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Efficacy of continuous venovenous hemodiafiltration in patients with metformin associated lactic acidosis and acute kidney injury

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Metformin associated lactic acidosis (MALA) and severe acute kidney injury (AKI) is a life-threatening condition, often requiring renal replacement therapy. However, the optimal renal replacement therapy regimen in this setting remains unclear. Furthermore, limited data exist on the use of regional citrate anticoagulation, as severe hyperlactatemia is associated with increased risk of citrate accumulation. We retrospectively analyzed the medical records of all patients with MALA and severe AKI requiring renal replacement therapy at our hospital between June 2011 and December 2021. All patients were treated with high dose CVVHDF. Anticoagulation was achieved using either heparin or regional citrate anticoagulation. A total of 27 patients with MALA and AKI requiring renal replacement therapy were identified. In all patients, CVVHDF was started within one hour of the diagnosis. Four deaths were recorded, resulting in an overall mortality rate of 14.8%. In the remaining 23 patients (85.2%), we observed the correction of the metabolic disorder and the recovery of renal function that allowed for the discontinuation of dialysis. Mean lactatemia at diagnosis was 12.9 mmol/l (range 7.0–24.0) and mean pH 6.99 (range 6.50–7.22). CVVHDF mean effluent rate was as high as 52.1 ml/kg/h. In thirteen patients regional citrate anticoagulation was safely employed. In our experience, CVVHDF prescribed at the appropriate dose have yielded favorable results, in terms both of patient survival and metabolic control of the disease. Regional citrate anticoagulation can be safely used in selected cases.

Background

Metformin is a biguanide that has been in use for more than 50 years in the treatment of type 2 diabetes mellitus (T2DM) as a first-line agent, according to the guidelines of the European and American Diabetes Associations[1].

Metformin toxicity can result in a severe form of lactic acidosis (LA). Although the exact mechanism of LA is not completely elucidated, metformin inhibits mitochondrial complex activity resulting in a decrease of ATP production. Consequently, cells shift from aerobic to anaerobic metabolism. This results in the accumulation of pyruvate upstream of the Krebs cycle, which is converted to lactate by lactate dehydrogenase[2,3]. Furthermore, the lactate cannot be efficiently cleared through the liver due to hepatic inhibition by metformin. Hence, the increase in lactate is the consequence of both production and clearance impairment[2].

Three forms of LA can be identified in patients under metformin therapy[4,5]:

- Metformin-induced lactic acidosis (MILA): when LA is caused by metformin, as in acute metformin toxicity, and when very high levels of metformin are documented in the absence of other likely causes.
- Metformin-unrelated lactic acidosis (MULA): when LA is not related to metformin.
- Metformin-associated lactic acidosis (MALA): when metformin is one of the possible causes of LA.

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Metformin itself does not induce acute kidney injury (AKI), and recent publications even speculate about its potential renoprotective effect in the context of sepsis[6]. Nonetheless, renal function is often altered in cases of MALA. The 'REMIND' study demonstrated that the risk of LA in patients treated with metformin, increases as the estimated glomerular filtration rate (eGFR) declines, even after adjusting for confounders[7]. This is due to the pharmacokinetics of metformin, a molecule with a high renal clearance (400 ml/min) that can consequently accumulate in individuals with renal impairment[8]. The guidelines of the European Medicines Agency recommend dose adjustment in patients with moderate renal impairment (GFR 30–59 ml/min) and advise against prescription when the eGFR falls below 30 mL/min[9].

In most types of LA in critically ill patients the treatment consists of supportive measures and, whenever feasible, correcting the underlying cause, with the benefit of RRT being dubious at best[10]. On the other hand metformin is a small molecule with a low drug-protein binding, so it is efficiently removed by RRT. Hence, in these cases, RRT is not only effective in correcting the acid-base imbalance, but also in treating the underlying disease by removing metformin.

Typically, RRT is unnecessary in milder cases, while it is required in instances where MALA is associated with severe renal insufficiency. The Extracorporeal Treatments in Poisoning (EXTRIP) guidelines recommend initiating RRT in cases of lactatemia > 20 mmol/L, pH < = 7.0, and/or failure of standard therapy. It is suggested in cases of lactatemia between 15 and 20 mmol/L and pH 7–7.1. If conditions such as shock, impaired kidney function, liver failure, or an altered state of consciousness are present, lower thresholds for RRT should be considered[11].

