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CASE REPORT Open Access

A rare case report of combined metformin-associated lactic acidosis and diabetic ketoacidosis

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Abstract

Background: Triad of diabetic ketoacidosis (DKA) comprises of hyperglycemia with serum glucose > 11 mmol/L, high anion gap metabolic acidosis and ketonemia. Hyperlactemia is often noted in patients with DKA. Metformin use is one of the risk factors of hyperlactemia, resulting in high anion gap metabolic acidosis, known as metformin associated lactic acidosis (MALA). This report is of a 60-year-old woman with type 2 diabetes mellitus who presented with combined metformin-associated lactic acidosis MALA and DKA.

Case presentation: A 60-year-old diabetic female presented to the emergency department with complaints of abdominal pain, vomiting and diarrhea. She was on metformin for the last 10 years, but despite compliance to medications, her HbA1c was 14.1. With an aim to improve her glycemic control, linagliptin 5 mg once a day was added 1 month ago. Initial investigations in ED including arterial blood gas analysis revealed metabolic acidosis, ketosis, hyperlactemia, and acute kidney injury. In view of metabolic acidosis and ketosis with elevated blood glucose level, she was diagnosed to have DKA. Compared to isolated DKA, patients with combined MALA and DKA have severe metabolic acidosis, a greater degree of hyperlactatemia but less extensive ketoacidosis. Hence, she was diagnosed to have combined MALA and DKA. She was admitted to intensive care unit and treated with intravenous fluids, insulin infusion, and continuous renal replacement therapy. Her metabolic acidosis, hyperlactemia, and kidney injury resolved and she was discharged well.

Conclusion: This report has shown the importance of rapid diagnosis and management of the rare and challenging diagnosis of combined MALA and DKA. The main goal of therapy is preventing hyperglycemia and ketosis, resolution of metabolic acidosis, and removal of accumulated metformin using intensive therapies like aggressive fluid resuscitation and early initiation of renal replacement therapy. Adjustment of dose of medications is needed to avoid this complication.

Keywords: Metformin, Acidosis lactic, Diabetic ketoacidosis

Introduction

Diabetic ketoacidosis (DKA) is a life-threatening emergency that may occur in patients with both type 1 and type 2 diabetes. It comprises of a triad of hyperglycemia with serum glucose > 11 mmol/L, metabolic acidosis (serum bicarbonate < 18 mEq/L), ketonemia (positive urine and serum ketones), and serum osmolality less than 320 mOsm/kg [1]. The onset of DKA is usually acute over a few days and the patients are dehydrated. The recommended management guidelines are aimed at preventing hyperglycemia and ketosis, with subsequent resolution of acidosis. The aim of treatment, with fluid replacement with 0.9% normal saline and insulin infusion at the rate of 0.1 units.kg/h, is reduction of the serum glucose level to

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< 11 mmol/L and any two of the following, reduction of serum bicarbonate level to ≥ 15 mEq/L, pH to > 7.3, or anion gap to ≤ 12 mEq/L [2]. Sodium bicarbonate should be given in severe DKA when the pH is < 6.9, as severe acidosis can lead to adverse cardiovascular and pulmonary effects.

Hyperlactemia is often noted in patients with DKA, and results from anaerobic glycolysis due to tissue hypoperfusion and hypoxia [2]. One of the risk factors associated with hyperlactemia is use of metformin [3], which is being increasingly used as a first-line therapy for the treatment of diabetes [4]. It is primarily excreted by the kidneys, and acute or chronic kidney injury may lead to accumulation of the drug, resulting in high anion gap metabolic acidosis, known as metformin associated lactic acidosis (MALA). It is a rare but severe complication and initially had a mortality rate of 30–50%, but with early recognition and treatment, the mortality rate has reduced to around 25% [5]. We report a challenging case of a 60-year-old woman with type 2 diabetes mellitus who presented to the emergency department (ED) with combined MALA) and DKA.

