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Diabetic Ketoacidosis - A Review And Update

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ABSTRACT

Diabetic ketoacidosis (DKA)is a life-threatening acute metabolic complication of diabetes mellitus caused by complete lack of insulin in type 1diabetes mellitus or inadequate insulin levels associated with stress or severe illness either in type 1 or type 2 diabetes mellitus. The onset of diabetic ketoacidosis varies considerably (between 15% and 67%) from one country to another. DKA is responsible for more than 500,000 hospital days per year at an estimated annual direct medical expense and indirect cost of 2.4 billion USD. Severe depletion of water and electrolytes from intra- and extracellular fluid compartments characterizes DKA. The key diagnostic feature in DKA is the elevation in circulating total blood ketone concentration. Treatment includes fluid replacement, insulin therapy, potassium replacement, bicarbonate therapy and phosphate therapy.As diabetes mellitus is increasing rapidly; more awareness is needed to care diabetic's complications such as DKA. Of diabetic complications, sudden deaths are mostly caused by DKA. In the past few decades standardized care and studies decreased the mortality of DKA. The prevention of DKA will require further study as well as patient education.The aim of this review is to find the cause, symptoms and treatment ofDKA, also to make aware of DKA.

Keywords: Diabetic ketoacidosis (DKA), insulin therapy, ketone concentration, cerebral edema, counter regulatory hormones, glycogenolysis and gluconeogenesis

INTRODUCTION

There are two major hyperglycemic crises associated with diabetes are diabetic ketoacidosis (DKA) and hyperosmotic hyperglycemic state[1]. DKAis a life-threatening acute metabolic complication of diabetes mellitus caused by complete lack of insulin in type 1diabetes mellitus or inadequate insulin levels associated with stress or severe illness either in type 1 or type 2 diabetes mellitus[2, 3].DKA is characterized by metabolicacidosis and increase in total body ketone concentration[4]. The common precipitating factor in the development of DKA is infection[5, 6]. Other precipitating

factors are discontinuation of insulin therapy, pancreatitis, myocardial infarction, drugs and cerebrovascular accidents. Other complications are adult respiratory distress syndrome and hyperchloremic acidosis[7-9]. Most deaths occur from intercerebral complications relating to cerebral edema[10].

EPIDEMOLOGY

In 1886 Dreschfeld described DKA. The mortality rate of this illness was almost 100%until insulin was discovered in 1922. Now mortality for both types of Diabetes remains at 1% to 2%[11]. In Africa the mortality of DKA is high with a rate of 26- 29%[12]. The onset of diabetic ketoacidosis varies considerably (between 15% and 67%) from one country to another[13].DKA is responsible for more than 500,000 hospital days per year at an estimated annual direct medical expense and indirect cost of 2.4 billion USD[4]. DKA associated fetal loss rates is excess of 50% and maternal mortality rates are less than 1%[14]. Mortality in children is predominantly due to cerebral oedema which occurs in 0.3% to 1% of all episodes of DKA[3]. Most patients with DKA were between 18 and 44 years (56%) and 45 and 65 years (24%) with only 18% of patients <20 years of age. In DKA patients 66% were considered to have type 1 diabetes and 34% to have type 2 diabetes also 50% were female and 45% were nonwhite[15.]

PATHOGENESIS

DKA results from deficiency of insulin and increased levels of the counter regulatory hormonescatecholamines, cortisol, glucagon, and growth hormone[16].In previously undiagnosed type 1 diabetes mellitusand patients on treatment deliberately do not take insulin, especially the longacting regimen, severe insulin deficiency will occurs. DKA can develop rapidly, when insulin delivery fails for any reason in patients who are using insulin pump[17]. In the patients who are taking usual insulin doses, insulin deficiency occurs when there is increase in counter regulatory hormones (glucagon, cortisol, catecholamines, growth hormone) markedly response to stress conditions such as trauma, GIT illness, vomiting etc., which disturb homeostatic mechanism lead to metabolic decomposition. The combination of the above states results in accelerated catabolic with increased glucose production via glycogenolysis and gluconeogenesis and also decreases the peripheral glucose utilization results in hyperglycemia. Increase in counterregulatory hormones and insulin deficiency leads to increase in lipolysis and ketogenesisresults in ketonemia and metabolic acidosis. Blood sugar level that exceeds the renal threshold, approximately 180 mg/dL with hyperketonemia cause osmotic diuresis, dehydration, and loss of electrolytes and vomiting associated with severe ketosis. The above changes lead to severe insulin resistance, hyperglycemia and hyperketonemia due to further stimulation of the stress hormones production.If this cycle is not interrupted by exogenous insulin, fluid and electrolyte therapy, fatal dehydration and metabolic acidosis will ensure. Acidosis contributes from hypoperfusion of lactic acidosis[18]. Severe depletion of water and electrolytes from intra- and extracellular fluid compartments characterizes DKA.Patients mainly have normal or high blood pressure, possibly due to elevated plasma catecholamine concentrations. Increase in release of ADH in response to hyperosmolality, which ultimately leads to increase in blood pressure via V2 receptors and other factors[19].Because of glucosuria, considerable urine output persists until extreme volume depletion leads to a critical decrease in renal blood flow and glomerular filtration[20]. Elevated cytokines are also documented in diabetic ketoacidosis[21].