Currently, the optimal RRT regimen for MALA and severe AKI remains unknown[2,12,13]. Based on available data, intermittent hemodialysis (IHD) provides higher metformin clearance[14,15], while continuous renal replacement therapy (CRRT) is often preferred for patients with hemodynamic instability. However, metformin has a large volume of distribution and can diffuse into different types of cells, especially erythrocytes, enterocytes, and hepatocytes[16]. This explains the occurrence of a 'rebound phenomenon', wherein metabolic parameters worsen some hours after the end of IHD treatment[11,17] (Fig. 1). CRRT avoids this complication by achieving a gradual correction of the metabolic disorder with constant removal of the drug. In contrast, some authors argue that CRRT may not effectively control severe cases of MALA due to its lower efficiency, leading to experiences of concomitant double CRRT to enhance treatment efficacy[12]. Furthermore, in cases of acute overdose, such as a suicide attempt, there may be a need for efficient removal of plasmatic metformin, making IHD the preferred choice. In chronic poisoning, a significant amount of metformin is already inside the cells, thus necessitating prolonged treatment.

Ten years ago, we developed a local protocol for treating patients with severe MALA and AKI with continuous venovenous hemodiafiltration (CVVHDF). The intensity of CVVHDF is set by the treating nephrologist to achieve a minimum of effluent dose of 37 ml/Kg/h. This dose exceeds the 20–25 ml/kg/h recommendation for other forms of AKI by KDIGO guidelines, in order to achieve a higher clearance of the drugs responsible for the intoxication[18].

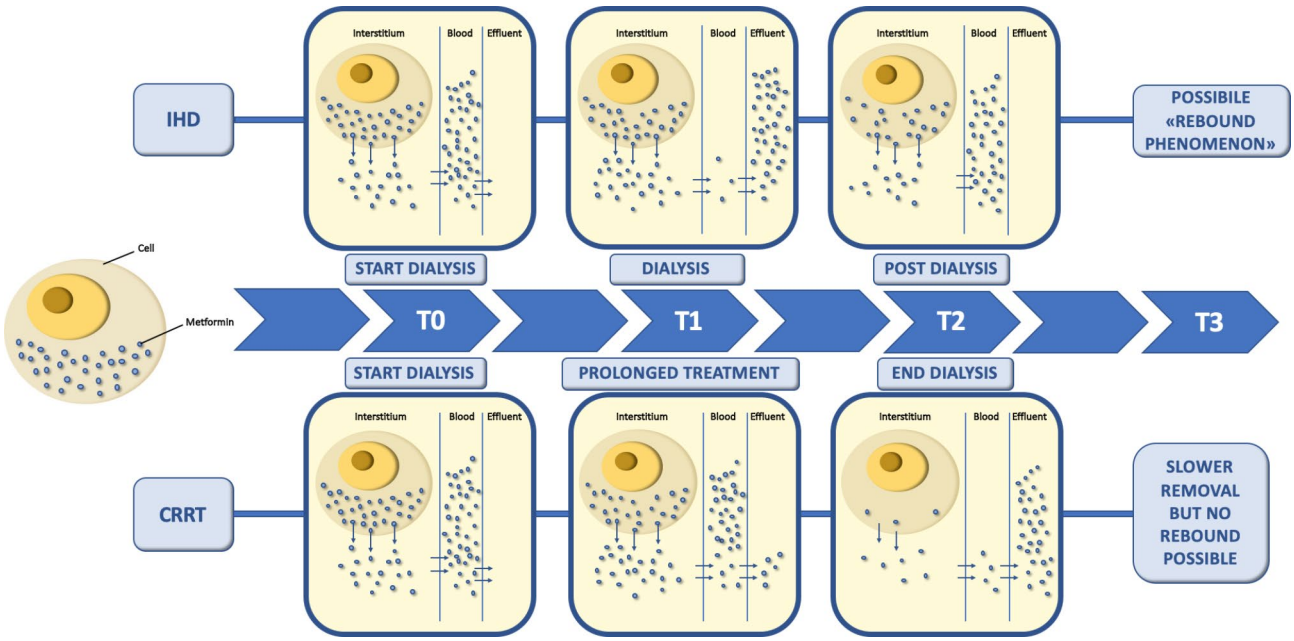

Fig. 1. Differences in metformin removal between intermittent and continuous treatments. In intermittent hemodialysis (IHD), metformin removal is faster but it could result in "rebound phenomenon" due to delayed release of metformin from intracellular space. In continuous renal replacement therapy metformin removal is slower, but "rebound phenomenon" is not possible.

