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Metformin-Induced Lactic Acidosis (MILA) with Acute Kidney Injury: Case Report

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ABSTRACT

Introduction: Metformin-Induced Lactic Acidosis (MILA) is a rare but life-threatening condition, primarily occurring with high doses of metformin and in patients with impaired renal function. Observation: We present the case of a woman in her 60s with type 2 diabetes mellitus, who was treated with high doses of metformin and developed severe metabolic acidosis due to acute kidney injury (AKI). She presented with epigastric pain, vomiting, generalized fatigue and oliguria. Laboratory tests revealed acute kidney injury, profound lactic acidosis, and hyperkalemia. Renal ultrasound excluded a potential obstructive cause. Emergency management included electrolyte correction and hemodialysis, leading to gradual metabolic improvement. Conclusion: This case underscores the importance of adhering to therapeutic doses of metformin as well as monitoring renal function in diabetic patients on metformin therapy and underscores the need for early recognition and intervention in cases of MILA to prevent fatal outcomes.

Introduction:

Metformin is a widely used first-line treatment for type 2 diabetes mellitus due to its efficacy in glycemic control and cardiovascular benefits. However, its use is contraindicated in patients with renal impairment due to the risk of lactic acidosis.

Metformin-induced lactic acidosis (MILA) is a rare yet severe form of high anion gap metabolic acidosis that occurs due to metformin accumulation, leading to impaired oxidative metabolism and increased lactate production. IT carries a high mortality rate if not promptly diagnosed and treated [1].

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The rising prevalence of diabetes and the widespread use of metformin highlight the need for clinicians to be vigilant about the risks and appropriate management of this condition. This case report underscores the importance of adhering to therapeutic dosing, regularly monitoring renal function, and promptly recognizing MILA in patients with diabetes [2].

Observation:

A 68-year-old woman with a history of Type 2 Diabetes Mellitus presented to the emergency department of Regional Hospital of Ben Arous with epigastric pain, persistent vomiting, and generalized fatigue. She also reported dysuria and oliguria, raising suspicion of a urinary tract infection. There was no past medical history of renal impairment, liver failure or alcoholism. She denied recent drug introduction, treatment discontinuation or prolonged fasting.

Her medication included Metformin (1000 mg two times daily) and Vidagliptin / Metformin (50 mg/1000mg two times daily) which had been introduced a month ago by her primary care physician due to inadequate glycemic control. The physical examination at admission indicated the following: The patient was alert and oriented, with no focal neurological deficits. She exhibited rapid, shallow breathing without accessory muscle use, consistent with Kussmaul respiration. Oxygen saturation was 99% on room air. Blood pressure measured 140/84 mmHg in both arms, with a regular pulse of 68 beats per minute. There were no peripheral signs of shock or edema. Body temperature was 37.3°C. Respiratory sounds were clear to auscultation with no crackles, wheezes, or bronchial breath sounds. Cardiac auscultation was normal. The abdomen was non-distended, soft, and non-tender. Capillary blood glucose was initially found to be 0.3 g/L, which was immediately corrected to 2.0 g/L with intravenous (IV) glucose administration. Urine test strip showed only 1+ of hematuria.

The initial laboratory findings revealed a severe metabolic acidosis with a pH of 7.1 and a bicarbonate level of 5.3 mmol/L. The anion gap was calculated to be 35 mmol/L, indicating an elevated anion gap metabolic acidosis. Lactate levels were markedly elevated at 12.24 mmol/L. Additionally, the patient had hyperkalemia (6.5 mmol/L) with no conduction abnormalities on the electrocardiogram (ECG), as well as a severe kidney insufficiency with a creatinine level of 530 µmol/L which corresponds to a clearance of 7 mL/min and elevated blood urea nitrogen levels. Urine culture was sterile. Initial laboratory findings are shown in (Table 1).

Table 1: Initial laboratory Findings.