Case report

A 60-year-old female was brought to the ED for complaints of upper abdominal discomfort with vomiting and diarrhea for three days and sudden onset of acute shortness of breath. She had a past medical history of hypertension and type 2 diabetes mellitus for the last 10 years. She was on amlodipine 5 mg once a day and metformin 500 mg three times per day since 10 years. She weighed 63.3 kg with a body mass index (BMI) of 27.4. Her HbA1c checked a month ago was 14.1 despite being compliant to medications. Her creatinine was 99 µmol/L and estimated glomerular filtration rate (eGFR) was 52 ml/min. Antibodies to glutamic acid decarboxylase (Anti-GAD) antibodies or Islet cell antibodies were not checked but elevated HbA1c was attributed to progressively worsening diabetes. So, for improving her glycemic control, linagliptin 5 mg once a day was added for the past 1 month. On arrival in ED, she had tachycardia with heart rate of 126 beats/min, tachypneic with a respiratory rate of 26 breaths/min, blood pressure of 124/64 mmHg, and oxygen saturation of 99% on 2 L supplemental oxygen. Initial laboratory investigations done in the ED are shown in Table 1, with an anion gap of 44 mmol/L on arterial blood gas analysis. Her chest X-ray and urine examination were normal. Computerized tomography (CT) scan of abdomen did not show signs of bowel ischemia or intra-abdominal sepsis.

In view of elevated blood glucose level of 11.8 mmol/L, severe metabolic acidosis (serum bicarbonate < 2 mmol/L) and ketosis (serum ketones 4.1 mmol/L), she was initially diagnosed to have DKA. She was treated with a total of 3 L of crystalloid intravenous fluids (0.9% normal saline), while simultaneously monitoring her urine output as well as inferior vena cava diameter on bedside ultrasound. She was also given intravenous insulin infusion at 5 units/h with an aim to clear ketonemia and improve acidosis. In view of severe metabolic acidosis with Ph of 6.86 and hyperkalemia, she was also given 50 ml of intravenous 8.4% sodium bicarbonate, intravenous 10 ml of 10% calcium gluconate and sodium polystyrene sulfonate. Along with severe metabolic acidosis, she also had a greater degree of hyperlactatemia but less extensive ketoacidosis. Hence, she was diagnosed to have combined MALA and DKA. She was admitted to the intensive care unit (ICU).

Table 1 Laboratory parameters upon arrival in emergency department

Serum	Patient values	Reference range
Arterial blood gas		
Ph	6.86	7.35–7.45
pO2	150 mmHg	80–105 mm Hg
PCO2	8.5 mmHg	35–45 mmHg
Bicarbonate (HCO3)	2 mmol/L	22–26 mmol/L
Base excess (BE)	− 30 mmol/L	− 2–3 mmol/L
White cell count	22.68 × 103/dL	4–10 × 10^3/dL
Glucose	11.8 mmol/L	3.9–11 mmol/L
Urea	16.7 mmol/L	2.7–6.9 mmol/L
Creatinine	592 µmol/L	37–90 µmol/L
Potassium	7.1 mmol/L	3.5–5.1 mmol/L
Bicarbonate	< 2 mmol/L	19–29 mmol/L
Procalcitonin	1.42 µg/ml	< 0.49 µg/L
Lactate	18 mmol/L	0.5–2.2 mmol/L
Ketones (beta-hydroxybutyrate)	4.1 mmol/L	0–0.6 mmol/L

In ICU, repeat arterial blood gas showed pH of 6.801, base deficit of 30 mmol/L, bicarbonate (HCO3) 2.1 mmol/L, pCO2 13.2 mmHg, and pO2 80 mmHg. Her serum ketones persisted at 4.4 mmol/L and there was rising lactate level of 36.4 mmol/L. In view of severe metabolic acidosis with high respiratory demand and patient fatigue, decision was made to intubate the patient. In view of persistent hypotension despite fluid resuscitation, central venous line was placed and she was commenced on norepinephrine infusion. She also underwent emergent continuous renal replacement therapy (CRRT) to facilitate recovery from severe acidosis and acute kidney injury. Her metabolic acidosis improved after commencement of CRRT. Hyperlactemia and creatinine levels continued to improve with fluid resuscitation and CRRT (Fig. 1A, B). The patient underwent CRRT for total duration of 30 h.

