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NEPHROLOGY - ORIGINAL PAPER

Treatment dose and the elimination rates of electrolytes, vitamins, and trace elements during continuous veno-venous hemodialysis (CVVHD)

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Abstract

Introduction During continuous renal replacement therapy, achievement of recommended treatment dose is important. However, relevant substrate loss may occur and recommended nutrition during critical illness could not be sufficient for higher dialysis doses. We investigated the correlation of dialysis dose and substrate loss for a broad range of dialysis doses.

Methods Forty critically ill patients with acute kidney injury undergoing citrate CVVHD were included in this prospective study. Three different corresponding blood flow (BF) and dialysate flow (DF) rates were applied (BF/DF: 100 ml/min, 2000 ml/h; 80 ml/min, 1500 ml/h; 120 ml/min, 2500 ml/h). Delivered effluent flow rate (DEFR) was calculated and correlated with losses of vitamins, electrolytes, and trace elements during recommended nutritional supplementation.

Results For folic acid, vitamin B12, zinc, inorganic phosphate, and magnesium, no correlation of losses and DEFR was detected. For ionized calcium, a correlation was observed and additional substitution was required.

Conclusion Clinically relevant loss of folic acid, vitamin B12, zinc, inorganic phosphate, and magnesium was not observed for differently used dialysis doses of CVVHD, and the loss was covered sufficiently by daily recommended nutritional supplementation. Increased loss of ionized calcium for higher dialysis doses occurred during citrate CVVHD. Therefore, a strict protocol must maintain calcium homeostasis to avoid calcium depletion.

Keywords Acute kidney injury · Continuous renal replacement therapy · Citrate anticoagulation · Critical illness · Trace elements

Introduction

Acute kidney injury (AKI) is a critical organ dysfunction and therefore associated with relevant morbidity and mortality [1]. Continuous renal replacement therapy (CRRT) is used to treat high-grade AKI [1]. Anticoagulation during CRRT is recommended in most cases to prevent filter clotting. Regional citrate anticoagulation is increasingly used due to prolonged circuit life span, diminished risk of bleeding and to avoid heparin-induced thrombocytopenia [2–4]. Body weight-adapted treatment doses are recommended for CRRT, but rarely performed in clinical practice [5]. Limited data are available concerning CRRT induced losses of electrolytes, vitamins, and trace elements [6–8]. Trace elements are small in size and thus dialyze readily [9]. We investigated different dialysis doses and hypothesized that these losses could be strongly clinically dependent on the dialysis dose.

Materials and methods

This prospective study was performed in a mixed surgical intensive care unit at a university hospital with approval of local ethics committee according to the Helsinki Declaration, and patients gave written informed consent. Patients with AKI as defined by the KDIGO criteria [10] and an indication for CRRT were included, independent

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of the reason for AKI. Inclusion criteria were anuria (< 100 ml/24 h), volume overload with pulmonary edema not responsive to diuretics, or hyperkalemia (> 5.5 mmol/l) and an anticipated CVVHD requirement of at least 3 days. Exclusion criteria were age < 18 years, pregnancy, or declined consent. Forty critically ill patients were included (Table 1). Citrate CVVHD was used in all patients using commercially available equipment (Multifiltrate®, integrated CiCa® system, AV1000S® filter kit (polycarbonate/polyurethane filter kit; surface area 1.8 m^2); CiCa® Dialysate K 2 without phosphate (dialysate with 2 mmol/l potassium); sodium citrate 4%, and 0.5 M $CaCl_2$ solution; *Fresenius Medical Care*™, *Bad Homburg, Germany*), and the kit was used over a period of 72 h according to the recommendations of the manufacturer. To maintain stable metabolic and hemodynamic conditions, a standard protocol for adjustments of blood flow, dialysate, citrate, and calcium flow was used. Plasma levels for calcium, magnesium, inorganic phosphate, urea, and creatinine were measured daily. Vitamins and trace elements were measured in plasma before start of citrate CVVHD (at baseline) and at the end of the 72 h treatment periods.

