Metformin is a biguanide antidiabetic agent frequently used in the treatment of Type 2 DM. Even though Metformin-Associated Lactic Acidosis (MALA) is not seen very frequently, MALA has a high mortality rate. This case is presented to draw attention to the efficiency of hemodialysis and CVVHDF in the treatment of MALA.

A 25-year-old female patient was brought to the emergency service with abdominal pain and confusion. In her detailed history, it was learned that she took 100 tablets of metformin (1000 mg per tablet). Hemodialysis initiated because of severe metabolic acidosis, elevation of blood urea and hyperkalemia were seen in laboratory results. After that, patient was intubated because of low Glasgow Coma Scale (GCS:3) and vasopressor agent were started due to hypotension. In the intensive care unit, blood glucose was seen 44 mg dl⁻¹ and treated with 10% dextrose solution. CVVHDF treatment was started because of anuria and metabolic acidosis. Patient who underwent CVVHDF treatment for 12-days transferral to nephrology service on the 23rd day of the ICU admission with full consciousness and stabilized vitals.

In conclusion, hemodialysis and CVVHDF should be the first treatment methods to be considered in patients with metformin-associated lactic acidosis. Renal replacement therapies, initiated rapidly and maintained for an adequate time period are promising in this high mortality rate cases.

Keywords: Hemodialysis; lactic acidosis; metformin intoxication.

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Metformin is a biguanide antidiabetic agent frequently used in the treatment of type 2 diabetes mellitus. Metformin is an anti-hyperglycemic agent used to achieve euglycemia. Lactic acidosis can be seen in acute and chronic use of biguanides. Although the incidence of acidosis is 5-9 per 100,000, metformin-associated lactic acidosis (MALA) has high mortality rates. Plasma half-life of metformin is approximately six hours. Its small molecular weight (165.8kD) and insignificant binding to plasma proteins increase the distribution volume of the drug (63-276 L). Its sequestration in blood cells, such as erythrocytes and platelets, can extend its elimination half-life up to 17 hours.

The major mechanism in the excretion of metformin is tubular secretion, and metformin is largely excreted unchanged in the urine. Its estimated renal clearance is 507±129 ml/min which is more than three times its creatinine clearance. However, in cases, such as the presence of underlying chronic renal failure and/or high doses of metformin used for suicidal intent, renal clearance is exceeded.
and drug excretion decreases. As a result of this situation, lactic acidosis with high anion gap occurs.\textsuperscript{[9, 10]}

Lactic acidosis seen in human beings is divided into two forms as type A and type B. Type A lactic acidosis arises from the cells’ orientation to non-oxidative breathing for energy production as a result of poor perfusion of tissues. Type B, on the other hand, occurs with an external agent that may cause intoxication in tissues without initial perfusion defect or with a decrease in lactate clearance.\textsuperscript{[10, 11]}

Metformin intoxication may present with nonspecific symptoms, such as nausea, vomiting, abdominal pain, hypoglycemia, hypothermia, tachypnea, tachycardia, bradycardia, hypotension/hypertension, agitation, somnolence, stupor and coma. Therefore, anamnesis is important to make differential diagnosis.\textsuperscript{[12, 13]}

The classical triad of metformin toxicity can be listed as acute renal failure, high plasma metformin concentration and severe lactic acidosis.\textsuperscript{[7]} Concerning its mechanism of action, metformin inhibits the complex necessary for hepatic gluconeogenesis and oxidative respiration in mitochondria and directs cells, primarily hepatocytes and intestinal cells, to anaerobic respiration (Fig. 1).

As a result, lactate accumulates in the body. Lactate formed may lead to high anion-gaped metabolic asidois even in patients with normal renal function.\textsuperscript{[7]} Severe metabolic acidosis may disrupt the neurological condition and endanger the patient’s airway. In addition, since metabolic acidosis may cause cardiovascular instability at a high rate, patients are usually followed up in controlled mechanical ventilation.