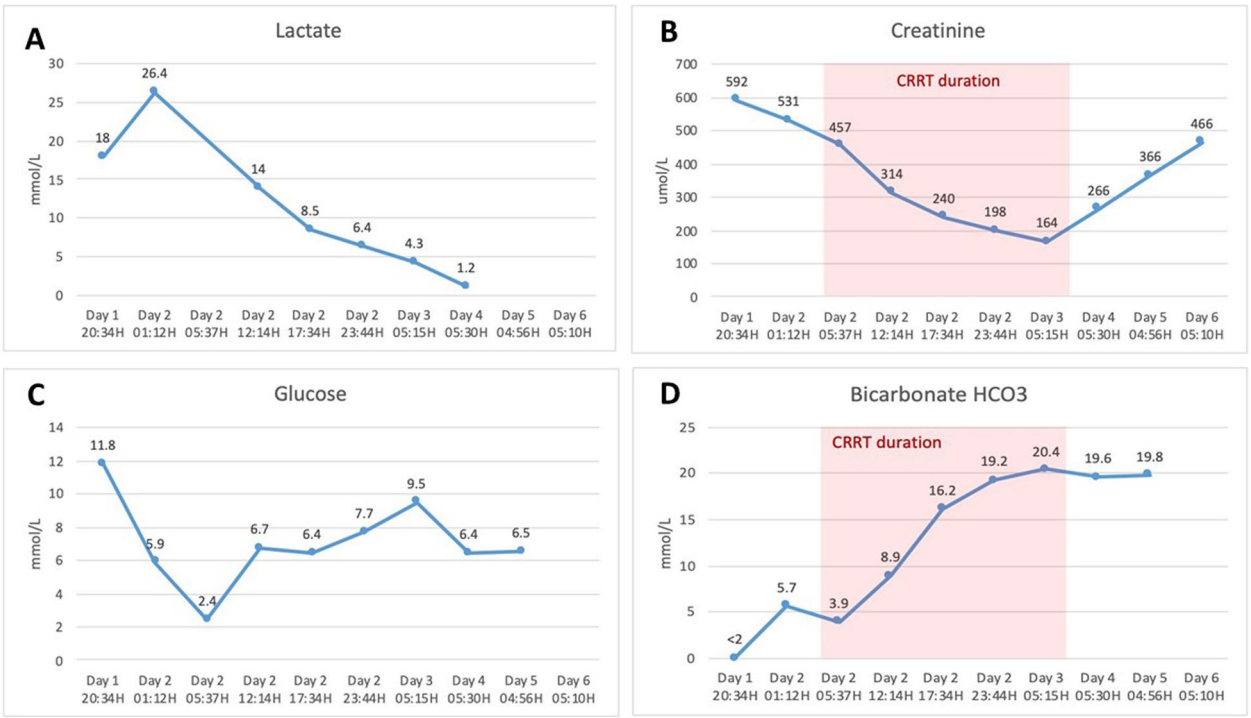

Fig. 1 Trend of change in laboratory parameters of serum lactate (**A**), serum creatinine (**B**), blood glucose (**C**), and serum bicarbonate (**D**) from patient's emergency department arrival till hospital discharge

Her vital signs stabilized, and the patient was extubated and vasopressor support was also stopped the next day. Her blood glucose stabilized the next day (Fig. 1C) including normalization of serum ketones to 0.7 mmol/L, and insulin infusion was stopped and she was commenced on subcutaneous insulin. Repeat serum lactate level was 2.5 mmol/L. Metformin was stopped since the day of admission. After a 3-day stay in the ICU, her intravenous antibiotics which were commenced for possible sepsis precipitating DKA were stopped, and she was then monitored in general ward with regular input/output charting. Her subsequent blood investigations including lactate, blood glucose and bicarbonate remained stable throughout the duration of admission (Fig. 1A, C, and D). Kidney function progressively improved with improved creatinine levels throughout the admission (Fig. 1B). In view of MALA, metformin was permanently stopped. She was discharged with subcutaneous actrapid insulin thrice a day, insulin glargine at bedtime, and oral linagliptin 5 mg once daily. She was given an outpatient follow-up with endocrinologist and family physician for monitoring her diabetes and renal function respectively.

Discussion

As metformin continues to be widely prescribed as a first-line agent for the treatment of diabetes, physicians need to be aware regarding early recognition and management of the life-threatening complication of combined MALA and DKA.

Lactic acidosis is routinely seen in DKA, but it is not associated with worse clinical outcomes including increased length-of-stay in intensive care unit [6]. Hyperlactatemia is defined as a persistent, mild to moderate (2–4 mmol/L) increase in blood lactate concentration without metabolic acidosis, whereas lactic acidosis is characterized by persistently increased blood lactate levels (usually > 5 mmol/L) in association with metabolic acidosis. The etiology of lactic acidosis in DKA is multifactorial, contributed by anaerobic glycolysis secondary to inadequate tissue perfusion and hypoxemia, as well as by the metabolic derangements and hyperglycemia present in DKA. Hyperglycemia causes elevated lactate levels by the glyoxalase pathway, which involves formation of intermediate metabolite methylglyoxal and its eventual conversion to lactate [3]. Thus, lactate levels should be interpreted with caution

in these patients, and clinicians should also consider the underlying disease state leading to hyperlactemia.

