

# An Unusual Case of Metabolic Acidosis: Clinical Case Education

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**A** 58-year-old female presented to the emergency department with severe nausea, vomiting, and abdominal pain. One week earlier she had undergone a laparoscopic gastric wedge resection due to gastric perforation. Her medical history was remarkable for peptic ulcer disease treated with Nissen fundoplication one year earlier, type 2 diabetes, and hypertension. The patient's chronic medications were stopped 2 days prior to hospital admission due to vomiting.

In the emergency department the patient was pale with signs of hypovolemia, and her abdomen was distended. Abdominal computed tomography (CT) scan revealed small bowel obstruction with distention of the stomach and small bowel and collapsed terminal ileum. Oral intake was withheld and she was treated with intravenous normal saline.

Laboratory tests at admission revealed leukocytosis of  $27 \times 10^9/L$ , hemoglobin 12.9 g/dl, platelets  $490 \times 10^9/L$ , creatinine 0.7 mg/dl, potassium 4.8 meq/L, glucose 110 mg/dl, sodium 129 meq/L, chloride 82 meq/L, and albumin level 3.6 g/dl with normal liver function test. The arterial blood gas showed a pH of 7.29,  $pCO_2$  15.5 mmHg, bicarbonate 7 mmol/L, base excess 16 mmol/L, and lactate 12 mg/dl.

The patient was treated with intravenous sodium bicarbonate for severe

metabolic acidosis with no adequate response. Urinalysis demonstrated ketonuria (+4) and glucosuria ( $> 2200$  mg/dl) despite normal serum glucose. Serum was positive for ketones as well.

## METABOLIC ACIDOSIS

The patient exhibited prominent metabolic acidosis, which is characterized by an increase in plasma acidity (defined as arterial pH lower than 7.35 and bicarbonate lower than 22). Metabolic acidosis is caused by either acid accumulation due to increased acid production or acid ingestion, decreased acid excretion, or gastrointestinal or renal bicarbonate ( $HCO_3^-$ ) loss.

The diagnosis of metabolic acidosis is based on blood pH and  $HCO_3^-$  levels. Respiratory compensation is determined by  $pCO_2$  based on Winter's formula:  $pCO_2 = 1.5 \times [HCO_3^-] + 8 \pm 2$ , or the simpler equation  $pCO_2 = [HCO_3^-] - + 15$ .

The next step is classifying metabolic acidosis by the primary mechanism. The serum anion gap (AG) is used to categorize metabolic acidosis into two groups: high AG metabolic acidosis and normal AG metabolic acidosis. AG should always be calculated because it may expose hidden metabolic acidosis that may not be apparent

from the pH level. AG is calculated as  $AG = Na^+ - (Cl^- + HCO_3^-)$ . Normal AG is approximately 12.

If elevated AG metabolic acidosis is present, the next step is to calculate the delta-delta ratio, from the equation:  $(AG-12)/(24-HCO_3^-)$ , where 12 and 24 are the normal reference values for AG and bicarbonate level, respectively. This ratio assesses the relationship between the change in AG and the change in bicarbonate. In the case of pure metabolic acidosis, the measure of the changes is similar. For example, if the AG is 20 (8 above normal), the expected bicarbonate should be 16 (8 below a normal value of 24). If there is a significant difference in the change in these parameters, a mixed acid base disorder is suggested. If the bicarbonate level is higher than expected, this indicates that metabolic alkalosis is also present. If the bicarbonate is less than expected, then a concurrent non-AG metabolic acidosis is present [Table 1].

On the patient's third hospitalization day, nephrology consultation was requested. On physical examination the patient's temperature was 36.1°C. Her heart rate was 69 beats per minute and her blood pressure was 108/59 mmHg. Oxygen saturation level was 94%. The

**Table 1.** Assessment of bicarbonate level

Delta ratio	Assessment guidelines
$< 0.4$	Hyperchloremic normal AG acidosis
$< 1$	High AG and normal AG
1–2	Pure high anion gap: lactic acidosis average value 1.6, DKA more likely to have a ratio closer to 1
$> 2$	High AG with concurrent metabolic alkalosis or pre-existing compensated respiratory alkalosis

AG = anion gap, DKA = diabetic ketoacidosis

patient was stuporous with signs of dehydration and kussmaul breathing.