Given that metformin preparations are cheap and sold without a prescription makes access to the drug quite easily. In addition, metformin has become a drug that can be easily accessed by the young population due to its use in the treatment of obesity in type 2 diabetes mellitus and nondiabetic patients. This easily available drug can be used for suicidal purposes like many other drugs that are easily available.

In this case, we aimed to draw attention to acute metformin intoxication treatment protocols in people without additional disease history by sharing the intensive care follow-up process of a patient who received a total of 100 g (1530mg/kg) of metformin to commit suicide and brought to our hospital emergency room.

**Case Report**

A 25-year-old female patient without additional disease history was brought to the emergency room of our hospital with complaints of nausea, vomiting, abdominal pain and confusion. It was learned from her family that the patient who had received 100 tablets of 1000 mg metformin was sent to hemodialysis unit by the emergency clinic after being consulted with nephrology upon the presence of severe lactic acidosis in the arterial blood gas, urea-creatinine elevation and hyperkalemia in blood biochemistry. The consultation was requested by our clinic in the emergency room for the patient whose inotropic support was initiated due to closure of consciousness and hypotension after hemodialysis. The general health condition of the patient was poor. Besides, loss of conscious IR -, fixed and dilated pupillas accompanied by GKS: E1 M1 V1 and hypotension (68/42 mmHg) were detected despite inotropic treatment. Then, the patient was taken to the intensive care unit after orotracheal intubation.

The patient was started to undergo invasive mechanical ventilation, and after the development of hypoglycemia (44 mg dL\textsuperscript{-1}), 10% dextrose IV was administered. In addition, despite the infusion of dopamine, her mean arterial pressure was <60 mmHg, so noradrenaline infusion together with continuous treatment with veno-venous hemofiltration (CVVHDF) was initiated (Table 1). The patient who was hypothermic (33.2 °C) was heated with a blow heater. Despite CVVHDF treatment, her blood pH remained at <7.15. Then, sodium bicarbonate infusion was initiated. When her pH was >7.15, sodium bicarbonate infusion was stopped. The patient regained consciousness on the 4th day of her intensive care stay. However, as a result of spontaneous ventilation attempts, sufficient ventilation capacity could not be

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**Figure 1.** Metformin’s mechanism of action.

AMPK: ATP –activated protein kinase; ACC: Acetyl-CoA carboxylase; SREBP-1: Sterol regulatory element-binding protein-1; GV-LDL, Group V LDL.
seen, and mechanical ventilation was continued under the infusion of dexmedetomidine. In the intensive care follow-up, liver function parameters (AST, ALT) increased (Table 2) and platelet counts decreased, therefore consultations from departments of internal medicine and gastroenterology were requested.

Pseudotrombocytopenia was excluded based on the results of the peripheral smear test performed by the department of internal medicine, and thrombocytopenia was associated with metformin overdose and no recommendation was made except for replacement with pooled platelet suspension. Gastroenterology suggested avoidance of hepatotoxic drug use.

Nasal discharge, sputum, and urine samples of the patient whose infection parameters (CRP, procalcitonin) tended to increase were sent for antibiotic susceptibility tests and broad-spectrum antibiotherapy (meropenem, teicoplanin) was initiated by the department of infectious diseases. Contact isolation was applied, and colistimethate sodium was added to antibiotherapy in accordance with culture antibiogram sensitivity.

CVVHDF was terminated in the patient who had spontaneous urine output on the 17th day of the intensive care stay was started on intermittent diuretic therapy (furosemide). In addition, the patient whose pneumonia improved and had adequate spontaneous breathing was intubated and noninvasive mechanical ventilation was performed intermittently according to arterial blood gas results.

Nephrology consultation was requested for the patient (Table 2) who did not have sufficient urine output and had high urea and creatinine value despite diuretic treatment. Then, the patient was included in the hemodialysis program by nephrology. On the 23rd day of the intensive care stay, the patient was in good general condition, conscious, cooperative, orientated, hemodynamically stable, so noninvasive mechanical ventilation was not required. However, her urea-creatinine level remained at high levels, so she was transferred to the nephrology service for the maintenance of her treatment.