Metformin is recommended as the first-line therapy in patients with type 2 diabetes [7]. Metformin associated lactic acidosis (MALA) is defined as a blood lactate level ≥ 5 mmol/L, decreased pH (< 7.35), decreased serum bicarbonate, and an increased anion gap metabolic acidosis. The incidence of MALA is reported as 4.3 cases per 100,000 patient years in patients who take metformin [8]. The pathogenesis of MALA in diabetic patients is complex. Metformin can decrease hepatic gluconeogenesis by inhibiting mitochondrial oxidative phosphorylation. Lactate being a substrate in this mechanism can lead to its increased levels causing lactic acidosis [3]. In the absence of other ketogenic conditions like pregnancy, malnutrition and alcohol intake, metformin also causes stimulation of fatty acid oxidation which is a co-factor for ketogenesis [9]. The risk factors for MALA include impaired renal and hepatic function, and underlying conditions like sepsis which increase the production of lactate, with severe cases requiring dialysis. Besides elevation of lactate, the acidosis is also contributed by uremia secondary to acute kidney injury as well as accumulation of metformin which increase ketogenesis, thus adding to the acidosis [10]. The most common symptoms of MALA are gastrointestinal (abdominal pain, nausea, vomiting, and diarrhea) followed by dyspnea, altered mental state, and hypotension. Thus, presentation of MALA can mimic the diagnosis of gastroenteritis, as seen in our patient [10].

As metformin normally undergoes rapid and unchanging glomerular filtration and tubular excretion, MALA occurs only if renal function is altered due to underlying sepsis, dehydration or use of nephrotoxic drugs, and rarely in cases of metformin overdose. Dehydration and acute kidney injury (AKI) are precipitating factors in the development of lactic acidosis in people on regular metformin therapy. Moreover, metformin use increases plasma lactate concentrations and the risk of lactate acidosis. This association is particularly important to recognize in the context of AKI, as it can be seen even in patients with normal renal function [11].

Many type 2 DM patients are unable to maintain optimal blood sugar control with metformin alone. The 2012 guidelines of American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) have suggested use of combination therapy of metformin with sulfonylureas, thiazolidinediones, dipeptidyl peptidase–4 (DPP-4) inhibitors or glucagon-like peptide (GLP)-1 antagonists to improve glycemic control [12]. As our patient had mild renal insufficiency and as linagliptin is primarily excreted through biliary tract, with kidney excretion accounting for only about 5%, our patient was commenced on linagliptin. Also, clinical trials have shown that the combination of metformin with linagliptin significantly improves glycemic control with a low risk of hypoglycemia [12]. But, there is a warning regarding the risk of lactic acidosis in patients on combination of metformin and linagliptin (Jentadueto), and the risk has been attributed to metformin [13].

There have been case reports of patients with metformin-associated lactic acidosis with euglycemic ketoacidosis (MALKA) due to accumulation of metformin secondary to acute renal failure, leading to combined lactic acidosis and ketoacidosis reflected by the elevated anion gap [8, 9]. In view of blood sugar level of 11.8 mmol/L, blood gas showing severe metabolic acidosis (bicarbonate < 2 mmol/L) and beta-hydroxybutyrate level greater than 3.8 mmol/L [14], an initial diagnosis of DKA was made. But compared to isolated DKA, patients with combined MALA and DKA have severe metabolic acidosis, a greater degree of hyperlactatemia but less extensive ketoacidosis. Our patient's lactate was 11.8 mmol, which indicated a higher degree of hyperlactemia compared to ketosis. As she was on metformin, this severe lactic acidosis can also be attributed to MALA, instead of DKA alone. Thus, our patient was diagnosed to have combined metformin-associated lactic acidosis and diabetic ketoacidosis.

Goals of treatment recommended for hyperglycemic emergencies include correction of dehydration, hyperglycemia, ketonemia, hyperosmolality, lactic acidosis, and electrolyte imbalances. Fluid therapy, insulin, potassium, and bicarbonate are the main stay of treatment. Underlying precipitating etiology also needs to be managed simultaneously. Metabolic acidosis is a major acid-base derangement in critically ill patients and is associated with increased mortality. Also, lactate concentration > 5 mmol/L in patients with severe acidosis pH < 7.35 or base deficit greater than 6 carries a mortality of 80%. This suggests an underlying relationship between mortality and the degree of acidosis and hyperlactemia [15, 16].

