

Case Report

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Metformin-associated lactic acidosis mistaken for alcohol-related acidosis in a patient abstinent for three months

Abdullah Talha ŞAHİN¹, Özkul Yılmaz ÇOLAK^{2,*}, Melda İŞEVİ³, Özgür KILIÇ²

¹Department of Internal Medicine, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Türkiye

²Division of Intensive Care, Department of Internal Medicine, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Türkiye

³Division of Intensive Care, Department of Anesthesiology and Reanimation, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Türkiye

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Abstract

Metformin-associated lactic acidosis is an uncommon but potentially fatal complication that develops when this renally eliminated drug accumulates during an acute illness, and it reaches the emergency department as an undifferentiated high anion gap metabolic acidosis with altered consciousness, exactly as alcoholic ketoacidosis, ethanol intoxication and toxic alcohol ingestion do. A documented history of alcohol use is therefore a powerful and potentially misleading diagnostic cue. We report a 62-year-old man with type 2 diabetes mellitus taking a fixed-dose vildagliptin and metformin combination who was found unconscious at home. His relatives could give no usable history beyond long-standing heavy drinking, and alcoholic ketoacidosis and methanol ingestion were pursued as the leading diagnoses. Arterial pH was below the measurable range of the analyser at the referring hospital and, six hours later on arrival at our intensive care unit, 6.60, with a bicarbonate of 1.2 mmol/L, a lactate of 16.9 mmol/L, an anion gap of 42 mmol/L and a creatinine of 7.21 mg/dL. Serum ethanol was undetectable, neuroimaging showed no lesion suggestive of methanol toxicity, and he was hypoglycaemic at both hospitals despite a glycated haemoglobin of 13.9%. He was treated with vasoactive support, sodium bicarbonate, mechanical ventilation, intermittent haemodialysis and 40 hours of continuous renal replacement therapy, and was extubated on the fourth day. Only then, when a history could be taken directly from him, did the decisive facts emerge: ten days of diarrhoea with minimal oral intake throughout which he had continued metformin, and three months of complete abstinence from alcohol. He was discharged neurologically intact and independent of renal replacement therapy. A drinking history can dominate the assessment months after the last drink; in metformin-treated patients it should widen the differential rather than close it, particularly when no reliable collateral history is available.

Keywords: Metformin; Acidosis, Lactic; Diagnostic Errors; Acute Kidney Injury; Hypoglycemia; Renal Replacement Therapy

1. Introduction

Metformin is eliminated unchanged by the kidney, so an acute fall in renal function allows it to accumulate; by inhibiting mitochondrial oxidative phosphorylation it then reduces lactate clearance, producing a type B lactic acidosis (1). Metformin-associated lactic acidosis (MALA) may be suspected in a metformin-treated patient with a high anion gap metabolic acidosis and is confirmed when lactate exceeds 5 mmol/L (1). It is uncommon, but in severe cases the death rate approaches 50% (2). MALA usually follows a precipitating illness that induces acute renal failure and an incidental overdose, rather than deliberate ingestion (3).

The physician meets this syndrome as an undifferentiated high anion gap acidosis with altered consciousness, as also occurs in alcoholic ketoacidosis, ethanol intoxication and toxic alcohol ingestion. A documented history of alcohol use is therefore a powerful and potentially misleading cue. We report a patient in whom that cue dominated the initial assessment

despite three months of abstinence and an undetectable serum ethanol, and in whom the decisive history could not be obtained until the fourth day, after extubation. The case illustrates how readily MALA is missed when no reliable collateral history is available, and how little of the diagnosis depends on tests most centres cannot perform.

2. Case Report

A 62-year-old man was found unconscious at home and brought to a district state hospital. He had type 2 diabetes mellitus, hypertension and stented coronary artery disease, and took vildagliptin/metformin 50/1000 mg twice daily, insulin glargine and amlodipine. For 30 years he had drunk three to four beers on three to four days weekly, some 60-80 g of ethanol per drinking day and around 245 g weekly; he had a 50 pack-year smoking history and no relevant family history. These details, and the three months of abstinence preceding admission, were established only later; at presentation his

*Correspondence: ozkulyilmaz.colak@omu.edu.tr

relatives could give no coherent account beyond long-standing heavy drinking and blurred vision that had begun around midday.