**Discussion**

Metformin, which is a frequently used agent in the treatment of type 2 diabetes mellitus, may rarely cause lactic acidosis. Lactic acidosis occurs due to the development of chronic kidney failure or acute kidney failure in people using normal doses of metformin. In addition, severe lactic acidosis, which may be life-threatening, can be observed in cases of acute intake of high doses of the drug for suicidal intent.

Metformin toxicity causes atypical symptoms and signs. As we encountered in our case, most of the patients apply to the emergency department with gastrointestinal symptoms (nausea-vomiting, diarrhea, epigastric pain), hypotension/hypertension, bradycardia/tachycardia, hypoglycemia, hypothermia, tachypnea, neurological changes (convulsion, somnolence, stupor, coma). Therefore, a detailed anamnesis constitutes a special place in terms of differential diagnosis.

The resulting metabolic acidosis affects the cardiovascular system negatively by depressing the calcium channels that open slowly. As a result of cardiovascular system depression, decreased systemic vascular resistance, severe arrhythmias (with the effects of hyperkalemia), profound

| Parameters             | Emergency service | ICU 1. hr | ICU 24. hr | ICU 2. day | ICU 4. day | ICU 10. day | ICU 17. day | ICU 23. day |
|------------------------|------------------|----------|-----------|-----------|-----------|-------------|-------------|-------------|
| pH                     | 7.03             | 7.11     | 6.90      | 7.26      | 7.30      | 7.37        | 7.40        | 7.42        |
| pCO₂                   | 30.4             | 32.5     | 56.7      | 36.3      | 38.5      | 49.5        | 41.4        | 35.3        |
| pO₂                    | 93.6             | 204      | 79        | 114       | 90.4      | 96.5        | 151         | 109         |
| HCO₃                   | 7.8              | 10       | 10.6      | 15.9      | 26.9      | 28          | 25.5        | 28.4        |
| BE                     | -20.7            | -17.6    | -19.7     | -9.8      | 1.2       | 3.1         | 1.3         | 5.2         |
| sO₂, %                 | 91.9             | 98.9     | 90        | 97.9      | 95.6      | 96.9        | 99.4        | 99.7        |
| Lac                    | 19               | 17       | 22        | 8         | 6.2       | 1.2         | 1           | 1.1         |
| PCT                    | 0.20             | 0.35     | 0.50      | 4.1       | 4.0       | 1.2         | 0.75        | 0.39        |
| CRP                    | 0.5              | 0.3      | 1.3       | 7.9       | 168.1     | 134         | 27.2        | 21.1        |
| Hb                     | 11.8             | 8.1      | 9.6       | 10.6      | 8.5       | 10.5        | 8.3         | 7.5         |
| Hct                    | 36.7             | 25.9     | 30.7      | 32.6      | 24        | 29.5        | 23.9        | 22.1        |
| WBC                    | 10.94            | 27       | 31.52     | 33.71     | 31.98     | 27.69       | 10.54       | 8.46        |
| Neu, %                 | 51.4             | 80.5     | 90.8      | 88.1      | 96.8      | 87.4        | 79.3        | 75          |
| Plt                    | 272              | 195      | 124       | 41        | 18        | 48          | 140         | 225         |

PCT: procalcitonin; Lac: lactate.
hypotension and cardiac arrest can be seen. These cardiac effects may cause organ hypoperfusion, leading to multi-organ failure, especially renal failure.

We also encountered multi-organ failure, particularly renal failure in our patient. Arıkan et al.\[14\] stated that they applied sodium bicarbonate and diuretic therapy to MALA patients with the normal state of consciousness, hemodynamically stable, good renal functions, and pH >7.20, and achieved successful results. However, the treatment for the cause of metabolic acidosis was incomplete.