Hence, it is crucial for early initiation of aggressive therapy from the ED in these patients. There are no standard guidelines for the treatment of patients with MALA, with resuscitation and supportive therapy being the mainstay of initial therapy. The utility of treatment with sodium bicarbonate and renal replacement therapy (RRT) have been documented in recent case reports. Treatment with sodium bicarbonate should be reserved for patients in ICU with high anion-gap metabolic acidosis, particularly severe lactic acidosis. It is independently associated with increased mean arterial pressure and reduced ICU mortality in this group of patients [17, 18]. But sodium bicarbonate alone may not be sufficient to correct the severe acidosis seen in these patients.

When standard supportive treatment fails, RRT should be considered as early adjunctive therapy. Early initiation of continuous renal replacement therapy (CRRT) appears to be safe and effective in treating patients with MALA. Metformin has low molecular weight, less protein binding and a large volume of distribution. Thus, a prolonged period of dialysis may be required to bring the patient's elevated plasma metformin to therapeutic levels. As prolonged therapy is required in these patients who are also hemodynamically unstable, initiation of CRRT compared to intermittent dialysis is a superior choice for patients with MALA [19–21]. It is recommended for patients with MALA who have decreased level of consciousness, are in shock despite adequate supportive management and a blood lactate level > 20 mmol/L and pH $\leq$ 7.0. It should be continued till a sustained correction of acid-base status (lactate level < 3 mmol/L and pH > 7.35) and patient attains hemodynamic stability [17, 22–25]. Currently, majority of the patients with severe MALA survive despite low pH and severity of metabolic acidosis. The primary goal of therapy is rapid restoration of acid-base status as well as removal of accumulated metformin, including aggressive fluid resuscitation and early initiation of renal replacement therapy.

Conclusions

This report has shown the importance of rapid diagnosis and management of the rare and challenging diagnosis of combined MALA and DKA. Patients with combined MALA and ketoacidosis present with severe metabolic acidosis and hyperlactemia. Compared to isolated DKA, patients with associated MALA have greater degree of hyperlactatemia, but less extensive ketoacidosis. The main goal of therapy is preventing hyperglycemia and ketosis, resolution of metabolic acidosis and removal of accumulated metformin using intensive therapies like aggressive fluid resuscitation and early initiation of renal replacement therapy. Physicians should also regularly monitor the patient for acute or chronic decline in kidney function. Majority of the patients with MALA have a good outcome despite the severity of metabolic acidosis and hyperlactemia. As metformin continues to be widely prescribed as a first-line agent for the treatment of diabetes, physicians need to be aware regarding early recognition and management of this life-threatening complication.

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Declarations

Ethics approval and consent to participate
Written informed consent has been obtained from the patient for publication of this case report.

Competing interests
All the authors declare that they have no conflict of interest.

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References

1. Barski L, Eshkoli T, Brandstaetter E, Jotkowitz A (2019) Euglycemic diabetic ketoacidosis. Eur J Intern Med. 63:9–14. https://doi.org/10.1016/j.ejim.2019.03.014
2. Dhatariya KK, Vellanki P (2017) Treatment of diabetic ketoacidosis (DKA)/hyperglycemic hyperosmolar state (HHS): novel advances in the management of hyperglycemic crises (UK versus USA). Curr Diab Rep. 17(5):33. https://doi.org/10.1007/s11892-017-0857-4
3. Bhat JA, Masoodi SR, Bhat MH, Bhat H, Ahmad PO, Sood M (2021) Lactic acidosis in diabetic ketoacidosis: a marker of severity or alternate substrate for metabolism. Indian J Endocrinol Metab. 25(1):59–66. https://doi.org/10.4103/ijem.IJEM_753_20
4. American Diabetes Association (2018) 8. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes - 2018. Diabetes Care 41(Suppl 1):S73–S85. https://doi.org/10.2337/dc18-S008
5. Kajbaf F, Lalau JD (2014) Mortality rate in so-called "metformin-associated lactic acidosis": a review of the data since the 1960s. Pharmacoepidemiol Drug Saf. 23(11):1123–1127. https://doi.org/10.1002/pds.3689
6. Cox K, Cocchi MN, Salciccioli JD, Carney E, Howell M, Donnino MW (2012) Prevalence and significance of lactic acidosis in diabetic ketoacidosis. J Crit Care. 27(2):132–137. https://doi.org/10.1016/j.jcrc.2011.07.071
7. American Diabetes Association (2021) Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes – 2021. Diabetes Care 44(Suppl 1):S111–S124. https://doi.org/10.2337/dc21-s009
8. Pallister E, Kannan T (2019) Persistent lactic acidosis - think beyond sepsis. Int J Anesthetic Anesthesiol 6:094. https://doi.org/10.23937/2377-4630/141009
9. Schwetz V, Eisner F, Schilcher G et al (2017) Combined metformin-associated lactic acidosis and euglycemic ketoacidosis. Wien Klin Wochenschr 129(17-18):646–649. https://doi.org/10.1007/s00508-017-1251-6
10. Kinoshita H, Yanai M, Ariyoshi K, Ando M, Tamura R (2019) A patient with metformin-associated lactic acidosis successfully treated with continuous renal replacement therapy: a case report. J Med Case Rep. 13(1):371. https://doi.org/10.1186/s13256-019-2311-5
11. Connelly PJ, Lonergan M, Soto-Pedre E, Donnelly L, Zhou K, Pearson ER (2017) Acute kidney injury, plasma lactate concentrations and lactic acidosis in metformin users: A GoDarts study. Diabetes Obes Metab. 19(11):1579–1586. https://doi.org/10.1111/dom.12978
12. Genuth S (2015) Should sulfonylureas remain an acceptable first-line add-on to metformin therapy in patients with Type 2 diabetes? No, its

