REVIEW ARTICLE

Diabetic Ketoacidosis and Intensive Care

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Abstract

Diabetic ketoacidosis (DKA) is one of the most common hyperglycemic complications of diabetes mellitus (DM) that is encountered in clinical practice as anesthesiologists and intensivists. Various stressors can lead to DKA in a diabetic patient, but it also remains a common manifestation at the outset of the disease among young diabetics. Thorough knowledge of the disease pathophysiology and treatment modalities help to reduce both duration of ICU stay and the morbidity and mortality associated with DKA.

Keywords: Complication, Diabetes, Diabetic ketoacidosis, Intensive care.

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Introduction and Epidemiology

Diabetic ketoacidosis (DKA), which is the most common hyperglycemic complication of type I diabetes mellitus (DM), is defined as an acute metabolic complication of diabetes which comprises a biochemical triad of hyperglycemia (plasma glucose >250 mg/dL), hyperketonemia (urine acetoacetate +), and metabolic acidosis (pH < 7.3).[1]

Diabetic ketoacidosis has been found to the second most common presenting symptom of type I DM, with figures varying from 15% to 67%.[2] This is particularly true in patients under the age of 6 years, where up to 44% of the children were found to present with DKA.[3] However, there is an increase in the incidence of "ketone prone type 2 DM (T2DM) syndrome" also known as "Flatbush Diabetes".[4] Though this variant has been primarily found in obese, African-Americans, its incidence is gradually increasing across all ethnicities.

Pathophysiology

Diabetic ketoacidosis represents an absolute or relative insulin deficiency with the body having to resort to the use of amino acids and triglycerides as sources of energy. The relative insufficiency of insulin occurs when physiologic or pharmacologic stressors push the insulin balance such that the demand far exceeds the supply. Table 1 given below indicates the common stressors.[1,4–6]

Absolute deficiency is usually caused by slips of administration of insulin among diagnosed diabetics.

There is also an increase in insulin counter regulatory hormones, such as, glucagon, glucocorticoids, catecholamines, and growth hormones. The breakdown of triglycerides for energy leads to increased glycerol and fatty acids, while muscle break down leads to increased alanine levels. The glucagon stimulates hepatic gluconeogenesis using glycerol and alanine while fatty acids are now converted to ketones by mitochondria. The insulin deficiency causes unhindered ketosis which would normally have a negative regulatory effect. Additionally, there is impaired glucose utilization in the periphery. This acute metabolic imbalance results in the ketosis, acidosis, and hyperglycemia, which herald the DKA.[1,5] Recent evidence suggests that DKA is a severe inflammatory state characterized by an elevation of proinflammatory cytokines (tumor necrosis factor-α and interleukin-β, -6, and -8), C-reactive protein, reactive oxygen species, and lipid peroxidation.[7]

Table 1: Common stressors

S. no.	*Physiologic*	*Pharmacologic*
1	Acute infection*	Corticosteroids
2	Myocardial infarction	Thiazide diuretics
3	Stroke	Sympathomimetics
4	Pancreatitis	Sodium glucose co-transporter 2 (SGLT-2) inhibitors
5	Trauma	Malfunction of subcutaneous insulin pumps

*Most commonly, lower respiratory tract infection, urinary tract infection

Hyperglycemia results in osmotic diuresis, with a loss of free water and electrolytes resulting in dehydration. Ketosis is due to strong organic acids, acetoacetic acid, and β-hydroxybutyric acid, which contribute to the acidosis.

Patients present with symptoms, which include, but are not restricted to, a rapidly evolving, polyuria, polydipsia, weight loss, nausea, vomiting, and abdominal pain.[1,2,8] Mental obtundation, though more common with HHS, can also be found with DKA, on account of severe systemic acidosis and hyperosmolarity.[9] Cerebral edema is a rare complication of DKA, in young children, with an incidence of 6.8 per 1000 episodes and a mortality of 24%.[10]

Classification

The American Diabetes Association (ADA) classifies DKA into mild, moderate, and severe as shown below (Table 2).[1]

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Table 2: American Diabetic Association classification of DKA

	Mild (plasma glucose >250 mg/dL)	*Moderate (plasma glucose >250 mg/dL)*	*Severe (plasma glucose >250 mg/dL)*
Arterial pH	7.25–7.30	7.00 to <7.24	<7.00
Serum bicarbonate (mEq/L)	15–18	10 to <15	<10
Urine ketone	Positive	Positive	Positive
Serum ketone	Positive	Positive	Positive
Effective serum osmolality	Variable	Variable	Variable
Anion gap	>10	>12	>12
Mental status	Alert	Alert/drowsy	Stupor/coma

Treatment[1,11–13]

The treatment of DKA is targeted to correct the dehydration, acidosis, hyperglycemia, and reverse the process of ketosis. At the same time, monitoring for dyselectrolytemia and other complications of DKA is vital.

- **Dehydration:** Fluid deficit correction to improve organ perfusion is the first priority. Fluid therapy should be aimed at the correction of fluid deficit over 24–48 hours. The fluid of choice is 0.9% NaCl and the preferred rates of correction are as given below.

