately 400 kcal should be taken into account to avoid overnutrition. Keeping this in mind, high-protein preparations/low-carbohydrate diets/solutions should be used for PD patients.

Electrolyte derangements are less frequent during PD than with other modalities. Nevertheless, hyperphosphatemia also can develop during PD especially in malnourished patients and during initiation of nutrition support/refeeding.

An adequate supplementation of water- and lipid-soluble vitamins and trace elements should be observed in PD patients.

CONCLUSION

All types of extracorporeal treatment modalities and renal replacement therapies induce a broad pattern of side effects on metabolism and nutrient balances, which, unfortunately, often go unrecognized. These side effects, however, have to be observed in the metabolic management and nutrition support of critically ill patients on RRT.

One group of side effects concerns nutrient balances. This constitutes the loss of many nutrients (such as amino acids, water-soluble vitamins) but also of peptides and proteins. RRT and the type of anticoagulation, respectively, can be associated also with an uptake of clinically relevant

amounts of energy substrates such as lactate and citrate (during CRRT) or glucose (during PD).

Because of the prolonged treatment time and associated high fluid turnover, the evolution of electrolyte derangements is most pronounced during CRRT. Metabolically most important is the risk of inducing hypophosphatemia because many dialysis/substitution fluids are phosphate free. This is especially true for malnourished patients after initiation of nutrition support (refeeding syndrome).

From a metabolic view, even more important, however, is the induction of an inflammatory reaction caused by the extracorporeal circuit and the sustained contact of blood and artificial surfaces. This is associated with multiple consequences and contributes to protein catabolism and the generation of reactive oxygen species and potentially may promote distant organ injury and impair immunocompetence.

A clinically relevant elimination of mediators during conventional RRT has not been demonstrated. Because also potentially beneficial molecules are eliminated, the impact on inflammatory reaction and immunocompetence of the organism is unpredictable and ill defined.

Clinical implications of this broad pattern of metabolic side effects are twofold. First, patients in RRT need more close metabolic monitoring than other ICU patients. Second, type and intensity of RRT must be regarded when designing a nutrition program for these patients to avoid providing an inadequate nutrition support and the evolution of metabolic complications.

Key Points

1. All types of RRT exert a profound impact on metabolism and nutrient balances.
2. Nutrient balances are affected by losses of various nutrients and peptides/proteins and potentially by an increased uptake of substrates (glucose, lactate, citrate), all of which have to be regarded when designing nutrition therapy.
3. All types of RRT induce an inflammatory reaction by obligatory phenomena of bioincompatibility and by the type of anticoagulation (heparin vs. citrate), which induces an inflammatory reaction.
4. Taken together, RRT induce/augment a proinflammatory, prooxidative, and catabolic state and a complex spectrum of metabolic side effects.

Key References

2. Honore PM, De Waele E, Jacobs R, et al. Nutritional and metabolic alterations during continuous renal replacement therapy. *Blood Purif*. 2013;35:279-284.
17. Ikizler TA, Pupim LB, Brouillette JR, et al. Hemodialysis stimulates muscle and whole body protein loss and alters substrate oxidation. *Am J Physiol Endocrinol Metab*. 2002;282:E107-E116.
39. Demirjian S, Teo BW, Guzman JA, et al. Hypophosphatemia during continuous hemodialysis is associated with prolonged respiratory failure in patients with acute kidney injury. *Nephrol Dial Transplant*. 2011;26:3508-3514.
46. Frankenfield DC, Badellino MM, Reynolds HN, et al. Amino acid loss and plasma concentration during continuous hemodiafiltration. *JPEN J Parenter Enteral Nutr*. 1993;17:551-561.
52. Berger MM, Shenkin A, Revelly JP, et al. Copper, selenium, zinc, and thiamine balances during continuous venovenous hemodiafiltration in critically ill patients. *Am J Clin Nutr*. 2004;80:410-416.

A complete reference list can be found online at ExpertConsult.com.