At the referring hospital his capillary glucose was 48 mg/dL. He was unkempt with evidence of poor self-care, rousable and oriented but mildly dysarthric, without focal neurological deficit, and in sinus rhythm. Arterial blood gas analysis returned a pH below the measurable range of the analyser, a carbon dioxide tension of 15.5 mmHg and a lactate of 22 mmol/L. Cranial computed tomography showed no acute pathology, and diffusion-weighted magnetic resonance imaging, although degraded by motion artefact, showed no restricted diffusion and no putaminal lesion.

Because of the drinking history, the depressed consciousness, the visual disturbance and the severity of the acidosis, alcoholic ketoacidosis and toxic alcohol ingestion, particularly methanol, were pursued as the leading diagnoses, and he was referred for haemodialysis. Fifteen minutes into the

first session he became hypotensive with a further decline in consciousness; dopamine was started and he was transferred to a tertiary intensive care unit, approximately six hours after the first blood gas.

On arrival at our intensive care unit (day 1) the Glasgow Coma Scale score was 4, blood pressure 60/40 mmHg and capillary glucose 36 mg/dL. Noradrenaline was titrated to a mean arterial pressure above 65 mmHg, a target reached at 0.85 µg/kg/min. Arterial pH, measurable for the first time, was 6.60, with bicarbonate 1.2 mmol/L, lactate 16.9 mmol/L and creatinine 7.21 mg/dL; sodium 143 and chloride 100 mmol/L gave an anion gap of 42 mmol/L (Table 1). Serum ethanol, on a fluoride-oxalate specimen transported on ice, was undetectable. Ophthalmological examination showed mid-dilated, unreactive pupils, nuclear sclerosis and changes of diabetic retinopathy; the optic disc margins were sharp, without papilloedema.

Table 1. Laboratory findings

Parameter	On intensive care arrival (day 1)	Later value
Arterial pH	6.60	7.43 (day 3, hour 54; CRRT cessation)
pCO ₂ (mmHg)	14.7	38 (day 3, hour 54)
Bicarbonate (mmol/L)	1.2	24 (day 3, hour 54)
Lactate (mmol/L)	16.9	1.4 (day 3, hour 54)
Anion gap (mmol/L)	42	-
Delta ratio	1.3	-
Sodium (mmol/L)	143	-
Potassium (mmol/L)	5.2	-
Chloride (mmol/L)	100	-
Ionised calcium (mg/dL)	4.67	Monitored four-hourly
Creatinine (mg/dL)	7.21	2.34 (day 24; off renal replacement therapy since day 9)
Glycated haemoglobin (%)	Not measured	13.9 (day 3)
Creatine kinase (U/L)	Not measured	2563 (day 3)
Lactate dehydrogenase (U/L)	325	570 (day 3)
AST / ALT (U/L)	36 / 23	≈8000 / ≈2400 (day 6)
International normalised ratio	Normal	Normal at transaminase peak (day 6)
Total / direct bilirubin (mg/dL)	0.32 / 0.05	-
Albumin (g/L)	36.4	-
Haemoglobin (g/dL)	10	-
Leucocytes / neutrophils (x10 ⁹ /L)	16.1 / 12.5	-
Platelets (x10 ⁹ /L)	249	-
C-reactive protein (mg/L)	7.44	-
Serum ethanol	Below limit of detection	-
Methanol, ethylene glycol, serum ketones, plasma metformin	Not available	Not available throughout
Urine ketones	Not obtainable (anuria)	-

AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRRT: continuous renal replacement therapy. All values were obtained at the receiving centre; at the referring hospital, approximately six hours earlier, arterial pH lay below the measurable range of the analyser, with a partial pressure of carbon dioxide of 15.5 mmHg, a lactate of 22 mmol/L and a reported creatinine of 8.8 mg/dL. Day 1 denotes the day of intensive care admission and hour 0 arrival at the receiving unit.

The anion gap was calculated as sodium minus the sum of chloride and bicarbonate and the delta ratio using reference values of 12 mmol/L for the anion gap and 24 mmol/L for bicarbonate; albumin correction altered the anion gap by less than 1 mmol/L. A dash in the second column indicates a parameter that was followed serially during the admission but showed no clinically relevant change.