The blood gas showed metabolic acidosis with respiratory alkalosis since  $p\text{CO}_2$  was 15.5 mmHg instead of the calculated 22 ( $p\text{CO}_2 = \text{HCO}_3^- + 15 = 22$ ).

Calculated AG was high,  $\text{Na} - (\text{Cl} + \text{HCO}_3^-) = 30$ , delta delta ratio was 1.1. The delta AG/delta  $\text{HCO}_3^-$  ratio of 1, including ketonuria, ketonemia, and glucosuria, led to a diagnosis of diabetic ketoacidosis (DKA). The trigger for ketoacidosis was the lack of carbohydrate intake, both orally and intravenous.

### GLUCOSURIA AND RENAL HANDLING

The patient was diagnosed with severe glucosuria with normal plasma glucose. Glucosuria is nearly always caused by elevated blood glucose, mostly due to untreated diabetes mellitus. When glucosuria is accompanied by normal plasma glucose, a primary defect in proximal tubule reabsorption such as Fanconi syndrome needs to be considered. Fanconi syndrome is characterized by other proximal tubular defects such as phosphaturia.

The patient was treated with an intravenous solution of 5% dextrose and an insulin drip of 0.1 unit/kg/hour. Consequently, the patient gradually improved, with rapid improvement in her blood gas: pH 7.345, bicarbonate 17 mmol/L,  $p\text{CO}_2$  31 mmHg, lactate 12 mg/dL, and AG 13. The patient's intravenous fluid regimen was changed to normal saline without any glucose. Insulin treatment was changed to subcutaneous injections rather than an intravenous drip. However, repeated daily urine analysis showed persistent ketonuria (+4) and glucosuria (> 4000 mg/dL).

Revision of the patient's chronic medications revealed that canagliflozin, a sodium-glucose transport protein 2 (SGLT2) inhibitor, was used until 2 days prior to admission.

The kidneys play an important role in the regulation of glycemic homeostasis;

90% of filtered glucose is absorbed in the proximal convoluted tubule by four members of two glucose transporter families: SGLT1, SGLT2, GLUT1, and GLUT2 [1].

SGLT1 and SGLT2 play an important role in the apical membrane of the proximal tubular cells in the kidney. SGLT2 is expressed predominantly in the luminal brush border of the proximal tubule in the renal cortex, where it is the principal transporter that mediates glucose reabsorption [2].

### SGLT2 INHIBITORS

SGLT2 inhibitors belong to the newest class of anti-diabetic medications. They decrease glucose absorption and optimize glycemic control. SGLT2 inhibitors have been extensively studied and were shown to improve cardio-metabolic markers in type 2 diabetes mellitus [3]. SGLT2 inhibitors are reversible and selective. They have a bioavailability of 65% and a half-life of 10 to 13 hours. They are excreted in the urine (~33%, as metabolites) and in the feces (~41% as unchanged drug and ~10% as metabolites). Their effect is monitored by urinary glucose excretion and should subside within 2–3 days after discontinuation of the drug [4,5]. In May 2015 the U.S. Food and Drug Administration (FDA) issued a safety warning regarding the risk of ketoacidosis associated with the use of SGLT2 inhibitors. The majority of the cases occurred among type 2 diabetic patients [6,7]. Euglycemic diabetic ketoacidosis is characterized by the presence of metabolic acidosis ( $\text{pH} < 7.3$ , and serum bicarbonate  $< 18$  mEq/L), ketonemia, and blood glucose of less than 200 mg/dL [8]. The human body produces a basal amount of glucose through gluconeogenesis and glycogenolysis, even without any carbohydrate intake. This is the trigger for the basal insulin release by the pancreas. SGLT2 inhibitors lower blood glucose by increasing urinary excretion of glucose. This fall in blood glucose decreases insulin secretion by the pancreas, which in turn leads to an increase of glucagon-to-insulin ratio. The end result is enhanced gluconeogenesis,

which leads to increased ketogenesis, hence the ketoacidosis [9]. Although characteristically type 2 diabetic patients have insulin resistance, the disease is also complicated by relative insulin deficiency, making these patients prone to develop ketonemia [10].