time to move on! Diabetes Care 38(1):170–175. https://doi.org/10.2337/dc14-0565
13. Learn more about Jentadueto. Important safety information. Website https://www.jentadueto.com/. Accessed online 31 March 2022.
14. Sheikh-Ali M, Karon BS, Basu A et al (2008) Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis? Diabetes Care. 31(4):643–647. https://doi.org/10.2337/dc07-1683
15. Stacpoole PW, Wright EC, Baumgartner TG, Bersin RM, Buchalter S, Curry SH, Duncan C, Harman EM, Henderson GN, Jenkinson S et al (1994) Natural history and course of acquired lactic acidosis in adults. DCA-Lactic Acidosis Study Group. Am J Med. 97(1):47–54. https://doi.org/10.1016/0002-9343(94)90047-7
16. Dell'Aglio DM, Perino LJ, Kazzi Z, Abramson J, Schwartz MD, Morgan BW (2009) Acute metformin overdose: examining serum pH, lactate level, and metformin concentrations in survivors versus nonsurvivors: a systematic review of the literature. Ann Emerg Med. 54(6):818–823. https://doi.org/10.1016/j.annemergmed.2009.04.023
17. Fujii T, Udy AA, Nichol A, Bellomo R, Deane AM, El-Khawas K et al (2021) Incidence and management of metabolic acidosis with sodium bicarbonate in the ICU: An international observational study. Crit Care. 25(1):45. https://doi.org/10.1186/s13054-020-03431-2
18. Lo KB, Garvia V, Stempel JM, Ram P, Rangaswami J (2020) Bicarbonate use and mortality outcome among critically ill patients with metabolic acidosis: a meta-analysis. Heart Lung. 49(2):167–174. https://doi.org/10.1016/j.hrtlng.2019.10.007
19. Barrueto F, Meggs WJ, Barchman MJ (2002) Clearance of metformin by hemofiltration in overdose. J Toxicol Clin Toxicol. 40(2):177–180. https://doi.org/10.1081/clt-120004407
20. Arroyo AM, Walroth TA, Mowry JB, Kao LW (2010) The MALAdy of metformin poisoning: Is CVVH the cure? Am J Ther. 17(1):96–100. https://doi.org/10.1097/MJT.0b013e318197eab6
21. Keller G, Cour M, Hernu R, Illinger J, Robert D, Argaud L (2011) Management of metformin-associated lactic acidosis by continuous renal replacement therapy. PLoS One. 6(8):e23200. https://doi.org/10.1371/journal.pone.0023200
22. Mariano F, Biancone L (2021) 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
23. Hermez K, Dudash-Mion C (2021) Profound metabolic acidosis due to metformin intoxication requiring dialysis. Case Rep Nephrol. 2021:9914982. https://doi.org/10.1155/2021/9914982
24. Kajbaf F, Lalau JD (2013) The prognostic value of blood pH and lactate and metformin concentrations in severe metformin-associated lactic acidosis. BMC Pharmacol Toxicol. 14:22. https://doi.org/10.1186/2050-6511-14-22
25. Seidowsky A, Nseir S, Houdret N, Fourrier F (2009) Metformin-associated lactic acidosis: a prognostic and therapeutic study. Crit Care Med. 37(7):2191–2196. https://doi.org/10.1097/CCM.0b013e3181a02490

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