

“Switched” metabolic acidosis in mitochondrial diabetes mellitus

A 72-year-old Japanese woman with mitochondrial diabetes was admitted to The Tazuke Kofukai Medical Research Institute Kitano Hospital, Osaka, Japan, because of altered mental status. She had gastroenteritis symptoms for 10 days and could not inject her insulin for a few days. Almost 30 years earlier, she was diagnosed as diabetes mellitus with the mitochondrial deoxyribonucleic acid 3243 (A–G) mutation, and she had been treated with subcutaneous insulin injections.

Initial laboratory tests showed a plasma glucose of 846 mg/dL, pH 7.002 and bicarbonate 5.9 mmol/L. White blood cells were 21,700/ μ L, arterial lactate level 3.20 mmol/L, acetoacetate 2,561 μ mol/L and β -hydroxybutyrate 13,110 μ mol/L. After making the diagnosis of diabetic ketoacidosis, intravenous normal saline and insulin infusion was initiated. Mero-penem was given for gastroenteritis. After saline infusion, the patient’s hemodynamics improved quickly, by which transiently impaired renal function was restored.

The next day, the patient’s plasma glucose level was 338 mg/dL, and acetoacetate and β -hydroxybutyrate decreased to 108 and 378 μ mol/L, respectively. In contrast, pH was still 7.033 and her arterial lactate level elevated to 10.20 mmol/L. During the initial treatment, although ketosis improved markedly, lactic acidosis developed (Figure 1). The patient had not taken any medication that can cause lactic acidosis, such as metformin. A vitamin cocktail including adequate thiamine was empirically added to initial therapy, because her blood thiamine level was

mildly decreased (18 ng/mL, normal 24–66 ng/mL). On the third day, the patient’s mental status and lactic acidosis improved. Eventually, intravenous insulin was discontinued, and her blood glucose was controlled with subcutaneous insulin injections.

DISCUSSION

Diabetic ketoacidosis is one of the most serious acute metabolic complications of diabetes, and the metabolic acidosis improves quickly with appropriate insulin therapy and hydration. In the current case, lactic acidosis developed as diabetic ketoacidosis improved with insulin treatment. Although lactic acidosis is often

observed in patients with diabetic ketoacidosis before medical intervention¹, to the best of our knowledge, there is no report that lactic acidosis worsened as ketoacidosis improved. This clinical course, referred to as “the switched metabolic acidosis,” may reflect the unique pathophysiology of the mitochondrial disorder.

Mechanistically, “the switched metabolic acidosis” might be caused by complex changes in lactate metabolism. First, it is well known that in patients with mitochondrial disorders, an impairment of oxidative metabolism results in an increased ratio of nicotinamide adenine dinucleotide to oxidized nicotinamide adenine dinucleotide, which promotes

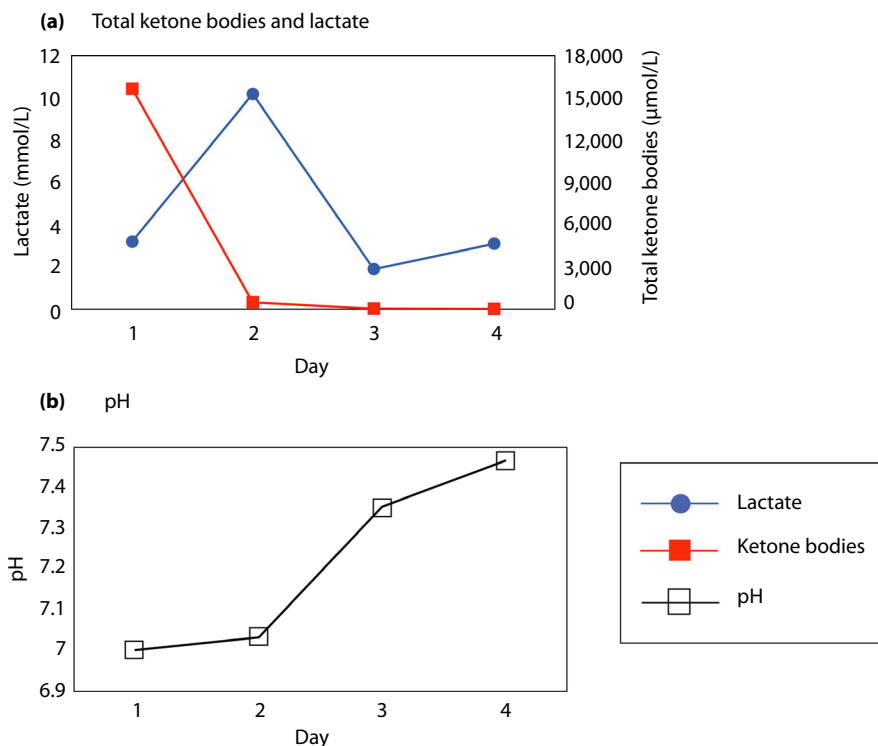


Figure 1 | Time course of change in (a) the total ketone bodies (the sum of acetoacetate and β -hydroxybutyrate), lactate and (b) pH.

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the conversion of pyruvate to lactate, leading to increased lactate production. In addition, a recent *in vitro* study showed that complex I enzymatic activity was improved in a continuous low-glucose condition², suggesting that a drastic increase in intracellular glucose after insulin treatment can deteriorate lactate accumulation while ameliorating ketosis. Finally, it is conceivable that mitochondrial dysfunction decreased lactate uptake in hepatocytes through 5' adenosine monophosphate-activated protein kinase activation, which could further exacerbate lactic acidosis³.

In the present patient, mildly decreased thiamine level would not be the primary cause of lactic acidosis. Although thiamine deficiency is common in diabetic ketoacidosis patients⁴, switched metabolic acidosis has not been reported. Nevertheless, we could not exclude the possibility that thiamine deficiency affected the clinical course in this setting.

In conclusion, in diabetic ketoacidosis patients with mitochondrial diabetes, “the switched metabolic acidosis” during insulin treatment should be considered.

DISCLOSURE

The authors declare no conflict of interest.

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