Sodium bicarbonate was infused and intermittent haemodialysis performed. The pH improved to 7.14, but consciousness deteriorated and the trachea was intubated electively. Continuous renal replacement therapy (CRRT) began eight hours later and continued for 40 hours, by which time the pH was 7.43 and the lactate 1.4 mmol/L (Table 2, Fig. 1). Mechanical ventilation had been set at a respiratory rate of 24/min and a tidal volume of 8 mL/kg (minute ventilation approximately 15 L/min) to assist respiratory compensation for the presenting acidaemia. As the metabolic component corrected, these settings were not yet down-titrated, and at 23 hours a transient alkalaemia to pH 7.61 was recorded, with bicarbonate still subnormal at 18.3 mmol/L and carbon dioxide tension low at 18.8 mmHg; the pattern therefore reflected a superimposed respiratory alkalosis from relative

hyperventilation rather than a bicarbonate or CRRT-fluid overshoot, and it resolved once minute ventilation was reduced and the bicarbonate infusion, by then no longer needed, was stopped. Sustained alkalaemia of this kind risks a paradoxical fall in cerebrospinal fluid pH, hypokalaemia and a left shift of the oxyhaemoglobin dissociation curve that reduces tissue oxygen delivery, underscoring the value of frequent blood gas review during rapidly evolving acid-base disturbances. Empirical broad-spectrum antibacterial therapy was given for fever in the presence of a discharging wound on the right leg. Shock was refractory to noradrenaline alone and required dobutamine on day 2 and, on day 4, the reintroduction of dopamine for symptomatic sinus bradycardia at 30 beats per minute. All vasoactive support ceased by day 8.

Hours from ICU arrival	pH	pCO ₂ (mmHg)	HCO ₃ (mmol/L)	Lactate (mmol/L)	Concurrent intervention
0	6.60	14.7	1.2	16.9	Noradrenaline; bicarbonate infusion; intermittent haemodialysis started
5.5	7.14	15.0	5.0	18.1	End of haemodialysis; elective tracheal intubation
8	7.03	22.9	6.0	14.6	Post-dialysis rebound acidaemia
14	7.16	30.6	10.8	11.7	CRRT commenced
23	7.61	18.8	18.3	6.8	Overshoot alkalaemia; bicarbonate infusion stopped
39	7.45	35.3	23.9	1.7	CRRT
54	7.43	38	24	1.4	CRRT discontinued

CRRT: continuous renal replacement therapy; ICU: intensive care unit. Hour 0 is arrival at the receiving intensive care unit, approximately six hours after the first blood gas at the referring hospital. Selected time points from arterial blood gas samples obtained every two hours.

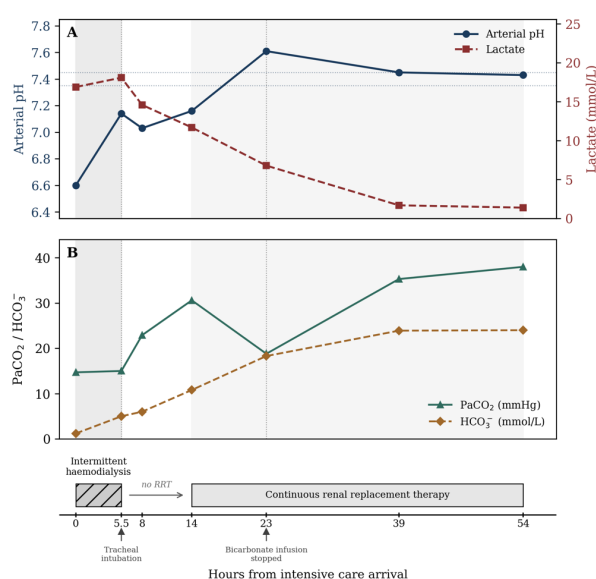


Fig. 1. Trajectory of arterial acid-base and metabolic parameters during the first 54 hours of intensive care, aligned with the timeline of renal replacement therapy.

He was extubated on day 4 with a Glasgow Coma Scale score of 14. Only then, when a history could be taken directly from him, did the decisive facts emerge: ten days of diarrhoea with almost no oral intake, throughout which he had continued his usual metformin dose, and three months of abstinence from alcohol. Together with the severity of the acute kidney injury and the magnitude of the lactic acidosis, this made MALA the most probable diagnosis, superimposed on a picture in which dehydration and shock had already compromised renal function before metformin could accumulate. Metformin had not been administered at any point after arrival, since he was unable to take enteral medication, but it was now formally and permanently discontinued. Two day-3 findings supported it: a glycated haemoglobin of 13.9%, contrasting sharply with the hypoglycaemia recorded at both hospitals, and a creatine kinase of 2563 U/L, indicating a rhabdomyolytic contribution after prolonged immobility.

