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Diabetic Ketoacidosis - Review Article

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ABSTRATCT
Diabetic ketoacidosis (DKA) is one of the most common hyperglycaemic complications of diabetes mellitus (DM) that is encountered in clinical practice as general physician, emergency medicine physician, endocrinologist, anaesthesiologists and intensivists. It is a fatal condition and can be very difficult to manage if presented late. Various stressors can lead to DKA in a diabetic patient, but it also be the 1st manifestation of the diabetes mellitus type I among young population. 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

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1. INTRODUCTION & EPIDIMIOLOGY

Diabetic ketoacidosis (DKA), is the most common yet preventable complication of type I diabetes mellitus (DM). It is defined as an acute metabolic complication of diabetes type I which comprises a biochemical triad of hyperglycaemia (plasma glucose >250 mg/dL), ketosis (urine acetoacetate +), and metabolic acidosis (pH < 7.3). In many patients DKA might also be the 1st presenting symptom of type I diabetes.[1] In patients with known diabetes mellitus type I, Diabetic ketoacidosis has been found to the second most common presenting symptom with Hypoglycaemia being the 1st most common presenting symptom of type I DM as they usually control their blood sugar with regular insulin but might present with DKA if they miss a dose, with figures varying from 15% to 67%.[2]This is true in patients under the age of 6 years, where up to 44% of the children were found to present with DKA.[3] In general, DKA is always described to be closely linked to type 1 DM. The occurrence of DKA has been thought to indicate the underlying significant and irreversible ß-cell damage that classifies these diabetic patients as type 1 DM

PATHOPHYSIOLOGY

Type I Diabetes presents with an absolute insulin deficiency requiring the breakdown of amino acids and triglycerides for 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. Text below indicates the common stressors. [1,4–6]

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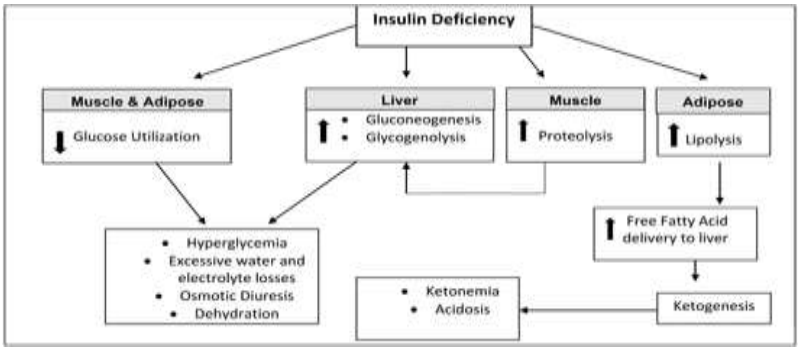

COMMON STRESSORS

S. no.	Physiologic	Pharmacologic
1.	Acute infection (UTI, LOWER RESPIRITORY TRACT)	Corticosteroids
2.	Myocardial infraction	thiazide diuretics
3.	Stroke	sympathomimetics
4	Pancreatitis	SGLT-2 Inhibitors
5.	Trauma	defected sub cutaneous pumps

Absolute deficiency is usually caused by missed or delayed administration of insulin among diagnosed type I diabetics . This leads to an increase in insulin counter regulatory hormones, such as, glucagon, glucocorticoids, catecholamines, and growth hormones that further cause breakdown of triglycerides for energy and therefor leads to increased glycerol and fatty acids to fulfil the body's requirement. Muscle breaks down to produce increased alanine levels, glucagon stimulates hepatic gluconeogenesis using glycerol and alanine and 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 hyperglycaemia, which characterise the DKA [1,5]

Recent evidence suggests that DKA is a severe inflammatory state characterized by an elevation of proinflammatory cytokines (tumour necrosis factor-α and interleukin-β, -6, and -8), C-reactive protein, reactive oxygen species, and lipid peroxidation.[7]

Hyperglycaemia causes 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 further contribute to the acidosis. Patients present with symptoms, which include a rapidly evolving, polyuria, polydipsia, weight loss, nausea, vomiting, and abdominal pain, ketotic smell of breath, dizziness, headache, and unconsciousness. [1,2,8]

