



Case reports

## ACUTE KIDNEY INJURY DUE TO METFORMIN-ASSOCIATED LACTIC ACIDOSIS

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### ABSTRACT

**Introduction:** Acute kidney injury is a clinical syndrome of rapid decline of renal function due to various causes and often occurs by more than one pathophysiological mechanism. It is associated with multiorgan involvement and correlates with high mortality, especially when it develops in already hospitalized patients. Metformin-associated lactic acidosis is a special case of lactic acidosis associated with the intake of antidiabetic drugs from the biguanide group in patients with diabetes mellitus type 2. Mortality in severe forms can exceed 50%.

**Case description:** We present two clinical cases of severe acute kidney injury due to metformin-dependent lactic acidosis requiring temporary use of renal replacement therapy, and offer a brief overview of the specific changes in metformin lactic acidosis, as well as our perspective on the behavior.

**Conclusion:** In our opinion, the use of metformin in patients with type 2 diabetes mellitus should be strictly controlled, and if it is not possible - should be avoided. We assume that the number of patients with metformin lactic acidosis and the mortality rate are lower than the real ones due to omissions or late diagnosis.

**Keywords:** diabetes mellitus type 2, metformin, lactic acidosis, acute kidney injury, hemodialysis treatment,

### INTRODUCTION

According to Kidney Disease Improving Global Outcomes (KDIGO) criteria, acute kidney injury (AKI) is a sudden decrease in kidney function that leads to the development of typical acute renal failure. AKI is defined by the following criteria:

- Increase in sCr  $\geq 0.3$  mg/dL ( $\geq 26.5$   $\mu\text{mol/l}$ ) within 48 hours; or
- Increase in sCr to  $\geq 1.5$  times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume  $< 0.5$  ml/kg/h, for 6 hours [1, 2].

The prevalence of AKI varies considerably in different reports, especially in relation to age, comorbidities, economic development and above all whether this condition develops in the community or in patients receiving hospital treatment, especially in intensive care units, cardio- and neurosurgery, etc., with estimated prevalence range from 1 and 66%. [3, 4, 5].

The old etiological classification of the syndrome, divided depending on the site of action of the main nox into pre-renal, renal and post-renal (obstructive), is still widely used today, but does not replace the clinical-laboratory classifications of KDIGO, RIFLE and AKIN [6, 7, 8].

Lactic acid is produced in the human body as part of physiological processes, but also as a result of a number of pathological conditions. When the increased production of lactate is combined with a reduced clearance, clinical manifestations are reached, such as: nausea, vomiting, abdominal pain, hypothermia and hemodynamic instability. Taking medications such as salicylates, halothane, biguanidine derivatives, cocaine, and large amounts of alcohol also cause increased lactate production [9, 10].

Serum lactate levels can be used as a diagnostic marker and a treatment criterion. Severe lactic acidosis is usually associated with disease processes intensifying lactic acid production and/or reduced lactate clearance. The more severe the degree of acidosis, the higher the mortality rate as a result of this condition, as according to Boris Jung et al., at  $\text{pH} < 7.2$ , mortality is 57% [11, 12].

## DESCRIPTION OF CASES

### Case 1

A sixty-five-year-old Caucasian woman with a history of long-standing diabetes mellitus and arterial hypertension was admitted to the Clinic with complaints of epigastric pain, repeated vomiting, and diarrhea for two days. Since the morning of the same day, she has been confused and disoriented, with impaired vision and anuria. The patient has been on oral treatment for diabetes mellitus type 2 with an oral preparation containing 1,000 mg of metformin hydrochloride for one year, with serum creatinine values of 155  $\mu\text{mol/l}$  and estimated GFR (eGFR) of 29.2 ml/min/1.73 m<sup>2</sup>. [Table 1A] During hospitalization, the following were found: severe general condition, confusion, disorientation, no pathological physical findings on the part of the lungs and heart were found, respiration rate – 24/min, heart rate – 104/min, BP – 100/70 mmHg, blood urea – 26.4 mmol/l; serum creatinine – 625  $\mu\text{mol/l}$ ; K<sup>+</sup> – 6.5 mmol/l, pH – 7.12, BE – (-17 mmol/l), lactate >15 mmol/l. [Table 1B]

Treatment was started with infusions of crystalloid solutions and a diuretic, alkalization. By the fourth hour of hospitalization, hemodialysis treatment was initiated. Several daily HD sessions were held with a total duration of 15 hours. The patient entered a polyuric stage with diuresis up to 6300 ml. She was discharged in good condition and serum creatinine – 162  $\mu\text{mol/l}$ , e-GFR – 29.0 ml/min/1.73 m<sup>2</sup>. Metformin intake was discontinued.