Arterial blood samples were obtained before start of CVVHD and every 24 h of treatment. Blood gas analyses were performed according to a standard protocol to check and adjust the citrate and calcium flow rates. During the 72 h treatment period, each 24 h were determined separately.

Substrate concentrations in the effluent were measured in representative aliquots. An aliquot sample of 100 ml was taken when the effluent bag was emptied. At 24 h, a representative sample (proportionate aliquots) was used for substrate analysis. The effluent volume was calculated via the dialysate and ultrafiltrate flow rates.

Measurements of each substrate were taken in serum and effluent. Photometric measurements were taken for calcium, inorganic phosphate, and magnesium (Calcium *o-Kresolphtalein-Komplexon*, Magnesium *MTB-complex*, inorganic phosphate *Molybdat complex*; *Siemens Dimension RxL*®). Isocratic high performance liquid chromatography with UV-detector was used to determine vitamin A/B1/B6/B12/E (*Waters®/Biorad®/Chromsystems®*), ECLIA (ElectroChemiLumineszenzlmmunoAssay) was carried out for folic acid (*Folate-III reagent Roche®*, *Roche Cobas 6000®*), copper and zinc were determined with flame absorption spectrometer (*1100B®, Perkin-Elmer®*). The intra-assay variation coefficients were < 10% for all assays.

The first treatment period was started with a blood flow (BF) of 100 ml/min and a dialysate flow (DF) of 2000 ml/h. The second period was started with a BF of 80 ml/min and a DF of 1500 ml/h. The third period was started with a BF of 120 ml/min and a DF of 2500 ml/h. One patient was treated without a BF of 80 ml/min and a DF of 1500 ml/h and was treated instead with a BF of 140 ml/min and a DF 3000 ml/h due to a body weight of 150 kg (BMI 46.3).

The delivered effluent flow rate (DEFR) was calculated for each individual treatment interval as a dimension of dialysis dose according to the following formula:

$$\text{Delivered effluent flow rate (DEFR)}\left[\frac{\text{ml}}{\text{kg} \times \text{h}}\right] = \frac{\text{Dialysate (ml)} + \text{Ultrafiltrate (ml)}}{\text{Body weight (kg)} \times \text{Time of treatment (h)}}$$

The exact amount of dialysate and ultrafiltrate as well as the time of treatment were determined using the CRRT protocol. DEFR was calculated separately for each patient every day.

Enteral and parenteral nutrition (Table 2) containing trace elements, vitamins, electrolytes, carbohydrates, amino acids, and lipids were performed according to the nutrition guidelines for patients' needs and morbidity [11]. Calcium, magnesium, and inorganic phosphate were substituted based on daily measurements.

Descriptive analyses were performed, and numerical data are shown as median [1st quartile–3rd quartile].

To investigate correlation between substrate loss and dialysis dose, the 24 h loss/DEFR were presented independently as scatter plots. Regression analysis was performed by

Table 1 Patient characteristics at baseline

Demographics	Median [IQR]
Age (years)	65 [59–70]
Sex	*n* (%)
Male	27 (67.5%)
Female	13 (32.5%)
BMI (kg/m^2)	26 [24–29]
Scores	**Median [IQR]**
APACHE II	19 [16–21]
SAPS II	42 [34–50]
SOFA	10 [8–13]
Cause of AKI	***n*** **(%)**
Sepsis	20 (50%)
Ischemia	9 (22.5%)
Maintenance dialysis	3 (7.5%)
Crush kidney	2 (5.0%)
Contrast-induced nephropathy	2 (5.0%)
Renal transplant failure	1 (2.5%)
Nephrotic syndrome	1 (2.5%)
Hepatorenal syndrome	1 (2.5%)
Acute on chronic renal disease	1 (2.5%)

n number; values as median and IQR (= interquartile range)