For circulatory anticoagulation, regional citrate anticoagulation (RCA) is the first choice in our centre. However, there is some concern in cases of severe hyperlactatemia where citrate may not be efficiently metabolized to bicarbonate potentially leading to citrate accumulation. However, our experience and literature data suggest that RCA can be safely used if serum lactate is not rising rapidly and under strict metabolic monitoring[19]. Therefore, either unfractionated heparin or RCA could be used in these cases.

The aim of this retrospective study is to review our single-centre experience with patients undergoing CVVHDF for severe MALA and AKI.

Methods

This is a retrospective single center study analyzing all patients presented at the San Giovanni Bosco Hospital of Turin between June 2011 and December 2021 with MALA and severe AKI (KDIGO stage III) requiring RRT.

The joint protocol of treatment for these cases required that CVVHDF should be initiated in an intensive care setting within one hour of diagnosis. CVVHDF should be prescribed to achieve a convective dose of at least 25 ml/kg/h and a diffusive dose of at least 12 ml/kg/h.

CVVHDF could be discontinued once the metabolic imbalance was corrected and signs of renal recovery were evident.

Patients underwent CVVHDF treatment using Gambro Baxter USA Prismaflex® machines and AN69ST membrane filters (ST150, 1.5 square meters). A central venous catheter placed in the jugular or femoral vein, depending on individual factors, was used for vascular access. We used polyurethane bulbous catheters (MahurkarTM, CovidienTM - USA) of 11.5 French gauge and 16–24 cm in length. For circuit anticoagulation either heparin or regional citrate anticoagulation (RCA) could be prescribed, according to the indication of the attending nephrologist. Sodium heparin was prescribed at a dose of 5–10 Units/kg/hour, using a continuous infusion pump with or without a starting bolus. Activated clotting time (ACT) or partial thromboplastin time (aPTT) measured at baseline, after 1 h and then every 4 h was used to adjust the heparin dose.

RCA was obtained with pre-dilution of sodium citrate 18.0 mmol/l (@Gambro Baxter USA). Post filter calcium was monitored to maintain it within the target range. To avoid the possible metabolic complications due to citrate accumulation the ratio between total plasma calcium and plasma ionized calcium (tCa/iCa) was measured as a surrogate for blood citrate levels (with a cut-off value < 2.5)[20].

The "territorial Ethical Committee (comitato etico interaziendale CTE Torino) approved this study (protocol 0073420 of 2022) and waived of informed consent.

Results

A total of 27 patients with MALA requiring CVVHDF were included in our retrospective analysis. Patients baseline characteristics are presented in Table 1. The mean age was 69.2 years (range 44–86 years), with a female predominance (20/27, 74%). The mean Glasgow Coma Scale score at presentation was 13.7 (range 5–15), and the mean daily metformin dose was 2330 mg (range 1000–3000 mg).

All patients had severe AKI classified as stage III KDIGO classification. Serum creatinine was compared with the pre-existing kidney function value estimated by reported history. The average presenting serum creatinine was 7.28 mg/dL. Only one patient had chronic kidney disease (stage IIIB). Twenty-five patients experienced a greater than threefold increase in serum creatinine compared to their baseline, meeting the KDIGO creatinine increase criterion for AKI stage III. Two patients had smaller increases: one between two and threefold, and one less than twofold. However, they were both anuric (defined as urine output less than 50 ml in 12 h) so they met the KDIGO urine output criterion for AKI stage III. Considering the urine output 51% (14 patients) were anuric and 33% (9 patients) had severe oliguria (urine output < 0.3 ml/kg/h for 12 h).

Twenty-two patients (81%) presented with gastrointestinal symptoms (vomiting and/or diarrhea), 10 (37%) with fever or other causes of dehydration. Four patients (15%) were diagnosed with severe infection and subsequently treated with antibiotics. Fourteen patients (51%) were receiving a renin angiotensin system blocker and 2 (7%) a non-steroidal anti-inflammatory drug.