He remained anuric acutely and received further haemodialysis on days 5 and 9. On day 6 the aspartate

aminotransferase rose to approximately 8000 U/L and the alanine aminotransferase to approximately 2400 U/L without any rise in the international normalised ratio; abdominal ultrasonography and transient elastography, performed because of the drinking history, showed no features of chronic liver disease, and both enzymes fell spontaneously. He moved to the nephrology ward on day 10 and urine output returned without diuretics. A 24-hour collection on day 24 yielded 2400 mL, urinary creatinine 29.4 mg/dL and urinary protein 48.5 mg/dL against a serum creatinine of 2.34 mg/dL, giving a creatinine clearance of 21 mL/min and protein excretion of approximately 1.2 g per day. He was discharged the same day, free of renal replacement therapy and neurologically intact.

3. Discussion

Two features of this presentation created substantial diagnostic overlap between MALA and the alcohol-related differential. The patient could not speak for himself and his relatives could give no usable account of the preceding ten days; what remained was a single salient and easily retrieved label, heavy drinker, attached to an unconscious patient with a profound high anion gap acidosis and visual disturbance, findings genuinely consistent with alcoholic ketoacidosis or methanol ingestion as well as with MALA. Reasoning that anchors on such a cue under incomplete history is common and arises largely from intuitive, pattern-driven processing (4), though we cannot claim to have documented the clinicians' reasoning directly. The cue was also stale: he had not drunk for three months, a fact that could not be known until day 4. Serum ethanol was negative and neuroimaging showed no putaminal lesion, but neither finding definitively excludes toxic alcohol ingestion, since methanol and ethylene glycol could not be assayed.

The biochemistry constrained the differential but did not by itself resolve it. Alcoholic ketoacidosis characteristically produces only a modest rise in lactate and spares renal function, whereas this patient had a lactate of 16.9 mmol/L, an anion gap of 42 mmol/L, a creatinine of 7.21 mg/dL and anuria requiring 40 hours of CRRT. Ketones could not be measured, however, and lactate accounted for only about 16 of the 30 mmol/L rise in the anion gap. A ketotic contribution is plausible, but after three months of abstinence it would represent starvation ketosis from ten days of minimal intake rather than alcoholic ketoacidosis, which requires recent heavy drinking. The diagnosis being pursued was therefore not merely unlikely but mechanistically unavailable. The acidosis was therefore mixed rather than a single entity: an initial contribution from dehydration and hypoperfusion (type A) was compounded by a metformin-associated component (type B) once renal clearance failed, and it is the latter that best accounts for the magnitude of the acidaemia and its rapid, sustained reversal after drug removal. No plasma metformin concentration was available to confirm this directly, so the diagnosis remains probable rather than certain. What the biochemistry did settle was acute ethanol intoxication, since

serum ethanol was undetectable. Methanol could not be assayed, but the absence of putaminal lesions and of optic disc oedema argued against it; the unreactive pupils reflect the depth of coma and shock rather than toxic optic neuropathy.

The diagnosis was made without a metformin concentration, as it must be in most centres. MALA is in any case not a sharply defined entity (2), and without a drug level the term metformin-associated is the appropriate one. It rests on documented exposure, a recognised precipitant, severe acute kidney injury, an acidosis disproportionate to hypoperfusion, exclusion of alternatives and resolution after drug removal, all available at the bedside. One observation deserves particular emphasis. This patient was hypoglycaemic at both hospitals, 48 and 36 mg/dL, despite a glycated haemoglobin of 13.9%, and the blurred vision that had been attributed to a toxic alcohol is readily explained by hypoglycaemia alone. No exogenous insulin was administered at the referring hospital, so a recent bolus dose does not account for it; ten days of minimal oral intake on a background of continued basal glargine, together with reduced insulin clearance as acute kidney injury developed, are plausible contributors and cannot be excluded. Dextrose was given at the referring hospital, though the dose is not recorded in the transfer documentation. Severe hypoglycaemia despite markedly uncontrolled chronic diabetes nonetheless argues against primary diabetic decompensation and, recognised on the first day, might have pointed earlier towards impaired hepatic gluconeogenesis and metformin accumulation. A discharging leg wound with fever raises the possibility of a septic contribution, and the creatine kinase indicates a rhabdomyolytic component; neither accounts for the magnitude of the acidosis.