DKA IN PREGNANCY

During pregnancy not only the mother is significantly affected by the development of DKA. The prenatal mortality rate related to DKA is 9-35%[22]. DKA during pregnancy results in reduced oxygenation of the fetoplacental unit due to reduced uterine blood flow and a left shift in the hemoglobin dissociation curve. Intervention for fetal compromise should be delayed until the mother is properly resuscitated, because this frequency reverses fetal distress[23].

SIGN AND SYMPTOMS[18]

1. Dehydration (which may be difficult to detect)
2. Tachycardia
3. Tachypnea (which may be mistaken for pneumonia or asthma)
4. Deep, sighing (Kussmaul) respiration; breath has the smell of acetone (variously described as the odor of nail polish remover or rotten fruit)

5. Nausea, vomiting (which may be mistaken for gastroenteritis)
6. Abdominal pain that may mimic an acute abdominal condition
7. Confusion, drowsiness, progressive reduction in level of consciousness and, eventually, loss of consciousness.
8. Weight loss
9. Polyphagia
10. Polydipsia
11. Loss of skin turgor
12. Dry mucus membranes

DIAGNOSIS

Table 1:- Diagnostic criteria and severity of DKA[24]

S. No	Biomarkers	Mild	Moderate	Severe
1	Plasma glucose (mmol/L)	>13.9	>13.9	>13.9
2	Arterial Ph	7.25-7.30	7-7.24	<7.00
3	Serum bicarbonate (mmol/L)	15-18	10-14.9	<10
4	Urine ketones	$+^{ve}$	$+^{ve}$	$+^{ve}$
5	Serum ketones	$+^{ve}$	$+^{ve}$	$+^{ve}$
6	Anion gap	>10	>12	>12
7	Sensorium	Alert	Alert/drowsy	Stupor/coma

The initial laboratory evaluation of patients include determination of plasma glucose, blood urea nitrogen, creatinine, electrolytes (with calculated anion gap), osmolality, serum and urinary ketones, and urinalysis, as well as initial arterial blood gases and a complete blood count with a differential. An electrocardiogram, chest X-ray, and urine, sputum or blood cultures should also be obtained[6]. As per most of the DKA guidelines' hyperglycemia of more than 13.9 mmol/L is necessary for the diagnosis. As DKA without hyperglycemia has been reported, this is not an absolute requirement. Duringpregnancy and in patients with prolonged vomiting or starvation DKA without hyperglycemia is mostly reported. It can also occur in patients with liver failure or in alcohol abusers[25]. The severity of DKA is classified as mild, moderate and severe based upon the severity of metabolic acidosisand the presence of altered mental status. The key diagnostic feature in DKA is the elevation in circulating total blood ketone concentration. Assessment of augmented ketonemia is usually performed by the nitroprusside reaction, which provides a semiquantitative estimation of acetoacetate and acetone levels. Although the nitroprusside test (both in urine and in serum) is highly sensitive, it can underestimate the severity of ketoacidosis because this assay does not recognize the presence of β- hydroxybutyrate, the main metabolic product in ketoacidosis[26]. If available, measurement of serum β- hydroxybutyrate may be useful for diagnosis[27].

TREATMENT

Numerous treatment guidelines are available in literature but these are not strictly applied.Looking upon pathophysiology the first therapeutic step is to restore extracellular fluid volume which has been depleted through vomiting osmotic and diuresis. To allow normal carbohydrate utilization and to stop ketogenesisinsulin must be given [28].In the management of DKA significantly a study says that an integrated care pathway improves key areas[29].

FLUID REPLACEMENT

The fluid deficit is nearly about 100 ml/kg body weight, which amounts to five to seven litres in an adult patient[30, 31].Significant fall in blood glucose levels will be resulted while fluids alone are administered. This is mediated by recovery of the glomerular filtration rate, which declines with severe dehydration caused by the DKA[32]. For the initial resuscitation, guidelines recommend the use of 0.9% NaClsolution and if the serum sodium concentration is high the use of 0.45% NaCl solution is recommended[15, 29, 31].