Average blood pressure was 113/59 mmHg and the mean blood pressure 75.4 mmHg. At the start of CVVHDF, 8 patients (29%) required vasopressor therapy with catecholamines. All received norepinephrine at a mean dose of 0.13 mcg/kg/h. Two patients also received co-administered epinephrine.

Four deaths occurred due to cardiovascular shock (4 women, mean age 80.8 years, range 74–86). The overall mortality rate was 14.8%. All four died patients were anuric. One required administration of 2 catecholamines at the start of CVVHDF due to severe hypotension in severely compromised left ventricular ejection fraction (25%). One patient has history of cachexia. One patient has pancreas neoplasm with no evidence of diffuse metastatic disease. One presented with severe neurologic impairment (GCS 5). Among the 23 surviving patients, all achieved renal recovery and discontinued CVVHDF treatment. Laboratory data at the start and the end of treatment are detailed in Table 2. Mean lactate and pH levels improved significantly, from 12.9 mmol/l (range 7.0–24.0) and 6.99 (range 6.50–7.22) at diagnosis to 1.5 mmol/l (range 0.6–3.6) and 7.38 (range 7.26–7.53) at dialysis discontinuation, respectively. The analysis of the rate of metabolic imbalance resolution after 12 h by the start of CVVHDF demonstrated a substantial improvement of mean pH 7.34 (7.13–7.48) and mean lactatemia 4.2 mmol/L (1.3–10.0).

No significant differences were found between survivors and non-survivors at presentation.

CVVHDF parameters and anticoagulation.

CVVHDF parameters are summarized in Table 3. The mean duration of CVVHDF treatments was 56.2 h with a mean downtime of 17.8 min. The prescribed effluent dose of CVVHDF averaged 52.1 ml/kg/h, with a convective dose of 31.9 ml/kg/h and a diffusive dose of 19.8 ml/kg/h. The right femoral vein was the most commonly used site for central venous catheter placement (22/27).

Patients	27	
Female	20	
	Mean (range)	
Age (years)	69.2 (44–86)	
Weight (kg)	72.3 (50–100)	
	Female	Male
	72.7 (50–100)	71.3 (60–90)
Glasgow coma scale	13.7 (5–15)	
Metformin daily dose (mg)	2330.4 (1000–3000)	
Comorbidities	• Hypertension: 19 • Obesity: 12 • COPD: 3 • PAD: 2 • Cancer history: 3 • CAD: 3 • Stroke 1 • Hydrocephalus: 1	
Causes for dehydration	• 22/27 Gastroenteric (vomit and/or diarrhea) • 10/27 Fever • 2/27 Reduced water intake	
Drugs	• 8/27 ACEIs • 6/27 ARBs • 2/27 NSAID	
Blood pressure* (mmHg)	Systolic BP (SBP): 109 ± 35.5 Diastolic BP (DBP): 58.6 ± 16.95 Mean BP**: 75.4 ± 23.1	
Catecholamines One Two Total	6/27 2/27 8/27	
CKD	1/27 (stage III-B)	

Table 1. Baseline characteristics of study patients. COPD: Chronic obstructive pulmonary disease, PAD: Peripheral artery disease, CAD: coronary artery disease, ACEIs: Angiotensin-Converting Enzyme Inhibitors, ARBs: Angiotensin receptor blockers, NSAID: Non-steroidal anti-inflammatory drugs *Mean and standard deviation **Mean blood pressure calculated with the formula: DBP + (SBP-DBP)/3

	Before CVVHDF	After 12 h of CVVHDF	End of CVVHDF
Patients (n)	27	26	23
	Mean (range)	Mean (range)	Mean (range)
pH	6.99 (6.50–7.22)	7.34 (7.13–7.48)	7.38 (7.26–7.53)
Serum bicarbonate mmol/L	8.78 (1.0–19.0)	18.5 (13.6–26.6)	24.96 (20.2–29.8)
Serum lactate mmol/L	*12.9 (7.0–24.0)	4.2 (1.3–10.0)	1.5 (0.6–3.6)
Serum creatinine (mg/dl)	7.28 (1.1-14.45)	n.d.	1.9 (0.9–4.4)
Potassium (mmol/l)	6.15 (3.73–8.5)	4.4 (3.6–5.8)	4.1 (3.2–5.1)
Base Excess mEq/L	-17.3 (-31/-6)	-3.3 (-10.4/-0.4)	-0.3 (-7.2 / +5.2)

Table 2. Mean values of laboratory parameters CVVHDF: continuous venovenous hemodiafiltration * Two cases exceeded the laboratory's upper limit of detection (24 mmol/L), which was used for calculations.