The Extracorporeal Treatments in Poisoning workgroup concluded that metformin is moderately dialyzable and listed as indications a lactate above 20 mmol/L, a pH of 7.0 or below, shock, failure of supportive measures and depressed consciousness, continuing until lactate falls below 3 mmol/L and pH exceeds 7.35 (5). All but the lactate threshold were met on arrival, and that threshold had been exceeded six hours earlier. Intermittent haemodialysis clears metformin more efficiently and is the preferred first modality, but haemodynamic instability often forces a change, as it did here: the escalating vasopressor requirement during the first session made CRRT the only tolerable option, and CRRT has been used successfully in severe MALA (6). This trade-off is worth anticipating before the first session begins. Six hours nonetheless elapsed between the first blood gas and definitive therapy, a delay inherent to interhospital transfer that is worth anticipating in centres without extracorporeal capacity.

The degree of acidaemia invites therapeutic pessimism and should not. In the largest series of severe cases, 56 patients with a pH below 7.0 and a lactate above 10 mmol/L had a mean pH of 6.75 and 53% survival; pH and lactate did not differ between

survivors and non-survivors, whereas sepsis, multidrug overdose and at least two triggering factors were significantly more frequent among those who died (2). Outcome tracked the triggering factors rather than the severity of the acidosis.

Published survivors at or below our patient's pH are few but they exist (Table 3), and this case adds to them rather than standing apart. Arterial pH should inform the intensity of treatment, not the decision to provide it.

Table 3. Reported survivors of metformin-associated lactic acidosis with an arterial pH of 6.80 or below

pH	Patient	Metformin exposure	Lactate (mmol/L)	Extracorporeal therapy	Outcome	Ref.
6.38	Adult	Metformin, dose not stated; hypothermia	NR	NR	Recovered	7
6.59	Adult	Overdose	40.0	Haemodialysis	Survival without sequelae	8
6.60	55, female	Therapeutic dose; prolonged dehydration	20.0	CVVHDF, 21 h	Survived; eGFR 27 mL/min/1.73 m ² at 5 weeks	9
6.60	62, male	Therapeutic dose; 10 days of diarrhoea	16.9 (peak 22.0)	Haemodialysis, then CRRT 40 h	Survived, neurologically intact; creatinine clearance 21 mL/min	Present case
6.618	70, female	Therapeutic dose; metformin 77.5 mg/L	18.0	CRRT, 3 days	Survived; creatinine 1.11 mg/dL at discharge	6
6.78	Adult	Therapeutic dose	29.0	Haemodialysis, 20 h	Survived	10

NR: not reported in the accessible record; CVVHDF: continuous veno-venous haemodiafiltration; CRRT: continuous renal replacement therapy; eGFR: estimated glomerular filtration rate. Only details confirmed in the source publications are given. This table reflects a targeted rather than a systematic literature search and is not a complete enumeration of published cases.

The transient transaminase rise without coagulopathy, followed by spontaneous normalisation, follows the pattern of ischaemic hepatitis attributable to the preceding hypotension; a creatine kinase of 2563 U/L is far too low for muscle to have been the principal source. Plasma acetaminophen was not measured; however, the transaminase peak occurred on day 6, later than the 24-72 hour window typical of acetaminophen-induced hepatotoxicity, and the international normalised ratio remained normal throughout, both arguing against a clinically significant ingestion and supporting the ischaemic hepatitis pattern favoured here. This abnormality was also attributed at first to alcohol, and imaging and elastography excluded chronic liver disease: a second attribution to the drinking history that objective testing did not support.