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CLASSIFICATION

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

	Mild DKA	Moderate DKA	Severe DKA
Plasma glucose (mg/dL)	>250	>250	>250
pH	7.25–7.3	7.0–7.24	<7.0
Serum bicarbonate (mEq/L)	15–18	10–15	<10
Ketones (urine or serum)	Positive	Positive	Positive
Anion gap	>10	>12	>12
Osmolality (mOsm/kg)	Variable	Variable	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma

TREATMENT (1,11–13)

The treatment of DKA is targeted to correct the underlying cause, dehydration, acidosis, hyperglycaemia, and reverse the process of ketosis. At the same time, monitoring for disturbed electrolytes and other complications of DKA is most important.

• 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. Rapid correction is not preferred as it can lead to osmotic demyelination and locked in syndrome.

Table 2 describes the possible hazards that could take place if fluid is corrected too rapidly.

Table 2. Treatment variables associated with the development of DKA-related cerebral edema.

- Too-rapid fall (>2 mmol/L/h) in corrected sodium.
- Failure of corrected or uncorrected sodium to rise.
- Too-rapid fall (>4 mOsm/kg/h) in active osmolality.
- Use of bicarbonate to treat acidosis.
- Early insulin treatment or large insulin boluses.
- Use of fluids: administration of ≥4 L/m^2/24 h or ≥50 mL/kg in the first 4 hours.

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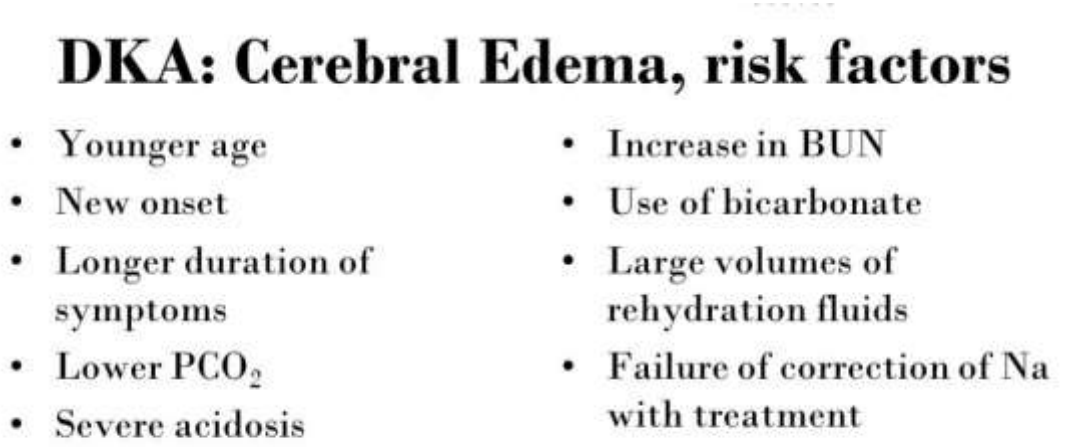

Hyperglycaemia: After confirming a baseline serum potassium level of 3.3 mmol/L, insulin is administered as a weight-based, fixed rate intravenous infusion, started at 0.1 U/kg bolus followed by 0.1 U/kg/hour infusion. In patients who are known diabetics and on insulin, long-acting basal insulin, may 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]

5% dextrose should be added to the intravenous infusion when blood glucose level falls below 200 mg/dL as per the ADA.

Disturbed Electrolytes: Infusion of insulin causes hypokalaemia due to intracellular migration of potassium. Table given below depicts the recommended rate of potassium supplementation (Table 3).

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)

- Acidosis: There is no evidence to recommend the infusion of sodium bicarbonate unless faced with life-threatening hyperkalaemia or severe acidosis (pH < 6.9) [15]

- 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, haemolytic anaemia, and respiratory depression, in the dose of 20–30 mmol/L of intravenous fluid.
- Calcium and magnesium: Mild hypocalcaemia and hypomagnesemia may occur, which must be monitored and treated.

