

Jakub TAMBOR<sup>1</sup>  
 Maja NOWICKA<sup>2</sup>  
 Anna ZAWIASA-BRYSZEWSKA<sup>2</sup>  
 Ilona KURNATOWSKA<sup>2</sup>

<sup>1</sup>Student Scientific Society affiliated with the Department of Internal Medicine and Transplant Nephrology, Medical University of Lodz, Lodz, Poland

<sup>2</sup>Department of Internal Medicine and Transplant Nephrology, Medical University of Lodz, Lodz, Poland

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- continuous renal replacement therapy
- type 2 diabetes mellitus

## Multiorgan failure in the course of metformin-associated lactic acidosis precipitated by acute hepatitis A infection: a case report

Metformin-associated lactic acidosis (MALA) is a rare but severe disorder, occurring primarily in patients with hepatic or renal impairment in the presence of additional triggers such as infection or toxemia.

A 69-year-old male with a history of type 2 diabetes mellitus, hypertension, and ischemic heart disease, without prior renal or hepatic impairment, presented to the Emergency Department with general malaise and progressive dyspnoea. Two weeks earlier, he had been treated with ciprofloxacin for otitis externa. His condition rapidly deteriorated, and he was admitted to the Intensive Care Unit with multiorgan failure. Laboratory evaluation revealed severe lactic acidosis with profound metabolic acidosis, acute kidney injury, and markedly elevated liver transaminases, consistent with metformin-associated lactic acidosis (MALA). Despite relatively low C-reactive protein levels, procalcitonin was markedly elevated. The patient required mechanical ventilation, vasopressor support, and continuous renal replacement therapy (CRRT). Extensive diagnostic work-up, including blood cultures, bronchoscopy with bronchoalveolar lavage, and viral testing for HBV and HCV, yielded negative results. Following intensive supportive therapy, the patient's clinical condition gradually improved. Subsequent detailed history-taking and extended serological evaluation revealed acute hepatitis A, confirmed by positive anti-HAV IgM antibodies. The patient reported consumption of fermented shark meat ("hákarl") during travel to Greenland approximately four weeks prior to admission, followed by transient gastrointestinal symptoms. Acute viral hepatitis was therefore considered a precipitating factor contributing to impaired metformin clearance and the development of severe lactic acidosis with multiorgan failure.

MALA is a severe complication that can be potentially reversed with immediate intervention. In this case, the patient recovered without persistent renal or liver damage, underscoring the importance of a thorough medical history and rapid diagnosis.

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### Introduction

Metformin-associated lactic acidosis (MALA) is a rare but potentially life-threatening complication of metformin therapy. The MALA incidence is assessed to be as much as 6.3 per 100,000 patient-years (1), with mortality ranging from 25% to 50% (2).

Metformin is currently recommended, by the European Association for the Study of Diabetes, as one of the first-line pharmacological therapy for type 2 diabetes mellitus

(T2DM), in conjunction with lifestyle modifications [3]. Its continued preference stems from its cost-effectiveness and favourable safety profile, particularly due to the low risk of hypoglycaemia compared with many alternative glucose-lowering agents (3). Nevertheless, there is a need to acknowledge the potential for adverse effects, including the rare but serious complication of MALA.

Metformin inhibits hepatic gluconeogenesis and increases peripher-

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### Corresponding author:

Jakub Tambor  
 Student Scientific Society affiliated with the Department of Internal Medicine and Transplant Nephrology, Medical University of Lodz, Lodz, Poland  
 ul. Stefana Kopcińskiego 22  
 Łódź 90-153  
 jakub.tambor@stud.umed.lodz.pl; +48 606 830 110

al glucose uptake, a mechanism that can lead to elevated lactate concentration, especially in conditions of impaired lactate clearance, such as renal, hepatic or heart dysfunction (4). While MALA typically occurs in patients with chronic kidney disease or liver impairment, case reports demonstrate that it can also develop in patients with previously normal organ function when additional precipitating factors are present. These risk factors include sepsis, hypoxia, dehydration, or concurrent use of nephrotoxic or interacting drugs (5). Recent literature also highlights that unusual trigger, such as acute viral hepatitis or dietary toxins, may transiently impair liver function and facilitate MALA (6).