The renal outcome deserves an honest reading. The patient became independent of renal replacement therapy, but a creatinine clearance of 21 mL/min and proteinuria of 1.2 g per day, against a background of diabetic retinopathy, indicate incomplete recovery on established diabetic nephropathy. A comparable patient presenting at pH 6.60 on therapeutic doses after prolonged dehydration retained an estimated glomerular filtration rate of 27 mL/min/1.73 m² five weeks later (9). Reduced renal function is both the precondition for metformin accumulation and frequently its residue. No dosing error occurred here; the drug was simply continued while an acute kidney injury developed that allowed it to accumulate. That injury most likely resulted from prolonged dehydration, with additional contributions from shock and mild rhabdomyolysis, the last reflected in a creatine kinase of 2563 U/L that was

modest relative to the degree of renal failure, so dehydration and hypoperfusion remained the dominant drivers. Explicit sick-day guidance, that metformin should be suspended during any acute illness associated with dehydration, vomiting or diarrhoea and restarted only after renal function has been reassessed, is a low-cost intervention that would have prevented this admission.

This report has limitations. Plasma metformin, serum ketones and serum osmolality are not measurable at our institution, and urinary ketones could not be obtained because the patient was anuric. The ethanol assay is enzymatic and specific, so a negative result does not exclude other alcohols. No baseline creatinine was available, and Table 3 reflects a targeted rather than a systematic search. The dose of dextrose administered at the referring hospital for the hypoglycaemia was not recorded in the transfer documentation.

A recorded history of alcohol use is a powerful diagnostic cue that can persist long after the exposure itself has ended. In a metformin-treated patient presenting with an unexplained high anion gap acidosis and acute kidney injury, that cue should widen the differential rather than close it, particularly when no reliable collateral history is available and the decisive information may not emerge for days. A serum ethanol concentration, a careful medication review and attention to unexplained hypoglycaemia settle more than the history does, and extreme acidemia is never in itself a reason to withhold treatment.

Conflict of interest

The authors declared no conflict of interest.

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Authors' contributions

Concept: Ö.Y.Ç., Ö.K., Design: Ö.Y.Ç., A.T.Ş., Ö.K., Data Collection or Processing: A.T.Ş., M.İ., Ö.Y.Ç., Analysis or Interpretation: Ö.Y.Ç., M.İ., Ö.K., A.T.Ş., Literature Search: A.T.Ş., Ö.Y.Ç., Writing: A.T.Ş., Ö.Y.Ç.

Ethical Statement

Ethics committee approval is not required for single case reports at our institution. The report was prepared in accordance with the Declaration of Helsinki as revised in 2013, and written informed consent was obtained from the patient.

References

1. KC. Metformin-associated lactic acidosis: a mini review of pathophysiology, diagnosis and management in critically ill patients. *World J Diabetes*. 2024; 15(6): 1178-1186.
2. Kajbaf F, Lalau JD. The prognostic value of blood pH and lactate and metformin concentrations in severe metformin-associated lactic acidosis. *BMC Pharmacol Toxicol*. 2013; 14: 22.
3. Seidowsky A, Nseir S, Houdret N, Fourrier F. Metformin-associated lactic acidosis: a prognostic and therapeutic study. *Crit Care Med*. 2009; 37(7): 2191-2196.
4. Croskerry P. From mindless to mindful practice - cognitive bias and clinical decision making. *N Engl J Med*. 2013; 368(26): 2445-2448.
5. Calello DP, Liu KD, Wiegand TJ, Roberts DM, Laverne V, Gosselin S, et al. Extracorporeal treatment for metformin poisoning: systematic review and recommendations from the Extracorporeal Treatments in Poisoning Workgroup. *Crit Care Med*. 2015; 43(8): 1716-1730.
6. Kinoshita H, Yanai M, Ariyoshi K, Ando M, Tamura R. A patient with metformin-associated lactic acidosis successfully treated with continuous renal replacement therapy: a case report. *J Med Case Rep*. 2019; 13(1): 371.
7. Ahmad S, Beckett M. Recovery from pH 6.38: lactic acidosis complicated by hypothermia. *Emerg Med J*. 2002; 19(2): 169-171.
8. Dell'Aglio DM, Perino LJ, Todino JD, Algren DA, Morgan BW. Metformin overdose with a resultant serum pH of 6.59: survival without sequelae. *J Emerg Med*. 2010; 39(1): e77-e80.
9. Pikwer A, Vernersson E, Frid A, Sterner G. Extreme lactic acidosis type B associated with metformin treatment. *NDT Plus*. 2011; 4(6): 399-401.
10. Kortli S, Amathieu R, Ghalayini M. Dancing with death at pH 6.8 and lactate of 29 mmol/L: extreme survival in severe metformin-associated lactic acidosis - a case report. *Front Med (Lausanne)*. 2025; 12: 1604360.