### Case 2

A seventy-two-year-old Caucasian woman with a long-standing history of type 2 diabetes mellitus, metabolic syndrome and arterial hypertension was hospitalized in the Neurology Clinic due to the acute onset of lumbar pain, accompanied by painfully limited movements in the lower right limb. Treatment was carried out with high doses of nonsteroidal anti-inflammatory drugs. During the course of treatment, deterioration of the general condition, oliguria and increased nitrogen products were observed. The patient has been on oral treatment for type 2 diabetes with two oral preparations since 2013, containing 1000 mg metformin hydrochloride and pioglitazone, with serum creatinine values of 13  $\mu\text{mol/l}$  and estimated GF (eGFR) of 38 ml/min/1.73 m<sup>2</sup>. [Table 1A] Since then, renal function has not been monitored. As the general condition worsened, the following were found: blood urea – 21.9 mmol/l; serum creatinine – 482  $\mu\text{mol/l}$ ; K – 6.4 mmol/l, pH – 7.02 mmol/l, BE – (-22.6 mmol/l), lactate - 11.3 mmol/l. [Table 1B]

Treatment was started with infusions of crystalloid solutions and diuretic, alkalization. By the second hour of registering lactic acidosis, hemodialysis treatment was also initiated. Several daily HD sessions were performed with a total duration of 15 hours. The patient entered a polyuria stage with diuresis up to 7000 ml. She was discharged from the hospital in good condition and serum creatinine – 178  $\mu\text{mol/l}$ , e-GFR – 26 ml/min/1.73 m<sup>2</sup>, lactate - 2.7 mmol/l. Metformin intake was discontinued.

**Table 1A.** Anamnestic, treatment data and outcome.

	sex	age	Diagnosis	Treatment of DM2	Treatment of AKI	Duration of dialysis (h)	Outcome
Case 1	F	65	DM2+HTN	Metformin	HD	15	restored
Case 2	F	72	DM2+HTN	Metformin +NSAIDs	HD	15	restored

(DM2 - diabetes mellitus type 2; HTN – hypertension; NSAID - nonsteroidal anti-inflammatory drugs; AKI – acute kidney injury; HD - hemodialysis)

**Table 1B.** Laboratory results at hospitalization.

	Lactate (mmol/L)	Hb(g/L)	Leuco (10 <sup>12</sup> /L)	PLT (10 <sup>9</sup> /L)	BUN (mmol/L)	Cr ( $\mu\text{mol/L}$ )	K <sup>+</sup> (mmol/L)	pH	BE (mmol/L)
Case 1	>15	104	21.3	138	26	625	6.5	<6.9	na
Case 2	11.3	115	9.9	335	19	406	7.3	7.02	-23

(Hb – hemoglobine; PLT – platelets; BUN - Blood Urea Nitrogen; Cr – creatinine; K<sup>+</sup> - potassium; pH – potential of hydrogen; BE – base excess; na – not available)

## DISCUSSION

Metformin is an oral antidiabetic drug of the biguanide class that is widely used in patients with type 2 diabetes mellitus. Its glucose-lowering effect is mainly due to reduced hepatic glucose production plus increased utilization in peripheral tissues [13]. It is absorbed primarily from the small intestine, has a bioavailability of 40 to 60% and an approximate plasma half-life of 1.5 to 4.9 hours, and is eliminated primarily by the kidneys by glomerular filtration and tubular secretion [13, 14, 15].

Lactic acidosis is divided into two types: Type A results from the accumulation of lactate through anaerobic glycolysis, and is primarily associated with hypoxia and hypoperfusion. Type B lactic acidosis, which occurs with metformin overdose, occurs during conditions when lactate production is increased and when lactic acid clearance by oxidation or gluconeogenesis is reduced [12, 15].

