**CLINICAL VIGNETTE**

# Metformin Induced Lactic Acidosis – A Series of Two Patients
# A Life-Threatening Complication of Metformin Use in Chronic Kidney Disease

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***Introduction***

Metformin has been a standard treatment for Type II diabetes since its introduction in the 1950s in Europe and in the 1990s in the United States.[1] It is often the first oral medication in patients with diabetes. It is also used in polycystic ovarian syndrome (PCOS).[2] The role for metformin may be greatly expanded since studies have shown a potential role in patients with pre diabetes and metabolic syndrome to delay or prevent diabetes mellitus type 2.[3] Concern has arisen given the association of diabetes mellitus and comorbid renal causing increased risk of lactic acidosis from metformin use.[4] This complication is rarer than previously thought[5] but when it does occur it is life threatening with a 25-50% mortality rate.[5,6]

The exact mechanism for metformin induced lactic acidosis is not well described, it is thought to be due to a class effect of the biguanides inhibiting cellular respiration at the level of the mitochondria. It is especially prominent in people with severe renal failure (estimated glomerular filtration rate-eGFR<30ml/min), those with hepatic failure, or shock.[7] The incidence is also much lower than previously thought with some estimates as low as <10/100,000 cases.[7] We report two cases of metformin-induced lactic acidosis and review diagnosis, management, treatment, outcomes, and possible prevention strategies.

***Case 1***

A 55-year-old male with ESRD due to diabetic nephropathy on chronic hemodialysis suddenly began feeling dizzy at home around midnight. Upon EMS arrival, the patient was mentating well but developed severe vomiting. His heart rate decreased to 30 BPM and he became unresponsive. In the ambulance, his systolic blood pressure dropped to the 40 mmHg with improvement to 80 mmHg with IV fluid boluses. An EKG en route showed ST elevations in lead V2 through V4. Upon arrival to the ED, the patient received atropine, IVF, aspirin, heparin, and Plavix, and he was placed on a dopamine and phenylephrine drip. He was minimally responsive and was emergently intubated. Emergent cardiac catheterization noted clean coronaries with a left ventricular ejection fraction of 65%. He was found to be acidemic with a pH 7.14, serum bicarbonate 12 mmol/L and anion gap 21 mmol/L. Continuous veno-venous-hemodialysis (CVVHD) was emergently initiated. Lactate was later found to be elevated, 48 mg/dL. Family reported that the patient was taking metformin. His serum bicarbonate improved with normalization of the anion gap and lactate level. Over 72 hours, the patient was weaned off pressors, extubated, and CVVHD stopped. He regained his baseline mental and functional status and was discharged after a 5-day hospitalization. His clinical status remained stable on chronic intermittent hemodialysis for 4 years before he moved out of the Los Angeles area.

***Case 2***

A 60 year old male was advised by his community nephrologist that his eGFR had improved enough to stop hemodialysis. He stopped hemodialysis with an estimated eGFR of about 25 ml/min and his permacath removed. He did not have cirrhosis or hepatic failure and the reason for CKD was listed as diabetes mellitus and hypertension. On the day of admission he complained of malaise and shortness of breath. He was evaluated in the emergency room and was profoundly acidotic with a metabolic acidosis with serum bicarbonate of 3 mmol/L and an arterial blood gas showing a pH of 6.82 with lactate 215 mg/dL. This was promptly treated with bicarbonate, kayexalate, calcium gluconate, insulin and dextrose. Dialysis orders were written –via the continuous renal replacement therapy modality (CRRT). During transit to ICU, he developed ventricular tachycardia and arrest. He had cardio pulmonary resuscitation and defibrillation with return of spontaneous circulation.

After intubation, a dialysis catheter was placed and he started CRRT (Continuous veno-venous-hemodiafiltration/with con-current hemofiltration-CVVHD/F) and pressors. His serum bicarbonate rose, and his pressor requirement gradually im-proved and he was weaned off of all pressors by day 4 in the ICU.