Fluid	*Volume and rate*
Sodium chloride 0.9%	1 L or 1000 mL over first hour
Sodium chloride 0.9% 1 L with potassium chloride	3000 mL at the rate of 500 mL per hour over next 6 hours
Sodium chloride 0.9% 1 L with potassium chloride	2000 mL at the rate of 250 mL per hour over next 8 hours

- **Hyperglycemia:** After confirming a baseline serum potassium level of 3.3 mmol/L , insulin is administered as a weight-based, fixed rate intravenous infusion, started at 0.1 U/kg bolus followed by 0.1 U/kg/hour infusion.In patients who are known diabetics, taking insulin, long acting basal insulin, human or analog, may be continued.[11] Low dose (0.05 U/kg) insulin has been studied as an alternative to the internationally recommended dose. The results suggest that the use of low dose did not significantly alter the outcome. However, both the studies were open label studies with small sample sizes, and therefore, larger studies are necessary to draw a relevant conclusion.[14,15]Five percent dextrose should be added to the intravenous infusion when blood glucose level falls below 200 mg/dL as per the ADA. The Joint British Diabetes Societies for inpatient care guideline differ in its recommendation such that they advise addition on 10% dextrose when the sugar level falls below 250 mg/dL.[1] Recent evidence suggests that there is no difference in the outcomes with either, but the incidence of hyperglycemia is more with the use of 10% dextrose.[1]
- **Dyselectrolytemia:** Infusion of insulin causes hypokalemia due to intracellular migration of potassium. Table given below depicts the recommended rate of potassium supplementation (Table 3).
- **Acidosis**: There is no evidence to recommend the infusion of sodium bicarbonate unless faced with life-threatening hyperkalemia or severe acidosis (pH < 6.9) along with impaired cardiac motility.[15]

Table 3: Rate of potassium supplementation

Serum potassium in first 24 hours (mmol/L)	*Potassium concentration in infusion solution (mmol/L)*
>5.5	0
3.5–5.5	40
<3.5	>40 (requires senior clinical review)

- **Phosphates:** Decreased phosphate intake, movement of phosphate into extracellular fluid in response to acidosis, and phosphaturia can result in hypophosphatemia. Supplementation is advised in the face of severe hypophosphatemia (<1 mg/dL) with impaired cardiac motility, hemolytic anemia, and respiratory depression, in the dose of 20–30 mmol/L of intravenous fluid.
- **Calcium and magnesium:** Mild hypocalcemia and hypomagnesemia may occur, which must be monitored and treated.
- **Treating the trigger:** The trigger or the source of infection that caused the DKA must be investigated, isolated, and then treated. Since the most common cause is infections, appropriate antibiotics must be started.

The role of glargine insulin and intravenous thiamine in the management of DKA is being investigated.[1] Hourly clinical and biochemical monitoring of serum electrolytes and blood gas analysis is recommended to track the therapeutic progress. The presence of indicators, such as, arterial pH < 7.1, blood ketones < 6.0 mmol/L, serum bicarbonate < 5 mmol/L, serum potassium < 3.5 mmol/L, impaired consciousness, saturation < 92%, and hemodynamic compromise, demands the need for critical care.[11]

Regular, consistent monitoring is necessary till evidence of resolution can be obtained. Markers of resolution include[11,12]

- Plasma glucose <200 mg/dL
- Venous pH >7.3
- Serum bicarbonate >18 mEq/L
- Anion gap <10
- Blood ketones <3.49 mg/dL

Urine ketostix forms an essential part of diagnosing DKA but is not recommended for monitoring since they only detect the acetoacetate in the urine. β-hydroxybutyrate is predominantly present in the blood and gets converted to acetoacetate. This could lead to a false impression of nonresolution of DKA.[11]

Transition to multiple doses of subcutaneous insulin is usually done when the DKA has resolved and the patient has started eating. The ADA recommends the switch when at least two of the following criteria are met: anion gap <12 mEq/L, serum bicarbonate >15 mEq/L, and pH >7.3.[11] Intravenous insulin is continued for two hours after initiation of subcutaneous therapy to prevent rebound hyperglycemia. Patients who were already on insulin before the episode can go back to their previous regimens. Insulin naïve patients are usually started with a weight-based subcutaneous regimen, using a total dose of 0.5–0.7 U/kg/day, giving 50% of the total dose as once daily basal insulin and dividing the other 50% equally between prebreakfast, prelunch, and presupper doses of rapid acting insulin.[1,11,12] Till the patients are able to start oral feeds, intravenous infusions are the best therapeutic regimen.

Prognosis and Outcomes

The incidence of DKA is increasing and it accounted for over 1,60,000 hospital admissions in 2017, in the USA alone.[1] The annual burden in

the USA due to DKA is estimated at a staggering $2.4 bn.[16] However, with the advent of point-of-care monitoring and availability of prompt medical attention, the mortality with DKA has reduced to <1% in most populations except those with major systemic illness and those with advanced ages.[17] The average length of hospital stay has reduced from 5.7 to 3.4 days with shorter durations of stay required in those admitted due to lapses in insulin administration.[18] The in-hospital mortality has been found to be significantly higher in patients who were not on insulin therapy.[19] While the statistical evidence points to improved outcomes after intensive care unit admissions, the 5-year readmission and mortality remain at 46.4% and 35%, respectively, thus proving that early targeted interventions may be the only way to reduce the morbidity and burden caused by this illness.[20]

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