Metformin-associated lactic acidosis (MALA) usually occurs in patients with elevated plasma metformin concentrations, which may be caused by its use in conditions of lactate overproduction or impaired clearance of metformin. Impaired clearance is associated with hepatic or renal insufficiency, and increased lactate production occurs in shock, malignancy, alcoholism, infection, antiretroviral therapy, and mitochondrial liver dysfunction. Contraindications to the use of metformin should be strictly observed, because with these limitations, the reported incidence of MALA in clinical practice remains very low, with less than 10 cases per 100,000 patient-years. In clinical practice, metformin is used in 24.5% to 94% of patients with type 2 diabetes, despite contraindications [14, 16, 17, 18]. Dosage guidelines for patients with chronic kidney disease (CKD) were published in 2013 [19]. The following maximum daily doses are recommended for the respective estimated creatinine clearance (e-GFR): 3 g (120 mL/min), 2 g (60 mL/min), 1 g (15 mL/min) and 500 mg (below 15 mL/min).

MALA is more likely to occur in patients who have acutely deteriorated renal function due to dehydration, vomiting or diarrhea, surgery, use of nephrotoxic medications, etc., especially in elderly patients who have a reduced glomerular filtration rate [15, 20, 21, 22]. In the cases we described, metformin use was combined with dehydration (case 1) and/or use of nephrotoxic medications (case 2), which further led to impaired elimination of the drug.

Treatment of severe lactic acidosis may be initiated with sodium bicarbonate infusion. There is insufficient evidence to support this treatment, but some recommend initiating bicarbonate infusion at pH <7.20 in the pres-

ence of underlying comorbidities. Bicarbonate infusion should be used to maintain pH >7.20. It should be noted that sodium bicarbonate acts in the extracellular space, whereas the problem in MALA involves intracellular acidosis that disrupts normal respiration and glucose uptake. There is a lack of well-documented evidence of the beneficial effects of crystalloid solutions and bicarbonate. In addition, its administration may also cause sodium overload, hyperchloremia, increased carbon dioxide production, and reflex vasodilation. [17, 23]

Metformin shows mixed characteristics regarding dialyzability. It is lipophilic and has a high volume of distribution; however, it also has low protein binding and a prolonged half-life. Intermittent hemodialysis appears to be more effective in clearing metformin and lactate than continuous clearance methods. However, given the large volume of distribution, there may be some benefit from prolonged hemodialysis sessions to successfully clear metformin and lactate. Some case reports have required between 21 and 31 hours of continuous treatment for complete clearance in the setting of acute renal failure. The decision to discontinue hemodialysis can be made once the lactate level is below 3 mmol/l and the pH is 7.35. [24]

Susan Kim et al. presented data from their study (2023) on a total of 19 patients with MALA criteria, of whom 15 patients had AKI and 4 had ESRD. In the group with AKI due to MALA, the reported mortality was 46.7%. A total of 12 of these patients received renal replacement therapy, and four patients died in this subgroup, representing a 33% mortality rate [25]. Angioi A, et al. (2018) reported a 21.4% mortality rate among 28 patients with MALA, over a 14-year period, all treated with continuous low-efficiency hemodialysis (SLED). Other authors have also reported good results with intermittent dialysis sessions, with a cumulative duration of 15 to 25 hours [26, 27, 28].

We initiated dialysis treatment in our patients on intermittent dialysis for the following indications: anuria lasting >12 hours, pH<7.2, lactate>15.0 mmol/l. The total duration in both cases was 15 hours, which was sufficient for the values of the monitored parameters to be stabilized: pH>7.35, lactate<3.0 mmol/l.

Despite the controversial literature data, we believe that metformin administration should be done cautiously, with periodic clinical and laboratory monitoring, in patients with CKD (e-GFR<60ml/min/1.73m<sup>2</sup>) and discontinued in patients with e-GFR<30 mL/min/1.73 m<sup>2</sup>, as reflected in the KDIGO good clinical practice guidelines [29, 30, 31].

## CONCLUSION

In our opinion, the use of metformin in patients with type 2 diabetes mellitus is not well controlled. In our daily practice, we often encounter cases treated with 1000 mg per day in terminal uremia, <15 ml/min/1.73 m<sup>2</sup>.

This treatment should be controlled more strictly, and if control is impossible - avoided. We assume that the reported number of patients with metformin lactic acidosis and the mortality from it are lower than the real ones due to omissions or late diagnosis.

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