A recent study showed that SGLT2 is also expressed on pancreatic cells and appears to function as part of the cellular glucose sensing mechanism [11]. Furthermore, exposure of pancreatic human islets to SGLT2 inhibitors increased glucagon secretion, presumably by exerting a direct effect on cell function. This increase in glucagon secretion may be another potential mechanism that contributes to ketone body production [12,13].

### TAKE HOME MESSAGE

SGLT2 inhibitor-induced DKA might easily be missed, given that it is not necessarily associated with the typical manifestations of DKA, such as marked hyperglycemia. Euglycemic diabetic ketoacidosis has to be considered in the differential diagnosis of high AG metabolic acidosis in diabetic patients treated with SGLT2 inhibitors.

The patient continued to experience unresolved bowel obstruction; therefore, on the fifth hospitalization day she successfully underwent laparoscopic lysis of abdominal adhesions. After 24 hours bowel peristalsis resumed, with passage of flatus and stool, which improved her general status. Shortly after, her blood gas normalized, with pH of 7.445 and bicarbonate levels of 26 mmol/L. Ketonuria resolved as well. Interestingly, glucosuria, which persisted for 7 days after cessation of SGLT2 inhibitor and 3 days after intravenous glucose was stopped, quickly resolved after bowel activity resumed.

### PROLONGED EFFECT OF SGLT2 INHIBITORS

The effect of the SGLT2 inhibitor in the patient was prolonged, over one week after

the last dose, as evidenced by persistent glucosuria despite normal blood glucose level and cessation of intravenous dextrose fluid. The prolonged effect of the SGLT2 inhibitor may be related to the patient's bowel obstruction. Since 41% of the drug is excreted in the gut as unchanged drug, bowel obstruction may induce persistent drug absorption through enterohepatic circulation. Our patient improved only after bowel obstruction was relieved and bowel activity resumed. A review of the literature yielded several other case reports describing a similarly prolonged effect associated with abdominal surgeries [14] or gastric paresis [15] that presumably induced gastrointestinal stasis and increased drug absorption.

### TAKE HOME MESSAGE

Prolonged effects of SGLT2 inhibitors may persist after drug cessation in diabetic patients with reduced gastrointestinal motility (e.g., gastroparesis, bariatric surgery, and bowel obstruction).

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### Capsule

#### Ultrasensitive serum interferon- $\alpha$ quantification during SLE remission identifies patients at risk for relapse

Maintenance of remission has become central in the management of systemic lupus erythematosus (SLE). The importance of interferon-alpha (IFN- $\alpha$ ) in the pathogenesis of SLE notwithstanding, its expression in remission has been poorly studied as yet. **Mathian** and co-authors studied its expression in remission and its prognostic value in the prediction of a disease relapse. Serum IFN- $\alpha$  levels were determined using an ultrasensitive single-molecule array digital immunoassay which enables the measurement of cytokines at physiological concentrations. A total of 254 SLE patients in remission, according to the definition of remission in SLE classification, were included in the study. Serum IFN- $\alpha$  concentrations were determined at baseline and patients were followed

up for one year. Of all patients in remission, 26% displayed abnormally high IFN- $\alpha$  serum levels that were associated with the presence of antibodies specific for ribonucleoprotein (RNP), double stranded (ds)DNA and Ro/SSA60, as well as young age. Importantly, elevated-baseline IFN- $\alpha$  serum levels and remission duration were associated in an independent fashion, with shorter time to relapse, while low serum levels of complement component 3 and anti-dsDNA Abs were not. Direct serum IFN- $\alpha$  assessment with highly sensitive digital immunoassay permits clinicians to identify a subgroup of SLE patients, clinically in remission, but at higher risk of relapse.

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Eitan Israeli

**"If we would have new knowledge, we must get us a whole world of new questions"**

Susanne Langer (1895–1985), philosopher

**"Genius is the ability to put into effect what is on your mind"**

F. Scott Fitzgerald (1896–1940), American fiction writer, whose works helped to illustrate the flamboyance and excess of the Jazz Age