Resuscitationof fluid should be aggressive with the administration of 1-1.5 L of fluid within the first hour and thereafter 250-500 ml/hour. The ultimate aim is to

replace half of the fluid deficit within the first 8-12 hours and the rest within the next 12-16 hours[30, 32].If the blood glucose level droped below 14 mmol/L, it is advised to change the fluid administration either to 5% dextrose water or 5% dextrose in 0.9% NaCl solution or 5% dextrose in 0.45% NaClsolution)[30, 33, 34].In patients with cardiovascular, renal and liver disease or elderly patients, take care of over hydration and overload of volume[35].

INSULIN THERAPY

IV administration of soluble insulin is the standard care in patients with DKA at low dose[31]. Note that, for IV administration regular insulin acts faster than synthetic insulin, so regular insulin is most preferable[36].Initial dose of insulin should be initiated with an IV dose of 0.1-0.15 U/kg followed by a continuous infusion of 0.1 U/kg/hour. Children should not receive an insulin since it may increase the risk of cerebral edema[37]. If the blood glucose level comes under 9 mmol/l, the infusion rate can be decreased[38].After resolution of DKA, the patient can be managed with a multidoseinsulin regimen with rapid-acting insulin for prandial requirements and long-acting insulin for basal requirements. After the first subcutaneous insulin injectioninsulin infusion should be stopped for 1-2 hours. Patients already on insulin therapy before the onset of the DKA can switch on their usual insulin regimen. Patients who were not on insulin before can start with0.5-0.6 U/kg/day[39].

POTASSIUM

Correction of acidosis, Insulin therapy and volume expansion decrease serum potassium concentration. The goal of the treatment is to maintain serum potassium levels within the normal range of 4–5 mEq/l. To prevent the hypokalemia codition, potassium replacement is initiated after serum levels fall below the upper level of normal (5.0 –5.2 mEq/l). Rarely, DKA patients may present with significant hypokalemia. In such cases, potassium replacement should begin with fluid therapy, insulin treatment should be delayed until potassium concentration is restored to >3.3 mEq/l to avoid respiratory muscle weaknessand life-threatening arrhythmias[6,8].

BICARBONATE THERAPY

The use of bicarbonate in DKA is controversial[40]. Most of experts those are treating DKA believe that the decrease in ketone bodies will be adequate bicarbonate except in severely acidotic patients during the treatment. Severe metabolic acidosis may lead to impaired myocardial contractility, cerebral vasodilatation, coma, and several gastrointestinal complications[41]. Some studies support the notion that bicarbonate therapy for DKA offers no advantage in improving cardiac or neurologic functions or in the rate of recovery of hyperglycemia and ketoacidosis. Several deleterious effects of bicarbonate therapy have been reported, such as increased risk of hypokalemia, decreased tissue oxygen uptake, cerebral edema, and development of paradoxical central nervous system acidosis[42].In most of the literatures, adult patients with a pH<6.9 should receive 100 mmolsodium bicarbonate in 400 ml sterile water with 20 mEq KCI administered at a rate of 200 ml/h for 2 h until the venous pH is >7.0 is recommended. If the pH is still <7.0 after this is infused, we recommend repeating infusion every 2 h until pH reaches >7.0[4].

PHOSPHATE

Phosphate concentration decreases with insulin therapy. Excessive phosphate therapy can cause severe hypocalcemia[43]. To avoid potential cardiac and skeletal muscle weakness and respiratory depression due to hypophosphatemia, careful phosphate replacement may sometimes be indicated in patients with cardiac dysfunction, anemia, or respiratory depression and in those with serum phosphate concentration <1.0 mg/dl [6,24]. When needed, 20–30 mEq/l potassium phosphate can be added to replacement fluids. The maximal rate of phosphate replacement generally regarded as safe to treat severe hypophosphatemia is 4.5 mmol/h (1.5 ml/h of K2 PO4)[44].

COMPLICATIONS IN TREATING DKA

The most common complications in treating DKA are

1. Hypoglycemia
2. Hypokalaemia
3. Relapse of DKA
4. Cerebral edema in children[34]
5. Seizure
6. Bradycardia
7. Incontinence
8. Respiratory arrest
9. Eventual brain-stem herniation
10. Vascular thrombosis[2]

CONCLUSION

Diabetes mellitus is found to be one of the five leading cause of death in the world. The number of diabetic people is expected to rise to 366 million in 2030. DKA is a life-threatening acute metabolic complication of diabetes mellitus. As diabetes mellitus is increasing rapidly; more awareness is needed to care diabetic's complications such as DKA. Of diabetic complications sudden deaths are mostly caused by DKA. In the past few decades standardized care and studies decreased the mortality of DKA[45]. The prevention of DKA will require further study as well as patient education.

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