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- 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. 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 >18mEq/L
- Anion gap <10

  Blood ketones <3.49 mg/dL (Urine ketosis 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 hyperglycaemia. 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, before lunch, and before supper 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 & OUTCOMES

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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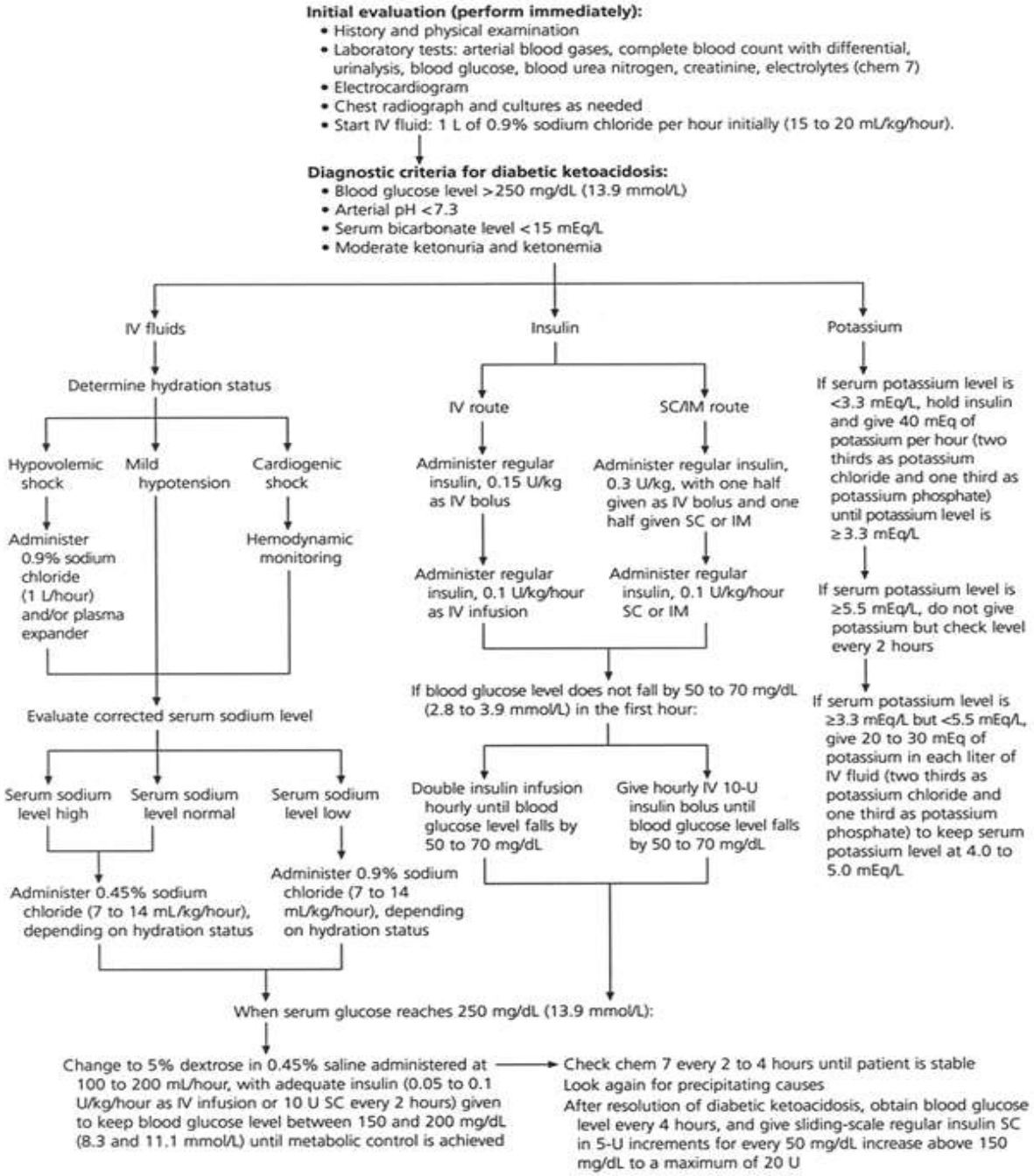
OVERVIEW[21]



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