Here, we present the case of a 69-year-old man who developed profound lactic acidosis complicated by multiorgan failure requiring mechanical ventilation and initiation of continuous renal replacement therapy (CRRT). A detailed medical history and virological evaluation revealed the underlying cause of these severe metabolic disturbances.

### Case report

A 69-year-old man, a professionally active physiotherapist and avid traveller, with a medical history of T2DM, hypertension, and atherosclerosis with ischemic heart disease (IHD), presented to the Emergency Department with rapidly deteriorating general condition, malaise, and progressive dyspnoea. Two weeks before admission, he had finished the treatment with ciprofloxacin for otitis externa.

The patient's long-term outpatient treatment prior to admission included the following medications: insulin lispro, insulin glargine, metformin 1000 mg three times a day, empagliflozin, dulaglutide, sotalol, apixaban, clopidogrel, perindopril, amlodipine, indapamide, doxazosin, spironolactone, rosuvastatin with ezetimibe, pregabalin, and allopurinol.

On admission, the patient was in critical condition, requiring immediate transfer to the Intensive Care Unit

(ICU). On physical examination, the patient presented signs and symptoms of shock: hypotension (BP < 80/60 mmHg), tachycardia (heart rate 110 bpm), with mild signs of dehydration. The laboratory tests indicated acute kidney and liver injury with profound metabolic acidosis. Arterial blood gas analysis demonstrated: pH 6.92, base excess (BE) -30.5 mmol/L, pCO<sub>2</sub> 8.8 mmHg, and HCO<sub>3</sub> 3.7 mmol/L, on mechanical ventilation with an FiO<sub>2</sub> of 0.6, accompanied by markedly elevated lactate levels (15.8 mmol/L) and an increased anion gap (32 mmol/L). Laboratory tests revealed markedly elevated liver transaminases: alanine aminotransferase (ALT) 5605 U/L (normal range: <40 U/L) and aspartate aminotransferase (AST) 4909 U/L (normal range: <40 U/L) as well as increased gamma-glutamyl transferase (GGT) 224 U/L (normal range: 5-48 U/L) and alkaline phosphatase (ALP) 128 U/L (normal range: 30-130 IU/L). with only mildly elevated total bilirubin (1.96 mg/dL, normal range: 0.3-1.2 mg/dL). C-reactive protein (CRP) was 22.1 mg/L (normal range: <5 mg/L) and procalcitonin >10 ng/mL (normal range: <0.05 ng/ml) - findings suggestive of a systemic inflammatory response (Table 1). In addition, clinical and laboratory features of acute kidney injury (AKI) were observed, including anuria, elevated serum creatinine 571 µmol/L (normal range: 64-104 µmol/L), increased blood urea 21.3 (normal range: 1.7-8.3 mmol/L), and serum potassium of 7.7 mmol/L (normal range: 3.5-5.1 mmol/L). Given the presence of profound metabolic acidosis, AKI, and circulatory shock, the initial differential diagnosis included diabetic ketoacidosis, acute pancreatitis, acute viral hepatitis, acute coronary syndrome (ACS), gastrointestinal malignancy, septic shock, and drug intoxication, including metformin-associated lactic acidosis. Serial measurements of cardiac troponin T (hs-cTnT) (28.9 ng/L at admission and 143.7 ng/L the following morning) showed mild elevations, but in the absence