Table 2 Nutrition and supplementation facts

Nutrition	kcal	Composition
Nutriflex® peri (parenteral)	340 kcal/l	Amin 40 g, Lip 0 g, Carb 80 g 3.6 mmol Ca^{2+}, 5.0 mmol Mg^{2+}, 8.0 mmol PO34-, 0.03 mmol Zn per 1000 ml
Nutriflex® Lipid peri (parenteral)	764 kcal/l	Amin 32 g, Lip 40 g, Carb 64 g 2.4 mmol Ca^{2+}, 2.4 mmol Mg^{2+}, 6.0 mmol PO34-, 0.024 mmol Zn each 1000 ml
Nutriflex® combi (parenteral)	800 kcal/l	Amin 50 g, Lip 0 g, Carb 150 g 4.24 mmol Ca^{2+}, 5.0 mmol Mg^{2+}, 15.0 mmol PO34-, 0.10 mmol Zn each 1000 ml
Nutriflex® Lipid special (parenteral)	1181 kcal/l	Amin 56 g, Lip 40 g, Carb 144 g 4.24 mmol Ca^{2+}, 4.24 mmol Mg^{2+}, 16 mmol PO34-, 0.032 mmol Zn each 1000 ml
AEK-Nephro (produced by local pharmacy) (parenteral)	1492 kcal/l	Amin 75 g, Lip 0 g, Carb 299.6 g 4.96 mmol Ca^{2+}, 3.79 mmol Mg^{2+} each 1000 ml
Nutrison multifiber® (enteral)	1000 kcal/l	Amin 3.9 g, Lip 4 g, Carb 12.3 g 80 mg Ca^{2+}, 23 mg Mg^{2+}, PO34–72 mg, Zn 1.2 mg, 27 µg folic acid, 0.21 µg vitamin B12 per 100 g Nutrison
FrekaVit® (parenteral)		Amin 0 g, Lip 0 g, Carb 0 g 0.4 mg folic acid, 5 µg vitamin B12 each pharmaceutical phial

Amin amino acids, *Lip* lipids, *Carb* carbohydrates

plotting the regression line into the diagram and calculating the coefficient of correlation R^2.

Results

For ionized calcium, magnesium, inorganic phosphate, urea, creatinine, zinc, folic acid, and vitamin B12 losses were detected by the described methods. Initially measured vitamin A, vitamin E, and copper were also measured, but they were below the detection limit and were therefore omitted from the analysis. Ionized calcium, magnesium, inorganic phosphate, zinc, vitamin B12, and folic acid measured in the effluent had a stability over 24 h. Overall, the DEFR ranged from 14 to 53 ml/kg/h and median was 27 ml/kg/h [IQR; 23–33] (Table 3). The values below 20 ml/kg/h resulted from two patients, each weighing ~ 150 kg. All other dialysis doses were above 20 ml/kg/h. The values above 40 ml/kg/h were assigned to two patients, each weighing 50 kg. Scatter plots and regression analysis of investigated substrates and calculated coefficients of correlation R^2 are shown in Figs. 1, 2. R^2 was < 10% for folic acid, vitamin B12, zinc, inorganic phosphate, and magnesium in all periods. Only ionized calcium had a R^2 between 21 and 25%. In this study, 21 of the 40 included patients died in the ICU [8].

Table 3 Blood flow/dialysate flow and delivered effluent flow rates

Blood flow (ml/min)/dialysate flow (ml/h)	80/1500	100/2000	120/2500
Delivered effluent flow rate			
Median (ml/kg/h)	23	27	33
IQR (ml/kg/h)	21–24	23–31	28–38

Values as median and IQR (= interquartile range)

Discussion

The present study investigated the impact of different treatment doses on loss of electrolytes, vitamins, and trace elements during citrate CVVHD in critically ill patients. Substrate loss was correlated with dialysis dose, separately for each day and thus independent of the filter lifetime. The present study was mainly focused on the specific conditions of nutritional supplementation under CVVHD in intensive care rather than on individual trace element supplementation. A dependency of filter lifetime and loss of electrolytes, vitamins, and trace elements was not described [8]. The coefficient of correlation R^2 was < 10% for folic acid, vitamin B12, zinc, inorganic phosphate, and magnesium and did not indicate higher correlation between the DEFR and substrate loss in all periods in the used dialysis doses. No comparable data could be found in the literature. Electrolyte disturbances such as hypocalcemia, hypomagnesemia, or hypophosphatemia in critically ill patients are extremely relevant and include cardiac arrhythmias, seizures, and coma [12]. Folic acid and vitamin B12 are indispensable nutrients for DNA synthesis [13], and zinc deficiency may also impair protein synthesis, antioxidant defense, and NFkB expression [14], and their balance is important especially for critically ill patients. A study on 10 critically ill adult patients with continuous veno-venous hemodiafiltration (CVVHDF) showed that the investigated trace element loss (chrome, copper, manganese, selenium, zinc) was less than the provided daily dose of trace element supplementation [6]. Similar results