	Values
CBC	Hemoglobin = 11.1g/dL RBC = 3.72.10^6/µL MCV= 95 fL ; MCH= 29.8 pg Platelets = 287.10^3/µL WBC= 10.4.10^3/µL Neutrophils= 7.98.10^3/µL Lymphocytes= 2.10^3/µL
PT(%)/INR	70/1.32
Creatinine Clearance Urea nitrogen	530 µmol/L 7 ml/min 20.6 mmol/l
Electrolyte panel	Na^+ = 137 mmol/L K^+ = 8 mmol/L Cl^- = 97 mmol/L
Calcium Albumin	2.31 mmol/L 46 g/L
AST / ALT	61/24 UI/l
Lipase	140 UI/L
Blood Gas	pH = 7.01 pCO2 = 21 mmHg paO2 = 138 mmHg HCO3-= 5.3 mmol/L SaO2 = 97% Lactate = 12.24 mmol/L
CBEU	Clear WBC < 10 /mm3 RBC = 10/mm3 Culture: negative

RBC: Red Blood Cells; CBC: Complete Blood Count; WBC: White Blood Cells; MCV: Mean Corpuscular Volume

PT: Prothrombin Time; INR: International Normalized Ratio; AST: Aspartate aminotransferase; ALT: Alanine transaminase; CBEU: Cyto-Bacteriological Examination of Urine.

Renal ultrasonography revealed kidneys of normal size with preserved cortico-medullary differentiation. This, in conjunction with a normal serum calcium level, favored an acute rather than chronic kidney injury. Obstructive etiology was excluded based on the absence of urinary tract dilatationThe normal serum calcium level, combined with preserved renal morphology, supported an acute rather than chronic kidney injury. Obstructive nephropathy was excluded by the absence of urinary tract dilatation.

Immediate management included correction of hyperkalemia with intravenous euglycemic insulin therapy (10 IU human insulin in 100 mL of 30% dextrose), beta-2 agonist nebulization (salbutamol 20 mg), and intravenous furosemide (120 mg) to enhance potassium excretion. Given the presence of severe metabolic acidosis and profound renal impairment, emergency hemodialysis was initiated on the same day.

Following the first hemodialysis session, lactate levels decreased to 7.28 mmol/L, with partial improvement of pH to 7.26. A second session further reduced lactate to 6.18 mmol/L, while pH remained at 7.12. A third session resulted in additional correction of metabolic derangements and gradual normalization of acid-base balance. Renal function, however, showed no improvement (Table 2).

Table 2: Follow up laboratory findings.

Hemodialysis	Day I Session 1	Day II Session 2	Day III Session 3	Day IV
Blood Gas: pH (mmHg) pCO2 (mmol/L) HCO3- (mmol/L) Lactate (mmol/L)	 7,26 20 9.1 7.28	 7,12 28.5 9.1 6.18	 7,36 23.5 13.1 1.88	 7,4 35.5 21.6 2.14
Creatinine (µmol/L) Clearence (ml/min)	306 14	491 8	493 8	647 6
Electrolyte: Na^+ (mmol/l) K^+ (mmol/l) Cl^- (mmol/l)	 140 4.5 95	 136 5.2 97	 138 4.4 101	 139 4.4 102

The patient was referred to the nephrology department for additional investigations

Discussion

Metformin is a biguanide oral antidiabetic agent used as a first-line treatment for type 2 diabetes [3]. The history of metformin can be traced back to *Galega officinalis* Linn, a herbal remedy used in medieval Europe. In the 1800s, *G. officinalis* was found to be rich in guanidine, and in 1918, guanidine was demonstrated to have hypoglycemic effects in animal models. These findings ultimately led to the development of the biguanide class of drugs [4].