of clinical, electrocardiographic, as well as echocardiographic evidence of ischemia, acute coronary syndrome was excluded. Diabetic ketoacidosis was excluded based on laboratory findings – hyperglycemia (240 mg/dL) was present, but there was no evidence of ketonemia or ketonuria. Despite an extensive diagnostic work-up, including repeated blood cultures, bronchoscopy with bronchoalveolar lavage, and viral testing for HBV and HCV, no infectious cause was identified. Otolaryngology consultation revealed no significant pathology, while echocardiography excluded acute heart failure or infective endocarditis. Doppler ultrasonography ruled out portal vein thrombosis. During the initial days of ICU hospitalization, the patient required high doses of vasopressors, mechanical ventilation, and CRRT. Over the following days, his condition gradually improved, vasopressors and CRRT were successfully discontinued. He was subsequently transferred to the Department of Nephrology, where the patient's condition improved day by day. Initially, intermittent dialysis was administered, which was discontinued after the return of diuresis and renal excretory function during next two weeks of hospitalization. However, the cause of these profound metabolic disturbances remained elusive. A more detailed history revealed that approximately four weeks prior to admission, the patient had consumed fermented shark meat during a trip to Greenland. About two weeks later, he developed transient gastrointestinal symptoms, including diarrhoea and vomiting, which resolved spontaneously. Extended laboratory testing, revealed positive anti-HAV IgM antibodies, thereby confirming acute hepatitis A as a major precipitating factor. Taken together, the acute viral hepatitis, recent ciprofloxacin exposure, dehydration caused by gastrointestinal disturbances and pre-existing comorbidities created a multifactorial environment favouring impaired metformin clearance and the development of profound lactic acidosis.

After approximately two weeks of hospitalization in the Department of Nephrology, the patient showed further clinical improvement, with significant normalization of kidney and liver function, remained stable at one-year follow-up (Table 1). The patient was discharged with an estimated glomerular filtration rate (eGFR) of 40 ml/min/1.73 m<sup>2</sup>, with a recommendation to continue a reduced dose of metformin in combination with insulin therapy, as well as nephroprotective treatment (ramipril;

empagliflozin). In accordance with the recommendations of the Polish Society of Nephrology, the patient was advised to maintain blood pressure below 140/90 mmHg, limit dietary salt intake, and engage in regular physical activity (7).

### Discussion

Characteristic biochemical features of severe MALA include profound high-anion gap metabolic acidosis with markedly reduced serum bicarbonate and significant hyper-

lactatemia, occurring in the context of metformin exposure and acute impairment of renal and/or hepatic function (8,9).

The acute management of metformin-associated lactic acidosis is primarily supportive and focuses on airway protection, respiratory support, and hemodynamic stabilization. In patients with severe acidemia, correction of acid-base disturbances may include intravenous sodium bicarbonate in selected cases. However, extracorporeal

**Tabl.1**  
Laboratory tests prior, at admission and in follow-up.

Parameter [normal range]	Last available results prior to admission	On admission to ER 04.08	On admission to nephrology department 07.08	At discharge 19.08	At one-year follow-up
RBC [4.5–6.5 T/L]	5.04	3.82	3.27	3.6	4.79
Hgb [13.5–18 g/dL]	14.5	11.5	9.6	10.5	13.8
WBC [4–10 G/L]	4.1	7.5	10.9	3.6	6.4
PLT [150–400 G/L]	204	189	90	137	168
Potassium [3.5–5.2 mmol/L]	4.8	7.7	4.8	3.6	4.2
Sodium [136–146 mmol/L]	136	133	135	138	140
Phosphates [0.81–1.45 mmol/L]	x	4.7	x	x	x
Creatinine [64–104 μmol/L]	89	571	179	144	135
eGFR [>90 ml/min/1.73 m <sup>2</sup> ]	76	8	32	40	45
Urea [10–50 mg/dL]	35	128.0	65	131	53
CRP [<5 mg/L]	1.1	22.1	12.3	2.7	0.4
PCT [<0.05 ng/ml]	x	10.79	1.89	0.36	x
LDH [<248 U/L]	x	1710.0	x	x	x
AST [<40 U/L]	24.0	5605.0	211	27	19
ALT [<40 U/L]	27.0	4909.0	498	23	31
GGTP [5–48 U/L]	x	x	224	281	x
ALP [30–130 IU/L]	x	x	128	220	x
Total Bilirubin [0.3–1.2 mg/dL]	x	1.96	1.42	1.28	x
Direct Bilirubin [<0.3 mg/dL]	x	1.66	x	x	x
INR [0.8–1.2]	0.97	2.65	1.06	x	x

