

High Anion Gap Metabolic Acidosis on Continuous Renal Replacement Therapy



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INTRODUCTION

Euglycemic ketoacidosis (EDKA) is an uncommon cause of high anion gap metabolic acidosis characterized by elevated urine and serum ketones and serum glucose <13.9 mmol/l. This condition should be suspected when high anion gap metabolic acidosis is noted in a diabetic patient with blood glucose levels within normal limits. Continuous renal replacement therapy (CRRT) theoretically may be complicated with EDKA when poor intake is accompanied by dialysate caloric losses. We describe a patient with EDKA on CRRT following an acute cardiac event. This case highlights the need to consider EDKA in the differential diagnosis of high anion gap metabolic acidosis in patients on CRRT.

CASE PRESENTATION

A 53-year-old white woman with a past medical history of hypertension, type 2 diabetes mellitus, and end-stage kidney disease was on intermittent hemodialysis 3 times weekly. She also had history of coronary artery disease and history of chronic heart failure with left ventricular ejection fraction of 43.5%.

After a few minutes of a mid-week hemodialysis treatment, she had an episode of cardiac arrest with pulseless electrical activity. She had a return of spontaneous circulation after resuscitation and required mechanical ventilation support. In the light of her previous coronary artery disease, she underwent coronary angiography, which showed triple vessel disease with moderately decreased ejection fraction. Given her comorbidities and the extent of her coronary artery disease, a decision was made to continue lifelong medical therapy. Meanwhile, she developed right lower lobe infiltrate on chest X-ray and became septic. Treatment with broad-spectrum antibiotics was initiated.

In view of her poor hemodynamic status requiring inotropic support, her renal replacement therapy was modified to continuous venovenous hemodiafiltration (CVVHDF). Her original CVVHDF prescription with PrismaSol (PrismaSol 4; Baxter Corporation, Mississauga, ON, Canada) was glucose-free dialysate and replacement fluid (as part of the institutional protocol) with potassium chloride and potassium phosphate as additives at 1000 ml/h each (for overall rate 24 ml/kg per hour). Replacement fluid was equally split into pre- and postpump delivery. Her nutrition was via nasogastric tube for 24 hours and was changed to oral feeds after extubation in 24 hours. Oral feeds, however, were compromised because of vomiting. She continued to receive low-dose rapid-acting insulin subcutaneously as per sliding scale.

HOSPITAL COURSE

Over the period of the first 3 days, her metabolic parameters, including acidosis, improved (Table 1). However, on day 4, she developed progressively worsening high anion gap metabolic acidosis. There was no history of diarrhea or hyperlactatemia, and blood glucose levels were 4.0 to 10.9 mmol/l since admission. She was not on any drugs known to cause metabolic acidosis. Uremia was unlikely, as she was on CRRT with normal serum urea and close-to-normal creatinine. Ketoacidosis was suspected and confirmed by serum β -hydroxybutyrate level (Table 1). Given her normal glucose level, a diagnosis of euglycemic ketoacidosis was made. She was started on i.v. glucose and insulin infusions. Within 24 hours of the above treatment, her bicarbonate normalized in parallel with a decrease in β -hydroxybutyrate. Both bicarbonate and serum β -hydroxybutyrate remained normal afterward. The patient recovered from sepsis, was extubated, and

Table 1. Metabolic parameters during the course of development and management of EDKA

Serum chemistry: normal range	Day 0	Day 2	Day 3	Day 4 (0500)	Day 4 (1600)	Day 5
Urea, mmol/l: 2.4–6.4	15	6.4	7.8	5.3	4.9	2.2
Creatinine, $\mu\text{mol/l}$: 49–84	385	148	130	96	94	57
Sodium, mmol/l: 136–144	134	136	139	138	137	136
Chloride, mmol/l: 98–107	98	100	102	105	99	100
Bicarbonate, mmol/l: 19–30	17	16	19	17	15	23
Albumin, g/l: 36–47	27	26	28	28	29	26
Anion gap, mmol/l (corrected): 8–16	21.5	23.7	20.5	23.5	25.5	16.7
Lactate, mmol/l: 0.5–2.5	1.9	1.3	1.6	1.0		0.7
Glucose, mmol/l: 4–11	6.8	9.8	7.3	4.8	11.1	9.3
β -Hydroxybutyrate, mmol/l: ≤ 0.27					7.14	1.29
Effluent dialysate glucose, mmol/l					11.1	
Insulin s.c.	Yes	Yes	Yes	Yes	No	No
IV insulin with i.v. glucose	No	No	No	No	Yes	Yes
CVVHDF	Yes	Yes	Yes	Yes	Yes	Yes

CVVHDF, continuous venovenous hemodiafiltration; EDKA, euglycemic ketoacidosis; s.c., subcutaneously.

was transitioned to intermittent hemodialysis after 1 week.

DISCUSSION

We describe a case report of EDKA in a patient with end-stage kidney disease who required temporary CVVHDF during admission for an acute cardiac event complicated by sepsis associated with lung right lower lobe infiltrate.

Euglycemic ketoacidosis is defined as a triad of high anion gap metabolic acidosis, positive serum ketones, and serum glucose level <13.9 mmol/l, unlike diabetic ketoacidosis, which is characterized by an elevated blood glucose level.^{1,2} Known causes of EDKA include starvation,³ pancreatitis,⁴ pregnancy,⁵ and, more recently, the use of SGLT2 inhibitors.⁶ We are aware of only 1 case series that has reported this complication in patients on CRRT. In that case series ($n = 18$), the median age of the patients was 64 years, 50% were diabetic, and 28% were insulin dependent. All the patients had multiorgan failure, and 84% of these admissions were secondary to cardiac disease. A total of 55% required ECMO, and the median CRRT flow rates were 29 ml/kg per hour.⁷ The median onset of EDKA was 43 hours (interquartile range: 26–75 hours), similar to the 72 hours seen in our case.