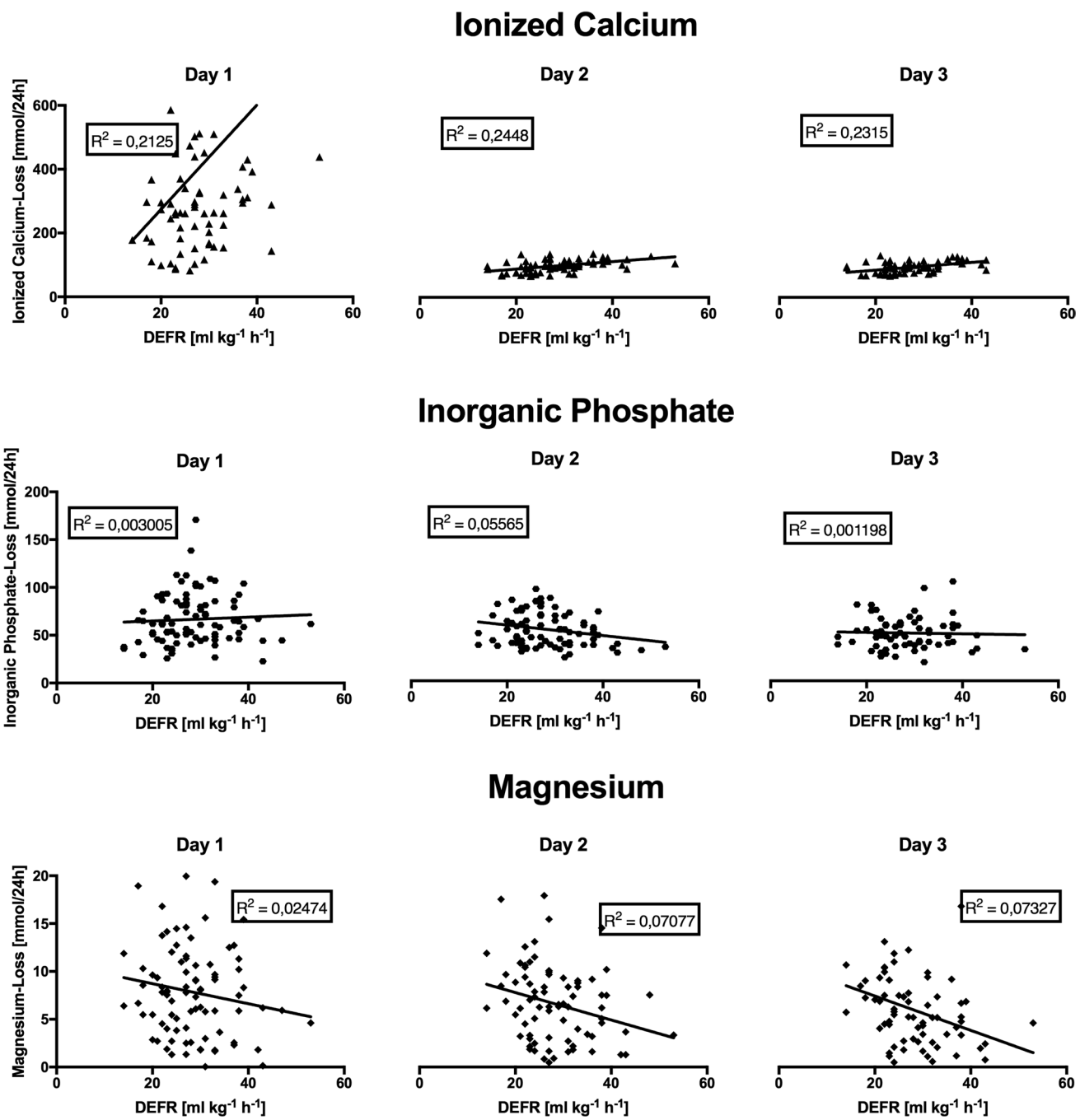

Fig. 1 Loss of ionized calcium, inorganic phosphate, magnesium, and dialysis dose (DEFR delivered effluent flow rate) [regression analysis: regression line and coefficient of correlation R^2]