Indeed, the decrease in plasma bicarbonate value is the body’s response to metabolic acidosis; in other words, bicarbonate deficiency is a result of a decrease in arterial blood gas values. In addition, sodium bicarbonate applied without eliminating metformin and lactate from plasma may cause excessive sodium burden and vasodilation. In addition, the pH value that shifts towards alkaline level after application of sodium bicarbonate increases the displacement of the hemoglobin-oxygen dissociation curve to the left and increases the oxygen affinity of hemoglobin and causes development of hypoxia at the tissue level. As a result, intracellular acidosis increases paradoxically. Therefore, when pH >7.15 was seen in this case, bicarbonate infusion was stopped and treatment was continued with CVVHDF until hemodynamic stability was achieved. In conclusion, hemodialysis or continuous renal replacement therapies should be considered firstly in patients diagnosed with MALA caused by metformin, which can also be used without requiring a prescription for slimming

| Table 2. Biochemical tests and blood parameters |
|-----------------------------------------------|
| Emergency service | ICU 1. hr | ICU 24. hr | ICU 2. day | ICU 4. day | ICU 10. day | ICU 17. day | ICU 23. day |
|-------------------|----------|------------|------------|------------|------------|------------|------------|
| Urea              | 15.83    | 10.65      | 11.36      | 31         | 42         | 122.09     | 90         | 107.62     |
| Cre               | 2        | 1.63       | 1.34       | 1.33       | 1.15       | 1.79       | 2.93       | 3.79       |
| eGFR              | 34       | 47         | 57         | 58         | 67         | 43         | 26         | 20         |
| AST               | 21       | 59         | 106        | 308        | 501        | 64         | 20         | 27         |
| ALT               | 13       | 37         | 74         | 148        | 223        | 85         | 11         | 11         |
| T. Bil            | 0.80     | 0.96       | 1.02       | 1.42       | 1.83       | 3.26       | 1.16       | 0.89       |
| D.Bil             | 0.16     | 0.74       | 0.72       | 0.75       | 0.80       | 1.05       | 0.41       | 0.26       |
| Albumin           | 3.75     | 3.02       | 2.61       | 3.41       | 3.31       | 2.74       | 2.80       | 2.94       |
| PT                | 32.2     | 22.2       | 23.6       | 14.4       | 12.9       | 13.3       | 12.7       | 13.3       |
| aPTT              | 178      | 38.7       | 59.5       | 33.8       | 31.5       | 32.4       | 28.9       | 30.1       |
| INR               | 2.9      | 1.95       | 2.01       | 1.22       | 1.08       | 1.12       | 1.05       | 1.14       |
| Glucose           | 49       | 241        | 139        | 147        | 158        | 89         | 115        | 108        |
| Na⁺               | 140      | 139        | 154        | 146        | 132        | 140        | 138        | 139        |
| K⁺                | 4.29     | 3.21       | 2.88       | 4.35       | 4.14       | 2.86       | 3.64       | 3.75       |
| Ca²⁺              | 9.70     | 7.10       | 7.80       | 8.60       | 8.40       | 7.10       | 9.30       | 8.50       |
| Cl                | 105      | 92         | 97         | 95         | 101        | 101        | 102        | 100        |
| CK-MB             | 18.20    | 14.30      |            |            |            |            |            |
| Trop I            | 0.010    | 0.020      |            |            |            |            |            |
| β-hCG             | 0.48     | 0.44       |            |            |            |            |            |

\(Trop: \) Troponin; \(T, \) bil: Total bilirubin; \(D. \) bil: Direct bilirubin.
purposes. Renal replacement therapies, which are started quickly and maintained for a sufficient period, continue to give hope even in this condition with high mortality rates.