The patient's wife and daughter affirmed he had continued taking metformin after hemodialysis was discontinued. The patient gradually improved, was extubated, and successfully transitioned to single pass hemodialysis. He is now on chronic hemodialysis three times a week without any physical or neurological disability.

***Discussion***

The growing prevalence of diabetes and hypertension increases the importance of treatment to delay or prevent diabetes. The

common comorbidity of renal dysfunction impacts the use of various drugs whose metabolism is impaired in renal disease or who have negative effects on renal heath. Metformin induced lactic acidosis is a relatively rare disease, but use of metformin in patients with hepatic disease, renal failure, or shock should be undertaken with great caution. The current guideline is a serum creatinine clearance (eGFR) of 30ml/min is sufficient renal function for the safe use of this agent. In light of the expanded roles given this agent it is not unreasonable that metformin induced lactic acidosis may rise as the number of people taking biguanide agents increases. Increased research is needed into the exact cause of this disorder on the molecular/ mitochondrial levels. The extended release of metformin should also be independently evaluated from a metabolic standpoint with regard to lactic acidosis risk.[7]

## REFERENCES


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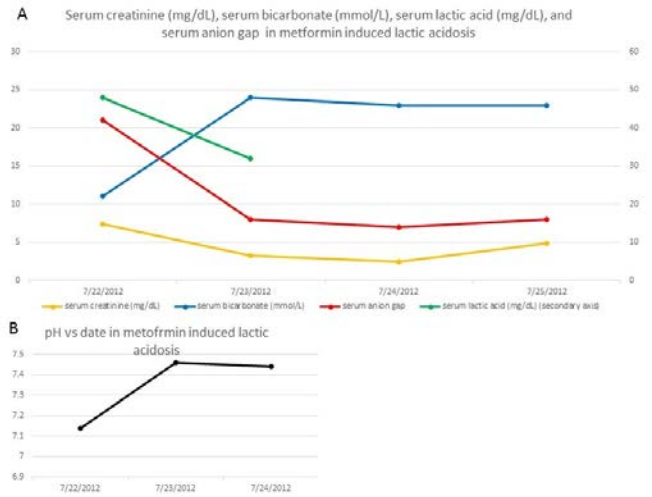


**Figure 1.** A) Plot of case 1, serum creatinine (mg/dL), serum bicarbonate (mmol/L), and serum lactic acid (mg/dL), anion gap, during acute admission for metformin induced lactic acidosis. B) Plot of case 1 arterial pH versus date during acute admission for metformin induced lactic acidosis.

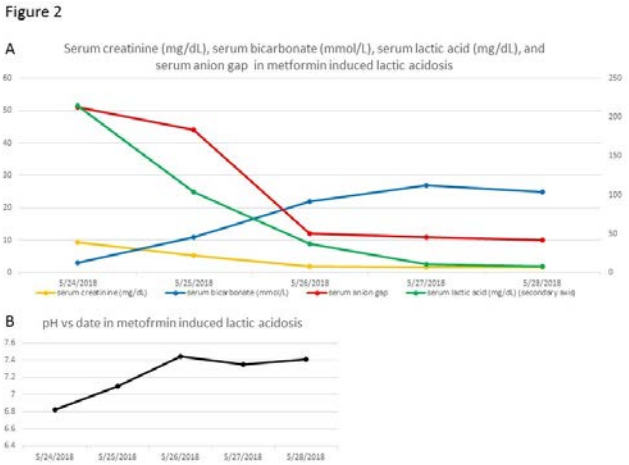


**Figure 2.** A) Plot of case 2, serum creatinine (mg/dL), serum bicarbonate (mmol/L), and serum lactic acid (mg/dL), anion gap, and arterial pH during acute admission for metformin induced lactic acidosis. B) Plot of case 2 arterial pH versus date during acute admission for metformin induced lactic acidosis.