**Abbreviations:** RBC – Red Blood Cells; Hgb – Hemoglobin; WBC – White Blood Cells; PLT – Platelets; K – Potassium; Na – Sodium; Phosphates – Inorganic Phosphate; Creatinine – Serum Creatinine; eGFR – Estimated Glomerular Filtration Rate; Urea – Blood Urea Nitrogen; CRP – C-reactive Protein; PCT – Procalcitonin; LDH – Lactate Dehydrogenase; AST – Aspartate Aminotransferase; ALT – Alanine Aminotransferase; GGTP – Gamma-glutamyl Transpeptidase; ALP – Alkaline Phosphatase; Total Bilirubin – Total Serum Bilirubin; Direct Bilirubin – Direct (Conjugated) Serum Bilirubin; INR – International Normalized Ratio; x – no results available.

RRT remains the cornerstone of treatment in severe MALA, as it enables both rapid correction of metabolic acidosis and effective removal of metformin. According to the recommendations of the Extracorporeal Treatments Poisoning Group Workgroup (EXTRIP), renal replacement therapy is recommended or strongly suggested in patients with severe MALA presenting with very low pH, marked hyperlactatemia, circulatory shock, or AKI. Intermittent hemodialysis is preferred when feasible, while CRRT is an acceptable alternative in hemodynamically unstable patients (10).

Importantly, observational studies have demonstrated that predialysis lactate concentration correlates with disease severity and mortality in patients with MALA requiring renal replacement therapy, supporting early escalation to extracorporeal treatment in appropriate clinical settings (11).

Current evidence on MALA is derived primarily from case reports, retrospective analyses, and observational cohorts, as randomized controlled trials are lacking (5, 12, 13). A recent analysis of 242 individual cases reported an overall mortality of 19.8%, despite most patients presenting with severe metabolic acidosis, hyperlactatemia, and frequent need for organ support. The majority (76.4%) developed toxicity while on therapeutic metformin doses in the setting of AKI, and RRT was used in nearly 70% of cases, with favourable outcomes even in those with the lowest pH and highest lactate or metformin levels (5).

Prognosis in MALA appears more favourable than in other forms of lactic acidosis (4). This phenomenon may be explained by the fact, that in contrast to lactic acidosis caused by profound tissue ischemia or shock, MALA arises predominantly from toxic accumulation of metformin. Importantly, this pathophysiological mechanism makes the condition potentially reversible, provided it is identified at an early stage and managed with immediate discontinuation of metformin together with

timely initiation of appropriate supportive therapy.

Metformin is eliminated primarily through kidneys, and its plasma concentration rises in the setting of impaired renal clearance. In addition to its glucose-lowering effects, the drug inhibits mitochondrial respiratory chain complex I, which shifts cellular metabolism toward anaerobic pathways and promotes lactate accumulation (4). In patients with kidney failure both acute and chronic, impaired renal clearance can lead to toxic metformin accumulation, thereby worsening lactic acidosis. The resulting severe acidosis and systemic hypoperfusion may further compromise renal perfusion and perpetuate the cycle (13). Metformin therapy is contraindicated in patients with eGFR below 30 mL/min/1.73 m<sup>2</sup>, while initiation is not recommended for those with an eGFR between 30 and 45 mL/min/1.73 m<sup>2</sup>; for patients taking metformin whose eGFR falls below 45 mL/min/1.73 m<sup>2</sup>, the risks and benefits should be reassessed, with discontinuation advised once the eGFR drops below 30 mL/min/1.73 m<sup>2</sup> (14). However, recent evidence suggests that metformin may be safely used in a broader range of eGFR than previously recommended, particularly in patients with stable chronic kidney disease. Excessive concern regarding the rare occurrence of MALA may unnecessarily deprive patients of the well-established metabolic and cardiovascular benefits of metformin therapy (15, 16).

It should be noted that although our patient had a long history of T2DM, there was no evidence of preexisting kidney damage. Routine laboratory tests performed in the diabetes outpatient clinic prior to hospitalization revealed no proteinuria, with a urine albumin-to-creatinine ratio (ACR) <30 mg/g and eGFR of 76 mL/min/1.73 m<sup>2</sup>. The patient also had no history of liver disease or heart failure despite positive history of IHD. The use of metformin in combination with insulin, empagliflozin, and a glucagon-like peptide-1 (GLP-1) receptor agonist

for the management of T2DM, particularly in an overweight individual, was therefore appropriate, and safe, and furthermore was consistent with the nephroprotective principles recommended by the Polish Society of Nephrology (7).