described a study of five pediatric patients treated with CVVHDF for the losses of chromium, copper, manganese, selenium, and zinc [7]. With regard to loss of calcium and magnesium, significant loss during CVVHDF necessitating higher administration than the standard parenteral nutrition was described in a study on 12 critically ill patients [15]. The results of these studies on trace element loss [6, 7, 15] indicate that nutritional supplementation covers daily losses with exception of calcium. Our results suggest that the recommendation for nutritional supplementation seem to be adequate concerning folic acid, vitamin B12, zinc, inorganic phosphate, and magnesium and the substrate loss is without high clinically relevant dependency for the range of our used dialysis doses for 72 h periods. Further studies are needed for long-term CRRT, because the duration of intensive care and the need for CRRT may impact nutritional needs. It is

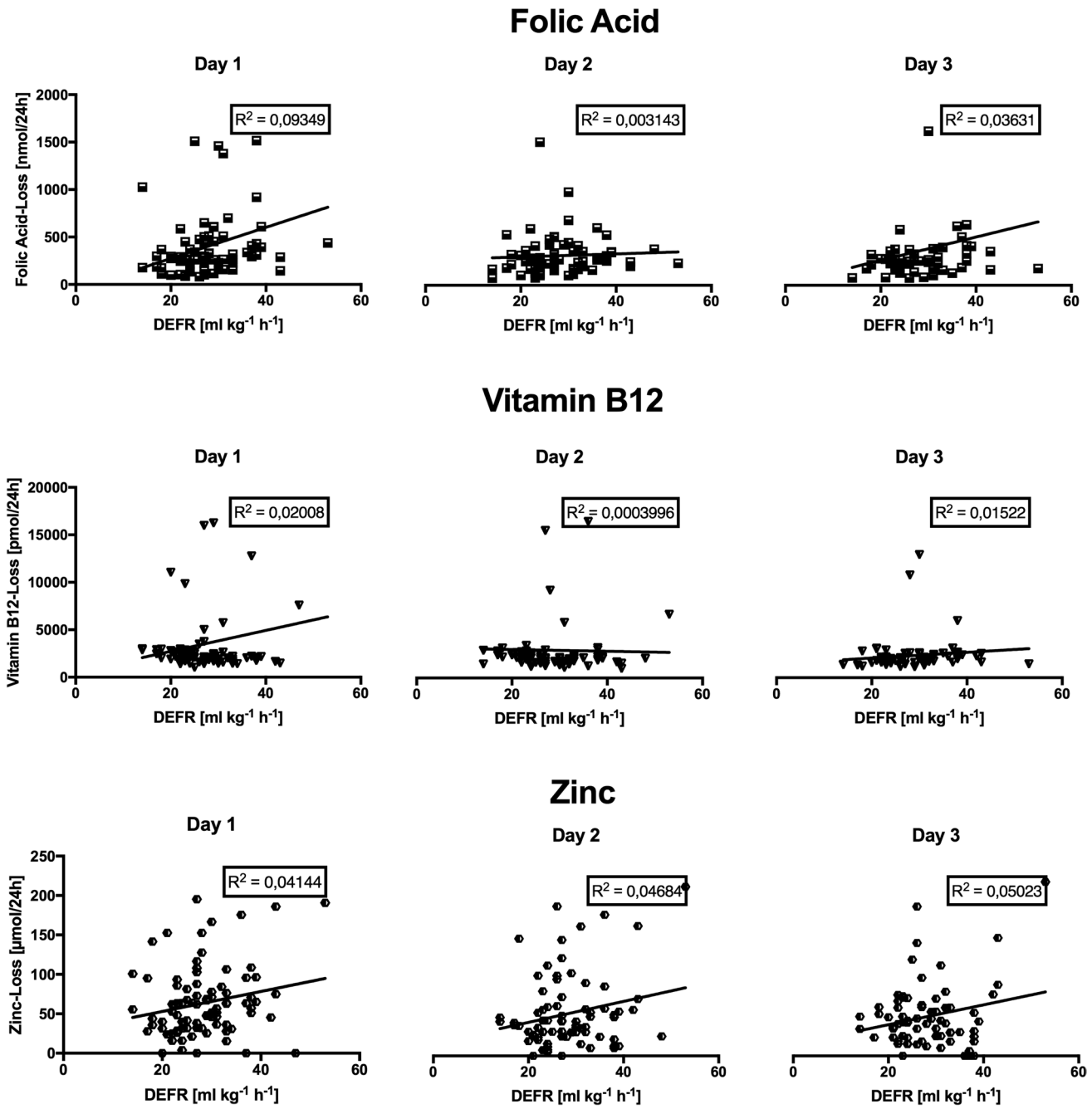

Fig. 2 Loss of folic acid, vitamin B12, zinc, and dialysis dose (DEFR delivered effluent flow rate) [regression analysis: regression line and coefficient of correlation R^2]

conceivable that the elimination become relevant in longer treatment periods of CVVHD. Only ionized calcium had a R^2 between 21 and 25% which indicates a dependency of DEFR. However, the calcium metabolism must be taken into account during citrate CVVHD. The treatment itself causes loss of ionized calcium [8]. The need of ionized calcium depends on the effluent flow [16], and the loss of calcium bound to citrate in the effluent may cause decreased values especially for high treatment intensities in citrate CVVHD [17]. Loss of ionized calcium and insufficient supplementation can lead to a negative calcium balance. Persistent systemic hypocalcemia can be followed by detrimental cardiovascular effects such as reduced vascular tone or decreased myocardial contractility, which may provoke a cardiac arrest [18]. Another relevant effect of ongoing hypocalcemia is the stimulation of parathyroid hormone, which leads to calcium mobilization from skeletal stores [18]. The combination of immobilization and prolonged CRRT of critically ill patients