As regard to anticoagulation, 14 out of 27 patients received heparin and 7 patients RCA. In the remaining 6 cases heparin was switched to RCA after dialysis initiation (Table 4).

The mean dose of sodium heparin administered was 4.4 U/Kg/h (range 2.7–10), the mean ACT value achieved was 165.9 s (range 144–200 s). No major or minor bleeding events occurred during the treatments. The mean treatment duration using heparin anticoagulation was 50.5 h (24–120) with a mean downtime of 23.3 min (0–120 min).

For RCA the mean serum ionized calcium value was 1.1 mmol/L (range 0.93–1.23). The average value of tCa/iCa-s ratio, measured as a surrogate of blood citrate levels, was 2.1 (range 1.78–2.74) after 24 h of treatment. One patient had a ratio of 2.74, and the sodium citrate dose was reduced, resulting in normalization of the ratio at the subsequent 4-hour control. No further adjustments were required.

CVVHDF parameters	Mean (ranges)
Q_b (ml/min)	162.6 (100–245)
Q_{inf} (ml/kg/h)	31.9 (20-58.3)
Q_{inf} pre (ml/kg/h)	18.4 (12.5–30.1)
Q_{inf} post (ml/kg/h)	13.5 (4.6–33.3)
Q_d (ml/kg/h)	19.8 (14.3–30.1)
Q_{eff} (ml/kg/h)	52.1 (34.3–76.7)
Mean TMP* (mmHg)	92.1 (44.3-162.6)
Duration (h)	56.2 (6-120)
Downtime (min)	17.8 (0-120)

Table 3. CVVHDF parameters. CVVHDF: continuous venovenous hemodiafiltration; Qb: blood flow; Qinf: infusion flow, total and pre and post filter, Qd: dialysate flow, Qeff: effluent flux including ultrafiltration, TMP: transmembrane pressure * Average of every 6 h TMP value

CVVHDF anticoagulation			
	Heparin (*n.* pts)	RCA (*n.* pts)	
	20	13*	
Anticoagulation	Mean dose (U/kg/h)		Mean iCa-s (mmol/l)
	4.4 (2.7–20)		1.1 (0.93–1.23)
	Mean ACT value (sec)	Mean tCa/iCa ratio	
	165.9 (144–200)	2.1 (1.78–2.74)	
Mean treatment time (h)	**50.5 (24–120)**	**68.3 (24–144)**	
Downtime (min)	**23.3 (0-120)**	**8.1 (0–90)**	

Table 4. CVVHDF anticoagulation. (CVVHDF: continuous venovenous hemodiafiltration, RCA: regional citrate anticoagulation, ACT: activated clotting time, tCa: total plasma calcium, iCa: ionized calcium) *6 patients were shifted from heparin to RCA; for these patients treatment time was evaluated separately.

No metabolic complications related to citrate accumulation were observed. The mean treatment duration using RCA was 68.3 h (24–144) with a mean downtime of 8.1 min (0–90 min).

Discussion

Our retrospective analysis of CVVHDF management in patients with MALA and AKI showed encouraging results in terms of overall survival and renal recovery. Notably, only 4 of 27 patients (14.8%) died, while the remaining 23 patients were able to discontinue dialysis. Higher mortality rates have been reported in the literature, ranging from 21.4% in the case series of Mariano et al.[21] to 30% in EXTRIP and even up to 50% as reported by Weisberg et al.[4]. A recent meta-analysis including 242 individual cases from 158 case reports and 26 case series showed a cumulative mortality rate of 19.8%[22]. The low mortality rate observed in our study may be partially attributed to the strict metabolic control achievable with our dialysis protocol, ensuring hemodynamic stability and gradual correction of the LA. Furthermore, once accumulated, metformin is released from the intracellular to the extracellular compartment[17]. Thus, it continues to inhibit the mitochondrial respiratory chain, promoting anaerobic metabolism and shifting glucose into the "Cori cycle". It also hinders the use of pyruvate and lactate for gluconeogenesis[23] and promotes the conversion of glucose to lactate in the intestine[24]. The constant clearance of metformin achieved with CVVHDF prevented from this 'rebound' phenomenon[11]. In fact, none of the 23 patients who discontinued CVVHDF experienced any relapse of metabolic acidosis or an increase in lactate levels, nor did they require further RRT treatment.

