Euglycemic Diabetic Ketoacidosis, a Misleading Presentation of Diabetic Ketoacidosis

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Abstract

Context: Diabetic ketoacidosis (DKA) is one of the most serious complications of diabetes. It is characterized by a triad of increased total body ketone concentration, metabolic acidosis, and uncontrolled hyperglycemia. Hyperglycemia is a key diagnostic criterion of DKA; however, in some rare cases, normal glucose levels can be present. Case Reports: We describe two patients with type 1 diabetes mellitus (DM1); one who presented with a Bartholin's gland abscess and the other with acute pancreatitis. Both patients had maintained adequate hydration and continued to take their insulin without sufficient carbohydrate intake in the previous days prior to presentation. Despite their normal serum glucose levels upon presentation, they were found to have ketonemia and acidosis consistent with DKA. If only the serum glucose level was taken into consideration, while ignoring the rest of their biochemical profiles and failing to obtain ketone levels, the diagnoses would have been missed. Conclusion: Euglycemic DKA is usually seen in otherwise healthy patients with type 1 diabetes mellitus who have decreased carbohydrate intake in the presence of adequate hydration and a degree of insulin intake. Recognition of this entity by the emergency provider is crucial when patients with DM1 present with a picture of DKA, regardless of their blood sugar.

Keywords: Diabetic ketoacidosis (DKA), Euglycemic DKA, Normal blood sugar

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Introduction

Hyperglycemia and ketosis in diabetic ketoacidosis (DKA) are the result of insulin deficiency and an increase in the counterregulatory hormones glucagon, catecholamines, cortisol, and growth hormone. Three processes are mainly responsible for hyperglycemia: increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral tissues. This might also be augmented by transient insulin resistance due to hormone imbalance, as well as elevated free fatty acids.[1]

DKA is most commonly precipitated by infections. Other factors include discontinuation of or inadequate insulin therapy, pancreatitis, myocardial infarction, cerebrovascular accident, and illicit drug use. The diagnostic criteria of DKA, established by the American Diabetic Association, consists of a plasma glucose of >250 mg/dL, positive urinary or serum ketones, arterial pH of <7.3, serum bicarbonate <18 mEq/L, and a high anion gap. The key diagnostic feature of DKA is elevated circulating total blood ketone concentration. Hyperglycemia is also a key diagnostic criterion of DKA; however, a wide range of plasma glucose levels can be present on admission.

Case Presentation

Case 1
A 41-year-old female, with a past medical history of DM1 treated with insulin glargine and insulin aspart, presented with a 1-day history of diffuse abdominal pain and weakness. Her symptoms were associated with chills, nausea, and just one episode of emesis. Over the preceding 4 days, the patient had developed a Bartholin’s gland cyst infection with abscess formation. She admitted to abstaining from any solid food intake in the previous 2 days; however, she maintained her liquid intake and continued taking her insulin glargine without insulin
aspart. She denied any alcohol intake or drug abuse. Her vital signs were within normal limits. Physical examination was significant for diffuse abdominal tenderness without rigidity or guarding and a ruptured Bartholin’s gland abscess with drainage to the skin. Blood work showed a white blood cell (WBC) count of 13,000 cells/mcL (normal range: 4,500-10,000/mcL), hemoglobin level 11.2 mg/dL (normal range: 12.3-15.5 g/dL), platelet count 448,000/mcL (normal range: 150,000-450,000/mcL), sodium 135 mmol/L (normal range: 136-145 mmol/L), potassium 3.6 mmol/L (normal range: 3.5-5.1 mmol/L), chloride 105 mmol/L (normal range: 98-107 mmol/L), carbon dioxide 6 mmol/L (normal range: 21-32 mmol/L), anion gap 24 mmol/L (normal range: 3-11 mmol/L), urea nitrogen 4 mg/dL (normal range: 7-18 mg/dL), creatinine 0.58 mg/dL (normal range: 0.6-1.3 mg/dL), glucose 191 mg/dL (normal range: 70-100 mg/dL), beta hydroxybutyrate >4.5 mg/dL (normal range: <0.4 mg/dL), magnesium 1.3 mg/dL (normal range: 1.6-2.3 mg/dL), phosphorus 1.3 mg/dL (normal range: 2.5-4.9 mg/dL), lactate 0.8 mmol/L (normal range: 0.4-2 mmol/L), and HBA1C 12.5% (normal range: 4-5.6%). Urinalysis was significant for +3 ketones and sugar. Arterial blood gas showed pH 7.07, pCO₂ 12. A urine drug screen was negative, and serum ethanol level was undetectable.

The patient was diagnosed with euglycemic DKA precipitated by an underlying infection. Intravenous fluid (IVF) resuscitation with normal saline was initially started at a rate of 1.0 L/h for a total of 2 L. The patient’s hydration status, serum electrolytes, blood urea nitrogen (BUN), creatinine, glucose, and urine output were monitored closely. After 2 h, repeat blood work showed a serum sodium 141 mmol/L, carbon dioxide 8 mmol/L, potassium 3.5 mmol/L, and glucose 153 mg/dL. Subsequently, IVFs were switched to 5% dextrose and 0.45% NaCl at a rate of 250 cc/h, and an insulin drip at a rate of 5 units/h was started. Then, 30 mEq potassium was added to each liter of the IVFs, excluding the first liter, to maintain a target sodium level of 135-145 mmol/L. Within 6 h, the serum bicarbonate and anion gap were within normal limits; hence, subcutaneous insulin was restarted, while the insulin drip was continued for an additional 1 h. However, aggressive hydration with normal saline at a rate of 250 cc/h was continued for a total of 12 h, as recommended by the guidelines for the management of acute pancreatitis.