Metformin is therapeutically effective because it improves peripheral insulin sensitivity, a central defect in type 2 diabetes mellitus (T2DM), without directly enhancing insulin secretion, thereby minimizing the risk of hypoglycemia and weight gain [5,6]. Metformin exerts its pharmacological effects primarily through inhibition of mitochondrial Complex I and activation of adenosine monophosphate-activated protein kinase (AMPK), leading to increased glycolysis, oxidative phosphorylation, and mitochondrial fatty acid β-oxidation [8]. Inhibition of Complex I decreases ATP production, shifting cellular energy metabolism toward glycolysis and promoting the conversion of pyruvate to lactate rather than its entry into the Krebs cycle [9]. Simultaneously, the resulting rise in cytoplasmic ADP/ATP and AMP/ATP ratios activates AMPK, which suppresses lipogenesis and enhances fatty acid oxidation, thereby reducing hepatic lipid stores and improving hepatic insulin sensitivity.

These pharmacokinetic properties explain the accumulation of metformin in patients with significant renal impairment, which may predispose to lactic acidosis, and support the use of extrarenal elimination techniques to enhance drug clearance [9].

Metformin exhibits negligible plasma protein binding, a large volume of distribution, is not metabolized, and is predominantly excreted unchanged via the kidneys (~90%) [10].

At therapeutic doses, metformin exerts its antihyperglycemic effect without significantly altering blood lactate levels, as lactate is efficiently converted to glucose in the liver via the Cori cycle. However, metformin accumulation can further inhibit hepatic gluconeogenesis, impairing the oxidative clearance of lactate and increasing anaerobic metabolism in hepatocytes. This may lead to elevated plasma lactate levels and, in rare cases, lactic acidosis [11].

Lactic acidosis is an uncommon but potentially life-threatening adverse effect of metformin, which can result in multi-organ failure. Although rare, studies have reported an association between metformin use and lactic acidosis in certain patients. For example, a review by Salpeter et al. (1966–August 2005) found no fatal or nonfatal cases of lactic acidosis; however, approximately 330 reported cases suggest that metformin may contribute to its development in specific circumstances [12].

Lactic acidosis is the most common cause of metabolic acidosis with an elevated anion gap. It is typically defined by an arterial lactate concentration exceeding 5 mmol/L and a pH below 7.35 [1], criteria that were present in our patient.

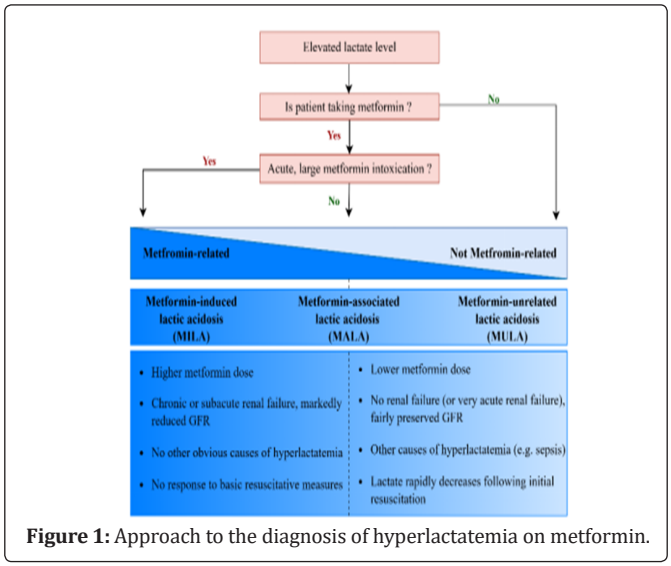

Figure 1: Approach to the diagnosis of hyperlactatemia on metformin.

Lalau and Race suggested in their review that the link between metformin and lactic acidosis may be causal, associated or coincidental [14]. This led to the following definition system (**Figure 1).**

- Metformin-Unrelated Lactic Acidosis (MULA): involving other causes of elevated lactate whereas metformin levels are low.
- Metformin-Associated Lactic Acidosis (MALA): metformin and concurrent causes of elevated lactate (e.g. hypoxemia, septic shock, cardiogenic shock, liver failure) as co-precipitating factors of lactic acidosis.
- Metformin-Induced Lactic Acidosis (MILA): metformin as the only precipitating factor.