We also assessed the rate of metabolic disturbance resolution by evaluating laboratory data at 12 h. This analysis demonstrated substantial improvement in the metabolic disturbance within 12 h, with mean pH and lactate levels approaching normal values (mean pH 7.34 and mean lactatemia 4.2 mmol/L). While CVVHDF is undeniably less rapid than IHD in correcting metabolic derangements, these findings suggest that the treatment demonstrates efficacy within 12 h, allowing for patient stabilization and the possible de-escalation of therapeutic interventions (e.g., vasopressor tapering or cessation). This is a crucial consideration, as certain complications and outcomes arise as a consequence of the emergency interventions employed in these situations.

EXTRIP guidelines identify IHD as the most effective technique for metformin intoxication[11]. Nevertheless, the optimal management of patients with severe AKI, such as those in our cohort, is not well-defined. In these patients, that frequently presented with hemodynamic instability, there is also the potential requirement for both depuration and ultrafiltration, which may make IHD less safe. Moreover, CRRT is most effective when renal metformin clearance is minimal[11]. Regarding the efficiency of CRRT it should be kept in mind that adequate dosing is crucial in cases of intoxication[25]. Notably, the mean effluent dose in our study (52.1 ml/Kg/h) was

twice the recommended dose for AKI. This is in line with the recommendation of the EXTRIP guidelines to increase the dose of CVVHDF in order to achieve more efficiency. Successful CRRT experiences described in the literature present high dialysis dose data that align with this assertion (>40 ml/kg/h)[12,16,26].

Since metformin has a high diffusion coefficient due to its low molecular weight (PM 165 Da) and low drug-protein binding, we used a high diffusive dose in our study (19.8 mL/kg/h) that exceeded our typical prescription for AKI. It should be noted, however, that at these dialysate flow rates, increasing blood flow rates has a very marginal effect on small molecule clearance[25].

Of note, RCA was successfully used in 13 patients. Despite elevated lactate levels, no complications such as hypocalcemia, citrate accumulation, or acid-base imbalance were observed. In one patient the rate of sodium citrate infusion was lowered without further complications. It should be noted that because sodium citrate infusion provides buffering capacity, it is generally combined with low-bicarbonate dialysis fluids. Nonetheless, in cases of profound acidosis, solutions with increased buffering capacity (in both the dialysate and replacement fluid) should be chosen. In patients who underwent a switch from heparin to RCA, we waited for lactate levels to stabilize below 10 mmol/L before switching to prevent potential citrate accumulation In our opinion, RCA could be used in selected cases of MALA, as also shown in a recent study of 23 MALA patients[27].

Conditions predisposing to an abrupt decline in eGFR are often described in such cases. Indeed, in our cohort, we observed that a precipitating condition for eGFR decline, such as gastrointestinal disease, hypovolemia and fever, often in combination with the administration of RAS blockers and NSAIDs, was present in all of our patients.

Our study has several limitations. The sample size, coupled with the retrospective and observational design, restricts the generalizability of the observed results. In addition, the study design does not allow for a direct comparison between IHD and CRRT. We also cannot provide an index of severity of illness at the start of CVVHDF, thus this limits the possibility to compare our results. Lastly, we were unable to assess blood levels of metformin and citrate. Notwithstanding the aforementioned limitations, this study comprises one of the most extensive single-center experiences reported on this subject. The severity of both renal damage and metabolic derangement, coupled with the common administration of vasopressors, underscores the clinical acuity of this patient population. The consistent application of high-dose CVVHDF, standardized by a joint protocol, enables outcome assessment despite the previously mentioned limitations.

Recent studies highlight the importance of not only blood levels, but also intracellular metformin concentrations, in understanding the pathogenesis of such cases[28]. Since conducting randomized controlled trials with sufficient sample size in patients with drug intoxications presents a significant challenge, furthering our understanding of the underlying pathogenetic processes could pave the way for improved management strategies.