References

1. Druml W. Metabolic aspects of continuous renal replacement therapies. *Kidney Int*. 1999;Suppl:S56-S61.
2. Honore PM, De Waele E, Jacobs R, et al. Nutritional and metabolic alterations during continuous renal replacement therapy. *Blood Purif*. 2013;35:279-284.
3. Druml W. Nutritional management of acute renal failure. *J Ren Nutr*. 2005;15:63-70.
4. Fiaccadori E, Maggiore U, Cabassi A, et al. Nutritional evaluation and management of AKI patients. *J Ren Nutr*. 2013;23:255-258.
5. Hynote ED, McCamish MA, Depner TA, et al. Amino acid losses during hemodialysis: effects of high-solute flux and parenteral nutrition in acute renal failure. *JPEN J Parenter Enteral Nutr*. 1995;19:15-21.
6. Wolfson M, Jones MR, Kopple JD. Amino acid losses during hemodialysis with infusion of amino acids and glucose. *Kidney Int*. 1982;21:500-506.
7. Kopple JD, Swendseid ME, Shinaberger JH, et al. The free and bound amino acids removed by hemodialysis. *Trans Am Soc Artif Intern Organs*. 1973;19:309-313.
8. Schmidt JJ, Hafer C, Spielmann J, et al. Removal characteristics and total dialysate content of glutamine and other amino acids in critically ill patients with acute kidney injury undergoing extended dialysis. *Nephron Clin Pract*. 2014;126:62-66.
9. Umber A, Wolley MJ, Golper TA, et al. Amino acid losses during sustained low efficiency dialysis in critically ill patients with acute kidney injury. *Clin Nephrol*. 2014;81:93-99.
10. Chua HR, Baldwin I, Fealy N, et al. Amino acid balance with extended daily diafiltration in acute kidney injury. *Blood Purif*. 2012;33:292-299.
11. Descombes E, Hanck AB, Fellay G. Water soluble vitamins in chronic hemodialysis patients and need for supplementation. *Kidney Int*. 1993;43:1319-1328.
12. Descombes E, Boulat O, Perriard F, et al. Water-soluble vitamin levels in patients undergoing high-flux hemodialysis and receiving long-term oral postdialysis vitamin supplementation. *Artif Organs*. 2000;24:773-778.
13. Morena M, Cristol JP, Bosc JY, et al. Convective and diffusive losses of vitamin C during haemodiafiltration session: a contributive factor to oxidative stress in haemodialysis patients. *Nephrol Dial Transplant*. 2002;17:422-427.
14. Madl C, Kranz A, Liebisch B, et al. Lactic acidosis in thiamine deficiency. *Clin Nutr*. 1993;12:108-111.
15. Donnino MW, Andersen LW, Chase M, et al. Randomized, Double-Blind, Placebo-Controlled Trial of Thiamine as a Metabolic Resuscitator in Septic Shock: A Pilot Study. *Crit Care Med*. 2016;44:360-367.
16. Schiffl H, Lang SM. Severe acute hypophosphatemia during renal replacement therapy adversely affects outcome of critically ill patients with acute kidney injury. *Int Urol Nephrol*. 2013;45:191-197.
17. Ikizler TA, Pupim LB, Brouillette JR, et al. Hemodialysis stimulates muscle and whole body protein loss and alters substrate oxidation. *Am J Physiol Endocrinol Metab*. 2002;282:E107-E116.
18. Gutierrez A, Bergstrom J, Alvestrand A. Protein catabolism in sham-hemodialysis: the effect of different membranes. *Clin Nephrol*. 1992;38:20-29.
19. Raj DS, Dominic EA, Pai A, et al. Skeletal muscle, cytokines, and oxidative stress in end-stage renal disease. *Kidney Int*. 2005;68:2338-2344.
20. Bitla AR, Reddy PE, Manohar SM, et al. Effect of a single hemodialysis session on inflammatory markers. *Hemodial Int*. 2011;14:411-417.
21. Tetta C, Biasioli S, Schiavon R, et al. An overview of haemodialysis and oxidant stress. *Blood Purif*. 1999;17:118-126.
22. Wratten ML, Tetta C, Ursini F, et al. Oxidant stress in hemodialysis: prevention and treatment strategies. *Kidney Int Suppl*. 2000;76:S126-S132.
23. Metnitz GH, Fischer M, Bartens C, et al. Impact of acute renal failure on antioxidant status in multiple organ failure. *Acta Anaesthesiol Scand*. 2000;44:236-240.
24. Oudemans-van Straaten HM, Kellum JA, Bellomo R. Clinical review: anticoagulation for continuous renal replacement therapy–heparin or citrate? *Crit Care*. 2011;15:202.