In our patient, acute hepatitis A likely contributed to hepatic dysfunction, as evidenced by the presence of anti-HAV IgM antibodies and a history of consuming fermented shark meat, which was followed by gastrointestinal symptoms. The unexpected history of consuming fermented shark (hákarl), a traditional Icelandic dish prepared from Greenland shark (*Somniosus microcephalus*), provided a pivotal etiological clue in this case. Greenland shark flesh contains elevated concentrations of urea and trimethylamine N-oxide (TMAO), which render it toxic if consumed raw; these toxins are degraded only through a prolonged fermentation and drying process (17). Enteral transmission of hepatitis A virus (HAV) via food is a well-documented route of infection. Shellfish such as oysters, clams, and mussels are recognized as frequent vectors, given their filter-feeding action concentrating pathogens including HAV from contaminated water (18). Although HAV is known for its stability in the marine environment and the potential for seafood contamination, no reports to date have directly linked HAV infection to the consumption of shark meat. Thus, it remains uncertain whether the ingestion of fermented shark meat (hákarl) represented the actual source of infection; nevertheless, this route of transmission cannot be excluded. Notably, the patient's history of shark meat consumption prompted the treating physicians to perform serological testing for anti-HAV antibodies, ultimately leading to the identification of the underlying cause of the patient's critical condition. It is plausible that ingestion of improperly fermented hákarl contributed to the development of acute hepatitis due to HAV infection, resulting in impaired metformin clearance, life-threatening lactic acidosis, and subsequent multiorgan failure.

Since metformin is primarily excreted through kidneys, drug accumulation and subsequent lactic acidosis can be effectively reversed with RRT (11). Importantly, early counselling on temporary discontinuation of metformin in case of an infection might have prevented progression to severe acidosis. In addition, caution is warranted when prescribing metformin to patients receiving concomitant therapies with nephrotoxic or nephro-ischemic potential, such as nonsteroidal anti-inflammatory drugs, or certain antibiotics. These drug combinations may lead to ischemia, acidosis and in consequence renal failure, impair metformin clearance, and thereby substantially increase the risk of MALA (9). In this context, recent exposure to ciprofloxacin was noted as a coexisting factor that may predispose to acute kidney injury. Fluoroquinolones have been associated with an increased risk of AKI and gastrointestinal adverse effects, which may contribute to hypovolemia and transient renal hypoperfusion (19). In patients receiving metformin, such conditions may impair renal clearance and facilitate drug accumulation within a multifactorial clinical setting. Accordingly, patients treated with metformin should be advised to temporarily discontinue the medication in the event of an infection accompanied by fever, diarrhoea, or vomiting (due to the risk of dehydration), as well as in the perioperative period, that is, in situations associated with an increased risk of metabolic acidosis and hypoglycaemia.

In the presented case the combination of chronic comorbidities, the HAV infection with acute hepatic dysfunction, hypovolemia during gastrointestinal disturbances and recent ciprofloxacin exposure subsequently created a multifactorial setting that impaired metformin elimination and ultimately led to profound lactic acidosis.

## Conclusions

In our patient with T2DM and multimorbidity, the acute hepatitis A with hepatic dysfunction, hypovolemia and recent ciprofloxacin exposure created a multifactorial high-risk environment that favoured toxic metformin accumulation with lactic acidosis and development of multiorgan failure. Early diagnosis and prompt initiation of appropriate therapy in MALA are crucial, as timely intervention can facilitate complete recovery and prevent progression to irreversible organ dysfunction. This case underscores the importance of a comprehensive clinical evaluation, including careful medical history thorough with assessment of concomitant medications, intercurrent illnesses, and possible dietary exposures, in order to identify unusual precipitating factors.