Conclusion

Metformin therapy in T2DM may pose a risk of serious LA. MALA associated with severe AKI may be difficult to treat and burdened with high mortality rates.

Based on our ten-year experience, CVVHDF have yielded favorable results, both in terms of patient survival and the metabolic control of the disease. We believe that with prompt initiation and appropriate dosing, CVVHDF ensures correction of the metabolic disorder and avoids the risk of rebound, which can occur due to metformin's large volume of distribution. In particular in our study a dose of CVVHDF as high as 52.1 ml/Kg/h, started within one hour from the diagnosis, was associated to an overall mortality rate of 14.8% with a substantial correction of the metabolic imbalance within 12 h of treatment.

In our experience, CVVHDF can be performed safely and efficiently in selected cases using RCA.

Data availability

The datasets used during the current study are available from the corresponding author on reasonable request.

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References

1. Davies, M. J. et al. Management of hyperglycemia in type 2 diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. **45**(11), 2753–2786. https://doi.org/10.2337/dci22-0034 (2022).
2. Mariano, F. & Biancone, L. Metformin, chronic nephropathy and lactic acidosis: A multi-faceted issue for the nephrologist. *J. Nephrol.* **34**(4), 1127–1135. https://doi.org/10.1007/s40620-020-00941-8 (2021).
3. Foretz, M., Guigas, B. & Viollet, B. Understanding the glucoregulatory mechanisms of metformin in type 2 diabetes mellitus. *Nat. Rev. Endocrinol.* **15**(10), 569–589. https://doi.org/10.1038/s41574-019-0242-2 (2019).
4. Weisberg, L. S. Lactic acidosis in a patient with type 2 diabetes Mellitus. *Clin. J. Am. Soc. Nephrol.* **10**(8), 1476–1483. https://doi.org/10.2215/CJN.10871014 (2015).
5. Lalau, J. D., Arnouts, P., Sharif, A. & De Broe, M. E. Metformin and other antidiabetic agents in renal failure patients. *Kidney Int.* **87**(2), 308–322. https://doi.org/10.1038/ki.2014.19 (2015).
6. Van Moorter, N., Tackaert, T., De Decker, K., Van Vlem, B. & De Neve, N. New potential for an old kid on the block: Impact of premorbid metformin use on lactate kinetics, kidney injury and mortality in sepsis and septic shock, an observational study. *Endocrinol. Diabetes Metab.* **6**(1), e382. https://doi.org/10.1002/edm2.382 (2023).
7. Chen, C-C. et al. Relationship between metformin use and lactic acidosis in advanced chronic kidney disease: the REMIND-TMU study. *Am. J. Med. Sci.* **364**(5), 575–582. https://doi.org/10.1016/j.amjms.2022.01.026 (2022).
8. Harding, S. A., Biary, R., Hoffman, R. S., Su, M. K. & Howland, M. A. A pharmacokinetic analysis of Hemodialysis for Metformin-Associated Lactic Acidosis. *J. Med. Toxicol.* **17**(1), 70–74. https://doi.org/10.1007/s13181-020-00802-7 (2021).