**Discussion**

Munro first described euglycemic DKA in 1973; he reported 37 episodes of severe euglycemic ketoacidosis in 17 young patients. He suggested that in insulin dependent diabetics who are unable to maintain sufficient carbohydrate intake, severe ketoacidosis without pronounced hyperglycemia can occur as a consequence of continuing insulin intake. This in turn leads to decreased gluconeogenesis and enhanced cellular utilization of the limited available glucose.[2]

Burge et al. studied the effect of fasting on the development of euglycemic ketoacidosis. Young, healthy subjects with DM1 were studied during a
5 h insulin withdrawal after fasting for 32 h, during which euglycemia was maintained by intravenous insulin infusion. They concluded that fasting can predispose patients to accelerated ketoacidosis and blunted hyperglycemic response, and attributed this to increased glucose utilization and decreased glucose production, with the latter being the primary mechanism.[3] Interestingly, the subjects in his study remained hydrated, as free access to water and noncaloric beverages during their fast was allowed. Effects of dehydration on the pathogenesis of diabetic ketoacidosis were later studied by Burge et al., who found that dehydration favors the development of hyperglycemia.[4] Adequate hydration could prevent hyperglycemia in the presence of ketoacidosis by enhancing renal excretion of glucose[5,6] and decreasing counterregulatory hormones and peripheral insulin resistance at the cellular level.[7]

The combination of decreased carbohydrate intake, adequate hydration, and a degree of insulin intake can lead to the development of euglycemic ketoacidosis in otherwise healthy patients. This is compatible with our two cases, as both of our patients maintained adequate hydration status and continued to take insulin without sufficient carbohydrate intake.

Euglycemic DKA can be distinguished from other causes of ketoacidosis, including starvation ketoacidosis and alcoholic ketoacidosis, by clinical history and serum bicarbonate levels, as the level of serum bicarbonate concentration in starvation ketosis is usually more than 18 mEq/L. In addition, DKA must be distinguished from other causes of high anion gap metabolic acidosis, such as lactic acidosis, drug toxicity, methanol, ethylene glycol and paraldehyde ingestion, and renal failure.[8]

Euglycemic DKA is part of the spectrum of DKA, and its management is similar to the management of DKA. Initial fluid therapy is directed toward expansion of the intravascular, interstitial, and intracellular volume and restoration of adequate renal perfusion. This can be achieved, as per the American Diabetes Association’s recommendations, by isotonic saline at a rate of 1-1.5 L/h during the first 1-2 h of treatment in the absence of cardiovascular disease, renal impairment, or other comorbidities that preclude aggressive fluid replacement. Subsequent fluid replacement depends on the patient’s hydration status, serum electrolytes, serum glucose, and urinary output. Notably, 5-10% dextrose should be added to the replacement fluids, targeting a serum glucose level of 150-200 mg/dL, in order to avoid hypoglycemia and allow the continuity of insulin administration until the ketonemia and acidosis are resolved. Generally, 5% dextrose and 0.45% NaCl infused at a rate of 250-500 cc/h are appropriate, given that the serum sodium is normal or elevated (case 1); whereas 5% dextrose and 0.9% NaCl at a similar rate are appropriate, given that the serum sodium is low or there is a need for further isotonic saline infusion, as in acute pancreatitis (case 2).[9] However, frequent assessments of volume status, cardiac function, renal function, and mental status, especially in the first few hours of resuscitation, are crucial to avoid iatrogenic fluid overload that might lead to cerebral or pulmonary edema, especially in children and young adults.[9] Low-dose intravenous regular insulin, at a rate of 0.1 units/kg/h and without an insulin bolus, was sufficient for successful recovery in our two cases. Associated potassium abnormality should also be corrected with a target serum potassium of 4-5 mEq/L. Generally, 20-30 mEq potassium in each liter of IVF is sufficient to accomplish this. In cases of pronounced hypokalemia, potassium supplement should begin with fluid therapy, and insulin treatment should be delayed until serum potassium is >3.3 mEq/L. Resolution of DKA can be assessed by the presence of two of the following: an anion gap ≤12 mEq/L, serum bicarbonate level ≤15, or a venous pH >7.3.[1,8]

Euglycemic DKA poses a challenge to physicians, as patients presenting with normal serum glucose levels in ketoacidosis may be overlooked, leading to disastrous consequences. A high index of suspicion and a low threshold for obtaining ketone levels in patients with unexplained acidosis could lead to successful diagnosis of this entity, as the clinician cannot exclusively rely on serum glucose levels. Despite euglycemia, ketoacidosis remains a medical emergency and must be treated quickly and appropriately.

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