MILA may occur in the setting of an acute metformin overdose, and whereas the accepted therapeutic range of metformin varies from 500 to 2550 mg, the amount of drug required to cause toxicity is unclear [9]. It can also occur because of a chronic or subacute renal failure that markedly reduces Glomerular Filtration Rate (GFR). In both cases no other major risk factor for lactic acidosis is identified.

This leads us to the contraindications and precautions associated with metformin, including renal impairment, conditions that predispose to metformin accumulation, and situations that may promote hypoxia (e.g., heart failure, tissue hypoxia, respiratory failure) or impair lactate clearance (e.g., alcohol abuse, liver failure) [15]. Assessing metformin plasma levels, renal function, arterial lactate concentrations, comorbidities, and the clinical context is essential to accurately interpret each case [12].

In our patient, metformin levels were not readily available; thus, the diagnosis was based on the clinical context. The patient was taking 4000 mg of metformin daily and showed no evidence of shock, tissue hypoperfusion, liver failure, hypoxemia, severe anemia, or any other obvious cause of elevated lactate. The presence of initial hypoglycemia and acute kidney injury suggested that metformin was the most likely contributing factor to lactic acidosis, supporting the diagnosis of metformin-induced lactic acidosis (MILA). Furthermore, the patient's rapid recovery following dialysis, without other significant interventions, supported this conclusion.

Considering the acute kidney injury (AKI), an obstructive etiology was promptly excluded by renal ultrasound. The course of renal function did not support functional AKI, as no improvement was observed despite adequate hydration. These findings pointed toward acute intrinsic kidney injury, likely secondary to metformin accumulation in the absence of other clinically identifiable causes [2]. However, confirmation would require correlation with renal biopsy findings.

The benefits of hemodialysis seem to be related to the correction of metabolic acidosis and drug elimination [17]. Given the large volume of distribution, there may be some utility to prolonged hemodialysis sessions for successful clearance of metformin and lactate.

The Extracorporeal Treatment in Poisoning (EXTRIP) workgroup, has published guidelines to help inform decision-making in the use of invasive extracorporeal therapies for overdoses and poisonings, including the management of metformin toxicity. The conditions to initiate dialysis in MILA include lactic acid of >20 mmol/L, pH of ≤7.0, hypotension, decreased level of consciousness, kidney failure, and lack of response to supportive treatment. When performed, dialysis should ideally be continued until the lactate <3 mmol/L and pH >7.35; which was the case with our patient.

Conclusion:

Metformin-Induced Lactic Acidosis (MILA) is a serious but avoidable complication associated with high doses of metformin and impaired renal function. Hypoglycemia in patients with diabetes mellitus treated with metformin should draw attention to lactic acidosis. Additionally, high anion gap metabolic acidosis with severe hyperlactatemia in a patient on metformin should prompt immediate evaluation for MILA. Early recognition and intervention, including discontinuation of metformin and hemodialysis in severe cases, are critical for patient survival. Hemodialysis remains the mainstay of treatment for severe cases, effectively clearing metformin and correcting metabolic derangements. It is the only way to stop the vicious circle from lactic acidosis to multiple organ failure.

Glossary/Abbreviation

MILA: Metformin-Induced Lactic Acidosis

AKI : Acute Kidney Injury

IV : Intervenus

CBC: Complete Blood Count

WBC: White Blood Cells

RBC: Red Blood Cells

MCV: Mean Corpuscular Volume

PT: Prothrombin Time

INR: International Normalized Ratio

AST: Aspartate aminotransferase

ALT: Alanine transaminase

CBEU: Cyto-Bacteriological Examination of Urine

ECG: Electrocardiogram

NIDDM: Non-Insulin-Dependent Diabetes Mellitus

UKPDS: United Kingdom Prospective Diabetes Study

AMPK: Adenosine Monophosphate-Activated Protein Kinase

ATP: Adenosine triphosphate

ADP: Adenosine diphosphate

AMP: Adenosine monophosphate

MALA: Metformin-Associated Lactic Acidosis

MULA: Metformin-Unrelated Lactic Acidosis

GFR: Glomerular Filtration Rate

EXTRIP: Extracorporeal Treatment in Poisoning

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