9. EMA. Use of metformin to treat diabetes now expanded to patients with moderately reduced kidney function recommendations for patients with kidney impairment updated in product. ;**44**(October):0–3. (2016).
10. Van De Ginste, L. et al. Patients with severe lactic acidosis in the Intensive Care Unit: A retrospective study of contributing factors and impact of renal replacement therapy. *Blood Purif.* **51** (7), 577–583. https://doi.org/10.1159/000518918 (2022).
11. Calello, D. P. et al. Extracorporeal treatment for metformin poisoning: Systematic review and recommendations from the extracorporeal treatments in poisoning workgroup. *Crit. Care Med.* **43**(8), 1716–1730. https://doi.org/10.1097/CCM.0000000000001002 (2015).
12. Reynolds, H. V., Pollock, H. H. G., Apte, Y. V. & Tabah, A. Achieving high Dialysis Dose via continuous renal replacement therapy in the setting of Metformin Associated Lactic Acidosis. A Case Series. *A&A Pract.* **16**(1), e01561. https://doi.org/10.1213/XAA.0000000000001561 (2022).
13. Alivanis, P. et al. Metformin-associated lactic acidosis treated with continuous renal replacement therapy. *Clin. Ther.* **28**(3), 396–400. https://doi.org/10.1016/j.clinthera.2006.03.004 (2006).
14. Lalau, J. D. et al. Hemodialysis in the treatment of lactic acidosis in diabetics treated by metformin: a study of metformin elimination. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **27**(6), 285–288 (1989).
15. Barrueto, F., Meggs, W. J. & Barchman, M. J. Clearance of metformin by hemofiltration in overdose. *J. Toxicol. Clin. Toxicol.* **40**(2), 177–180. https://doi.org/10.1081/clt-120004407 (2002).
16. Correia, M. S. & Zane Horowitz, B. Continuous extracorporeal clearance in metformin-associated lactic acidosis and metformin-induced lactic acidosis: A systematic review. *Clin. Toxicol.* **60**(11), 1266–1276. https://doi.org/10.1080/15563650.2022.2127363 (2022).
17. Greco, P. et al. Sustained low-efficiency dialysis for metformin-associated lactic acidosis in patients with acute kidney injury. *J. Nephrol.* **32**(2), 297–306. https://doi.org/10.1007/s40620-018-00562-2 (2019).
18. Khwaja, A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin. Pract.* **120**(4), c179–c184 (2012).
19. Khadzhynov, D. et al. Hyperlactatemia, lactate kinetics and prediction of citrate accumulation in critically ill patients undergoing continuous renal replacement therapy with Regional Citrate Anticoagulation. *Crit. Care Med.* **45**(9), e941–e946. https://doi.org/10.1097/CCM.0000000000002501 (2017).
20. Cubattoli, L., Teruzzi, M., Cormio, M., Lampati, L. & Pesenti, A. Citrate anticoagulation during CVVH in high risk bleeding patients. *Int. J. Artif. Organs.* **30**(3), 244–252. https://doi.org/10.1177/039139880703000310 (2007).
21. Mariano, F. et al. Metformin-Associated Lactic Acidosis undergoing renal replacement therapy in Intensive Care units: A five-million Population-based study in the North-West of Italy. *Blood Purif.* **44**(3), 198–205. https://doi.org/10.1159/000471917 (2017).
22. Juneja, D., Nasa, P. & Jain, R. Metformin toxicity: A meta-summary of case reports. *World J. Diabetes.* **13**(8), 654–664. https://doi.org/10.4239/wjd.v13.i8.654 (2022).
23. Vecchio, S. et al. Metformin accumulation: Lactic acidosis and high plasmatic metformin levels in a retrospective case series of 66 patients on chronic therapy. *Clin. Toxicol. (Phila).* **52**(2), 129–135. https://doi.org/10.3109/15563650.2013.860985 (2014).
24. Bailey, C. J., Wilcock, C. & Day, C. Effect of metformin on glucose metabolism in the splanchnic bed. *Br. J. Pharmacol.* **105**(4), 1009–1013. https://doi.org/10.1111/j.1476-5381.1992.tb09093.x (1992).
25. Bouchard, J. et al. Principles and operational parameters to optimize poison removal with extracorporeal treatments. In *Seminars in Dialysis* (Vol. 27, No. 4, pp. 371–380). (2014), July.
26. Dichtwald, S., Weinbroum, A. A., Sorkine, P., Ekstein, M. P. & Dahan, E. Metformin-associated lactic acidosis following acute kidney injury. Efficacious treatment with continuous renal replacement therapy. *Diabet. Med.* **29**(2), 245–250 (2012).
27. Uusalo, P. & Järvisalo, M. J. Mortality and renal prognosis in isolated metformin-associated lactic acidosis treated with continuous renal replacement therapy and citrate-calcium-anticoagulation. *Acta Anaesthesiol. Scand.* **64**(9), 1305–1311. https://doi.org/10.1111/aas.13659 (2020).
28. Lalau, J. D. et al. Metformin-associated lactic acidosis (MALA): Moving towards a new paradigm. *Diabetes Obes. Metab.* **19**(11), 1502–1512. https://doi.org/10.1111/dom.12974 (2017).

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. This audit study adhered to ethical guidelines outlined by ASL Città di Torino (UNI EN ISO 9000:2000 and ISO 19011:2003 as dictated by the Italian Health Ministry Quality (REF), ensuring the protection of participants' confidentiality, voluntary participation, and compliance with ethical standards in data collection and analysis. All data were recorded as non-identifiable information.

Additional information

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