Glucose-free CRRT solutions, as in our institution, are associated with losses of significant amounts of

glucose in the effluent. An *in vitro* study describing glucose kinetics in a variety of CRRT modalities and prescriptions showed net glucose losses ranging from 6 g/d to 160 g/d for variable dialysate glucose levels and dialysate flow rates.⁸ In our case, the glucose level in the CRRT effluent was 10 mmol/l as compared to serum glucose of 11.1 mmol/l. The actual prefilter blood glucose level was more likely about 10.4 mmol/l, taking into account about 5% hemodilution by the split of the replacement fluid flow rate of 1000 ml/h equally to pre- and postfilter. Calculated net glucose loss in our patient was 47.5 g/d, compared to median losses of 54 g/d (interquartile range: 44–60) reported in the case series.⁷

Although the exact mechanism of EDKA in patients on CRRT was never proposed, some inferences can be drawn from the studies on SGLT2 inhibitors.⁹ As with these drugs causing glycosuria, hemodiafiltration leads to constant losses of glucose from the body. This, together with potentially compromised caloric intake and increased metabolic demands and stress from underlying critical illness, may lead to a decrease in endogenous insulin production (and insulin resistance) and a simultaneous increase in glucagon levels. As for the results, use of lipids leading to lipolysis and ketogenesis is favored as the source of intracellular energy over carbohydrate metabolism. Low insulin and high glucagon levels will increase production of endogenous glucose, decrease tissue glucose disposal, and maintain a state of euglycemia despite factual intracellular carbohydrate starvation (Figure 1).

Management in our case involved infusing glucose and insulin with rapid correction of EDKA (Table 2). The same management was adopted in all the patients in previous case series. Insulin will promote use of administered glucose by peripheral tissues including muscle and adipose tissue, suppress ketogenesis, and diminish glycogenolysis and gluconeogenesis. That being said, it is important to acknowledge that our patient was on subcutaneous insulin, and several patients in the reported case series were receiving i.v. insulin while they developed EDKA. Hence it appears that it is the relative imbalance between intracellular glucose availability and demand that likely differs from patient to patient based on comorbidities, critical illness, and CRRT prescription.

New high anion metabolic acidosis in patients on CRRT frequently raises suspicion of elevated lactate or inadequate CRRT (Table 2). Often it is managed by increasing the dose of CRRT rather than searching for the underlying cause. Early identification of EDKA in patients on CRRT leads to simple corrective therapy and avoids potentially catastrophic complications (Table 2).

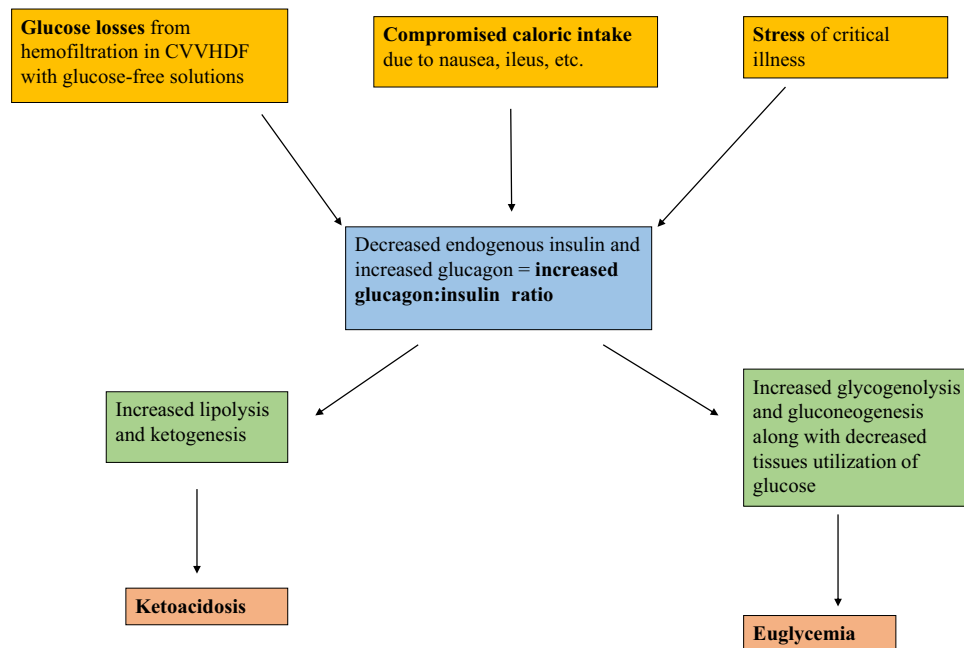


Figure 1. Proposed pathophysiology of euglycemic ketoacidosis (EDKA) in patients on continuous venovenous hemodiafiltration (CVVHDF) with glucose-free solutions.

Table 2. Teaching points

1. Euglycemic ketoacidosis (EDKA) is a potentially missed etiology of unexplained high anion gap metabolic acidosis in patients on continuous renal replacement therapy (CRRT).
2. Euglycemic ketoacidosis is rapidly correctable with insulin (and glucose) infusion.
3. Unrecognized and untreated euglycemic ketoacidosis could have catastrophic clinical consequences.

DISCLOSURE

All the authors declared no competing interests.

AUTHOR CONTRIBUTIONS

All authors contributed to data collection, critical evaluation of collected data, and writing the manuscript. MR had full access to the data in the study and has final responsibility for the decision to submit the manuscript for publication.

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