## References

1. **Bruijstens LA, van Luin M, Buscher-Jungerhans PMM et al.** Reality of severe metformin-induced lactic acidosis in the absence of chronic renal impairment. *Neth J Med.* 2008; 66: 185–190.
2. **Kajbaf F, Lalau JD.** Mortality rate in so-called “metformin-associated lactic acidosis”: a review of the data since the 1960s. *Pharmacoepidemiol Drug Saf.* 2014; 23: 1123–1127.
3. **Cosentino F, Grant PJ, Aboyans V et al.** 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J.* 2020; 41: 255–323.
4. **Kalantar-Zadeh K, Uppot RN, Lewandrowski KB.** Case records of the Massachusetts General Hospital. Case 23-2013. A 54-year-old woman with abdominal pain, vomiting, and confusion. 23-2013. *N Engl J Med.* 2013; 369: 374–382.
5. **Juneja D, Nasa P, Jain R.** Metformin toxicity: A meta-summary of case reports. *World J Diabetes.* 2022; 13: 654–664.
6. **See KC.** Metformin-associated lactic acidosis: A mini review of pathophysiology, diagnosis and management in critically ill patients. *World J Diabetes.* 2024; 15: 1178–1186.
7. **Adamczak M, Kurnatowska I, Naumnik B et al.** Pharmacological nephroprotection in chronic kidney disease patients with type 2 diabetes mellitus—clinical practice position statement of the Polish Society of Nephrology. *Int J Mol Sci.* 2024; 25: 12941.

8. **Friesecke S, Abel P, Roser M et al.** Outcome of severe lactic acidosis associated with metformin accumulation. *Crit Care.* 2010; 14: R226.
9. **Seidowsky A, Nseir S, Houdret N et al.** Metformin-associated lactic acidosis: a prognostic and therapeutic study. *Crit Care Med.* 2009; 37: 2191–2196.
10. **Calello DP, Liu KD, Wiegand TJ et al.** Extracorporeal treatment for metformin poisoning: systematic review and recommendations from the EXTRIP Workgroup. *Crit Care Med.* 2015; 43: 1716–1730.
11. **Yeh HC, Ting IW, Tsai CW et al.** Serum lactate level and mortality in metformin-associated lactic acidosis requiring renal replacement therapy: a systematic review of case reports and case series. *BMC Nephrol.* 2017; 18: 229.
12. **Hayashi A, Ishimura T, Sugimoto H et al.** Metformin-associated lactic acidosis exacerbated by acute kidney injury in an overseas traveler. *CEN Case Rep.* 2022; 11: 278–282.
13. **Silverii GA.** Optimizing metformin therapy in practice: tailoring therapy in specific patient groups to improve tolerability, efficacy and outcomes. *Diabetes Obes Metab.* 2024; 26 (Suppl 3): 42–54.
14. **Duong JK, Furlong TJ, Roberts DM et al.** The role of metformin in metformin-associated lactic acidosis (MALA): case series and formulation of a model of pathogenesis. *Drug Saf.* 2013; 36: 733–746.
15. **Lambourg E, Fu E, McGurnaghan S et al.** Stopping versus continuing metformin in patients with advanced CKD: a nationwide Scottish target trial emulation study. *Am J Kidney Dis.* 2025; 85: 196–204.e1. doi:10.1053/j.ajkd.2024.08.012.
16. **Yang A, Shi M, Wu H et al.** Clinical outcomes following discontinuation of metformin in patients with type 2 diabetes and advanced chronic kidney disease in Hong Kong: a territory-wide, retrospective cohort and target trial emulation study. *eClinicalMedicine.* 2024; 71: 102568.
17. **Davis B, VanderZwaag DL, Cosandey-Godin A et al.** The conservation of the Greenland shark (*Somniosus microcephalus*): setting scientific, law, and policy coordinates for avoiding a species at risk. *J Int Wildl Law Policy.* 2013; 16: 300–330.
18. **Lin D, Chen W, Lin Z et al.** Viral transmission in seafood systems: strategies for control and emerging challenges. *Food.* 2025; 14: 1071.
19. **Bird ST, Etminan M, Brophy JM et al.** Risk of acute kidney injury associated with the use of fluoroquinolones. *CMAJ.* 2013; 185: 475–482.