25. Cano NJ, Aparicio M, Brunori G, et al. ESPEN Guidelines on Parenteral Nutrition: adult renal failure. *Clin Nutr*. 2009;28:401-414.
26. Pupim LB, Flakoll PJ, Brouillette JR, et al. Intradialytic parenteral nutrition improves protein and energy homeostasis in chronic hemodialysis patients. *J Clin Invest*. 2002;110:483-492.
27. Yagi N, Leblanc M, Sakai K, et al. Cooling effect of continuous renal replacement therapy in critically ill patients. *Am J Kidney Dis*. 1998;32:1023-1030.
28. Stevenson JM, Heung M, Vilay AM, et al. In vitro glucose kinetics during continuous renal replacement therapy: implications for caloric balance in critically ill patients. *Int J Artif Organs*. 2013;36:861-868.
29. Monaghan R, Watters JM, Clancey SM, et al. Uptake of glucose during continuous arteriovenous hemofiltration. *Crit Care Med*. 1993;21:1159-1163.
30. Balik M, Zakharchenko M, Leden P, et al. Bioenergetic gain of citrate anticoagulated continuous hemodiafiltration–a comparison between 2 citrate modalities and unfractionated heparin. *J Crit Care*. 2013;28:87-95.
31. Heering P, Ivens K, Thumer O, et al. The use of different buffers during continuous hemofiltration in critically ill patients with acute renal failure. *Intensive Care Med*. 1999;25:1244-1251.
32. Barenbrock M, Hausberg M, Matzkies F, et al. Effects of bicarbonate- and lactate-buffered replacement fluids on cardiovascular outcome in CVVH patients. *Kidney Int*. 2000;58:1751-1757.
33. Oudemans-van Straaten HM, Bosman RJ, Koopmans M, et al. Citrate anticoagulation for continuous venovenous hemofiltration. *Crit Care Med*. 2009;37:545-552.
34. Bauer E, Derfler K, Joukhadar C, et al. Citrate kinetics in patients receiving long-term hemodialysis therapy. *Am J Kidney Dis*. 2005;46:903-907.
35. Balik M, Zakharchenko M, Otahal M, et al. Quantification of systemic delivery of substrates for intermediate metabolism during citrate anticoagulation of continuous renal replacement therapy. *Blood Purif*. 2012;33:80-87.
36. Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med*. 2008;359:7-20.
37. Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med*. 2009;361:1627-1638.
38. Locatelli F, Pontoriero G, Di Filippo S. Electrolyte disorders and substitution fluid in continuous renal replacement therapy. *Kidney Int Suppl*. 1998;66:S151-S155.
39. Demirjian S, Teo BW, Guzman JA, et al. Hypophosphatemia during continuous hemodialysis is associated with prolonged respiratory failure in patients with acute kidney injury. *Nephrol Dial Transplant*. 2011;26:3508-3514.
40. Yang Y, Zhang P, Cui Y, et al. Hypophosphatemia during continuous veno-venous hemofiltration is associated with mortality in critically ill patients with acute kidney injury. *Crit Care*. 2013;17:R205.
41. Kleinberger G, Gabl F, Gassner A, et al. Hypophosphatemia during parenteral nutrition of patients with renal insufficiency (author's transl). *Wien Klin Wochenschr*. 1978;90:169-172.
42. Marik PE, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. *Arch Surg*. 1996;131:1043-1047.
43. Broman M, Carlsson O, Friberg H, et al. Phosphate-containing dialysis solution prevents hypophosphatemia during continuous renal replacement therapy. *Acta Anaesthesiol Scand*. 2011;55:39-45.
44. Godaly G, Carlsson O, Broman M. Phoxilium((R)) reduces hypophosphataemia and magnesium supplementation during continuous renal replacement therapy. *Clin Kidney J*. 2016;9:205-210.
45. Davies SP, Reaveley DA, Brown EA, et al. Amino acid clearances and daily losses in patients with acute renal failure treated by continuous arteriovenous hemodialysis. *Crit Care Med*. 1991;19:1510-1515.
46. Frankenfield DC, Badellino MM, Reynolds HN, et al. Amino acid loss and plasma concentration during continuous hemodiafiltration. *JPEN J Parenter Enteral Nutr*. 1993;17:551-561.
47. Maxvold NJ, Smoyer WE, Custer JR, et al. Amino acid loss and nitrogen balance in critically ill children with acute renal failure:

a prospective comparison between classic hemofiltration and hemofiltration with dialysis. *Crit Care Med*. 2000;28:1161-1165.
48. Novak I, Sramek V, Pittrova H, et al. Glutamine and other amino acid losses during continuous venovenous hemodiafiltration. *Artif Organs*. 1997;21:359-363.
49. Berg A, Norberg A, Martling CR, et al. Glutamine kinetics during intravenous glutamine supplementation in ICU patients on continuous renal replacement therapy. *Intensive Care Med*. 2007;33:660-666.
50. Story DA, Ronco C, Bellomo R. Trace element and vitamin concentrations and losses in critically ill patients treated with continuous venovenous hemofiltration. *Crit Care Med*. 1999;27:220-223.
51. Fortin MC, Amyot SL, Geadah D, et al. Serum concentrations and clearances of folic acid and pyridoxal-5-phosphate during venovenous continuous renal replacement therapy. *Intensive Care Med*. 1999;25:594-598.
52. Berger MM, Shenkin A, Revelly JP, et al. Copper, selenium, zinc, and thiamine balances during continuous venovenous hemodiafiltration in critically ill patients. *Am J Clin Nutr*. 2004;80:410-416.
53. Nakamura AT, Btaiche IF, Pasko DA, et al. In vitro clearance of trace elements via continuous renal replacement therapy. *J Ren Nutr*. 2004;14:214-219.
54. Churchwell MD, Pasko DA, Btaiche IF, et al. Trace element removal during in vitro and in vivo continuous haemodialysis. *Nephrol Dial Transplant*. 2007;22:2970-2977.
55. Hoffmann JN, Faist E. Removal of mediators by continuous hemofiltration in septic patients. *World J Surg*. 2001;25:651-659.
56. De Vriese AS, Colardyn FA, Philippe JJ, et al. Cytokine removal during continuous hemofiltration in septic patients. *J Am Soc Nephrol*. 1999;10:846-853.
57. Bellomo R, McGrath B, Boyce N. Effect of continuous venovenous hemofiltration with dialysis on hormone and catecholamine clearance in critically ill patients with acute renal failure. *Crit Care Med*. 1994;22:833-837.
58. Park JT, Lee H, Kee YK, et al. High-Dose Versus Conventional-Dose Continuous Venovenous Hemodiafiltration and Patient and Kidney Survival and Cytokine Removal in Sepsis-Associated Acute Kidney Injury: A Randomized Controlled Trial. *Am J Kidney Dis*. 2016.
59. Joannes-Boyau O, Honore PM, Perez P, et al. High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. *Intensive Care Med*. 2013;39:1535-1546.
60. Mokrzycki MH, Kaplan AA. Protein losses in continuous renal replacement therapies. *J Am Soc Nephrol*. 1996;7:2259-2263.
61. Gasche Y, Pascual M, Suter PM, et al. Complement depletion during haemofiltration with polyacrilonitrile membranes. *Nephrol Dial Transplant*. 1996;11:117-119.
62. Goldstein SL, Ikizler TA, Zappitelli M, et al. Non-infected hemodialysis catheters are associated with increased inflammation compared to arteriovenous fistulas. *Kidney Int*. 2009;76:1063-1069.
63. Riegel W, Ziegenfuss T, Rose S, et al. Influence of venovenous hemofiltration on posttraumatic inflammation and hemodynamics. *Contrib Nephrol*. 1995;116:56-61.
64. Taylor BE, McClave SA, Martindale RG, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *Crit Care Med*. 2016;44:390-438.
65. Cullis B, Abdelraheem M, Abrahams G, et al. Peritoneal dialysis for acute kidney injury. *Perit Dial Int*. 2014;34:494-517.
66. Goes CR, Berbel MN, Balbi AL, et al. Metabolic implications of peritoneal dialysis in patients with acute kidney injury. *Perit Dial Int*. 2013;33:635-645.
67. Burkart J. Metabolic consequences of peritoneal dialysis. *Semin Dial*. 2004;17:498-504.