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References
1. Pilmore HL. Review: metformin: potential benefits and use in chronic kidney disease. Nephrology (Carlton) 2010;15:412–8.
2. Lalau JD, Lacroix C, Compagnon P, de Cagny B, Rigaud JP, Blichner G, et al. Role of metformin accumulation in metformin-associated lactic acidosis. Diabetes Care 1995;18:779–84. [CrossRef]
3. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010:CD002967. [CrossRef]
4. Biradar V, Moran JL, Peake SL, Peter JV. Metformin-associated lactic acidosis (MALA): clinical profile and outcomes in patients admitted to the intensive care unit. Crit Care Resusc 2010;12:191–5.
5. Nguyen HL, Concepcion L. Metformin intoxication requiring dialysis. Hemodial Int 2011;15 Suppl 1:S68–S71. [CrossRef]
6. Acquistapace G, Rossi M, Garbi M, Cosci P, Canetta C, Manelli A, Ricevuti G. Acute metformin intoxication: 2012 experience of Emergency Departement of Lodi, Italy. Clin Chem Lab Med 2014;52:1489–97. [CrossRef]
7. Protti A, Lecchi A, Forunato F, Artoni A, Greppi N, Vecchio S, Fagiolari G, Moggio M, Comi GP, Mistalettii G, Lanticina B, Faraldi L, Gattinoni L. Metforminoverdosecausesplateletmitochondrialdysfunction in humans. Critical Care. 2012; 16:R180. [CrossRef]
8. Piel S, Ehinger JK, Elmér E, Hansson MJ. Metformin induces lactate production in peripheral blood mononuclear cells and platelets through specific mitochondrial complex I inhibition. Acta Physiol (Oxf) 2015:213:171–80. [CrossRef]
9. Scheen AJ. Clinical pharmacokinetics of metformin. Clin Pharmacokinet 1996;30:359–71. [CrossRef]
10. Bailey CJ, Turner RC. Metformin. N Engl J Med 1996;334:574–9.
11. Lalau JD, Moulignon C, Bergeret A, Lacroix C. Consequences of metformin intoxication. Diabetes Care 1998;21:2036–7. [CrossRef]
12. Friesecce S, Abel P, Roser M, Felix SB, Runge S. Outcome of severe lactic acidosis associated with metformin accumulation. Crit Care 2010;14:R226. [CrossRef]
13. Soyoral YU, Begentinik H, Emre H, Aytemiz E, Ozturk M, Erkoc R. Dialysis therapy for lactic acidosis caused by metformin intoxication: presentation of two cases. Hum Exp Toxicol 2011;30:1995–7.
14. Arıkan Ş, Tuzcu A, Bahçeci M, Kaplan MA, Gökalp D. Massive Metformin Overdose in Two Subjects with Suicidal Behavior: Brief Communication. Turkiye Klinikleri J Med Sci 2012;32:559–62.
15. Akinci B, Yener S, Bengi G, Yesil S. Alterations of coagulation in metformin intoxication. Hormones (Athens) 2008;7:325–9. [CrossRef]
16. Teale KF, Devine A, Stewart H, Harper NJ. The management of metformin overdose. Anaesthesia 1998;53:698–701. [CrossRef]
17. Lalau JD, Andrejak M, Morinière P, Coevoet B, Debussche X, Westeel PF, 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 1989;27:285–8.
18. Regolisti G, Antoniotti R, Fani F, Greco P, Fiaccadori E. Treatment of Metformin Intoxication Complicated by Lactic Acidosis and Acute Kidney Injury: The Role of Prolonged Intermittent Hemodialysis. Am J Kidney Dis 2017;70:290–6. [CrossRef]
19. Turkcuer I, Erdur B, Sari I, Yuksel A, Tura P, Yuksel S. Severe metformin intoxication treated with prolonged hemodialyses and plasma exchange. Eur J Emerg Med 2009;16:11–3. [CrossRef]
20. Rifkin SI, McFarren C, Juvvadi R, Weinstein SS. Prolonged hemodialysis for severe metformin intoxication. Ren Fail 2011;33:459–61.
21. Lacher M, Hermanns-Clausen M, Haefner K, Brandis M, Pohl M. Severe metformin intoxication with lactic acidosis in an adolescent. Eur J Pediatr 2005;164:362–5. [CrossRef]