can be followed by bone resorption and can cause major fractures as described in the literature [19]. An effective delivered effluent volume of 20-25 ml/kg/h is recommended by the KDIGO Clinical Practice Guideline for Acute Kidney Injury for continuous renal replacement therapy [20]. DEFR above 25 ml/kg/h did not improve outcomes in critically ill patients [21] and rates below 20 ml/kg/h should also be avoided [21]. In order to achieve a delivered dosage of 20–25 ml/kg/h, it was recommended by the KDIGO Guidelines to prescribe a treatment dose in the range of 25–30 ml/kg/h. It is important to take into account potential interruptions of treatment [20], because the delivered dialysis dose is considerably lower than that prescribed [22].

In the present study, three different dialysis doses were used: 100 ml/min BF with 2000 ml/h DF, 80 ml/min BF with 1500 ml/h DF, 120 ml/min BF with 2500 ml/h DF. Thus, 90% of patients of the present study were treated with the standard BF of 100 ml/min and a DF of 2000 ml/h and achieved dialysis dose within the best practice range between 20 and 40 ml/kg/h [21]. A possible benefit of higher dialysis dose for septic patients, the most frequent cause of the acute renal damage in the present study, has not yet been clarified [1, 20], and no beneficial effects were described in a Cochrane review for more intensive CRRT (> 35 ml/kg/h) on mortality or recovery of kidney function in critically ill patients with AKI [1].

Clinically relevant losses of folic acid, vitamin B12, zinc, inorganic phosphate, and magnesium were not observed for the used different dialysis doses of CVVHD and seem to be covered by daily recommended nutritional supplementation. An increased loss of ionized calcium for higher doses in citrate CVVHD occurred and required additional supplementation. Therefore, a strict protocol must maintain calcium homeostasis to avoid calcium depletion.

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Compliance with ethical standards

Conflict of interest Karl Träger received honoraria for lectures from Fresenius Medical Care.

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