

Diabetic Ketoacidosis

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Diabetic ketoacidosis (DKA) is an acute and life-threatening metabolic complication mostly attributed to type 1 diabetes mellitus and in some cases to type 2 diabetes mellitus, as well as to gestational diabetes. DKA was first described in 1886 and, until the introduction of insulin therapy in the 1920s, it was almost universally fatal. DKA occurs in 4.6-8.0 per 1000 people with diabetes annually. DKA is the first event in T1DM at a rate of 21.1%, more often in children under 5 years old. Mortality rate in DKA is at 4%.

DKA is characterized by a complete lack of insulin and hypersecretion of competitive hormones leading to increased release of glucose by the liver (a process that is normally suppressed by insulin) from glycogen via glycogenolysis and also through gluconeogenesis. High glucose levels spill over into the urine, taking water and solutes (such as sodium and potassium) along with it in a process known as osmotic diuresis. This causes polyuria, dehydration and polydipsia. The absence of insulin also provokes release of free fatty acids from adipose tissue (lipolysis), which are converted through a process called beta oxidation, again in the liver, into ketone bodies (acetoacetate and β -hydroxybutyrate acids). The ketone bodies, however, have a low pKa and therefore turn the blood acidic (metabolic acidosis).

No causative factor is present at a rate of 22-25%. Triggers may include infection, not taking insulin correctly, myocardial infarction and certain medications such as steroids. The symptoms of an episode of diabetic ketoacidosis usually evolve over a period of about 24 hours. Predominant symptoms are nausea and vomiting, pronounced thirst, excessive urine production and abdominal pain. In severe DKA, breathing becomes rapid and of a deep, gasping character, called "Kussmaul breathing". The abdomen may be tender to the point that a serious abdominal condition may be suspected, such as acute pancreatitis, appendicitis or gastrointestinal perforation. In severe DKA, there may be confusion or a marked decrease in alertness, including coma.

On physical examination there is usually clinical evidence of dehydration, such as a dry mouth and decreased skin turgor as well as rapid heart rate and low blood pressure. Often, a "ketotic" odor is present, which is often described as "fruity". Small children with DKA are relatively prone to brain swelling, also called cerebral ede-

ma, which may cause headache, coma, loss of the pupillary light reflex, and can progress to death. It occurs in about 1 out of 100 children with DKA and more rarely occurs in adults.

DKA is typically diagnosed when testing finds high blood sugar, low blood pH, and ketoacids in either the blood or urine. The average adult with DKA has a total body water shortage of about 6 liters (or 100 mL/kg), in addition to substantial shortages in sodium, potassium, chloride, phosphate, magnesium and calcium. Glucose levels usually exceed 13.8 mmol/L or 250 mg/dL. The hallmark of DKA is a high-anion-gap metabolic acidosis. Glucose serum levels are not always extremely elevated. In addition to the above, blood samples are usually taken to measure urea and creatinine (measures of kidney function, which may be impaired in DKA as a result of dehydration) and electrolytes. Furthermore, markers of infection (complete blood count, C-reactive protein) and acute pancreatitis (amylase and lipase) may be measured. Given the need to exclude infection, chest radiography and urinalysis are usually performed.

The American Diabetes Association categorizes DKA in adults into one of three stages of severity:

Mild: blood pH mildly decreased to between 7.25 and 7.30 (normal 7.35-7.45); serum bicarbonate decreased to 15-18 mmol/l (normal above 20); the person is alert

Moderate: pH 7.00-7.25, bicarbonate 10-15, mild drowsiness may be present

Severe: pH below 7.00, bicarbonate below 10, stupor or coma may occur

DKA must be differentiated from hyperosmolar hyperglycemic state and other severe cases such as lactic acidosis, alcoholic ketoacidosis, starvation, poisoning from salicylics, methanol, ethylenoglycol and paraldehyde.

The cornerstones of treatment are rehydration, IV insulin and potassium supplementation. The primary treatment of DKA is with intravenous fluids. A special but unusual consideration is cardiogenic shock, where the blood pressure is decreased not due to dehydration but due to inability of the heart to pump blood through the blood vessels. This situation requires ICU admission.

Insulin regular can be infused intravenously after the potassium level is known to be higher than

3.3 mmol/l; if the level is any lower, administering insulin could lead to a dangerously low potassium level. Intravenous insulin administration should continue until acidosis has been reversed. Usually, potassium chloride is needed to prevent the development of low blood levels of potassium which increases the risk of dangerous irregularities in the heart rate. In those with severely low blood pH (pH < 6,9), sodium bicarbonate may be given; however, its use is of unclear benefit and typically not recommended. Throughout treatment blood sugar and potassium levels should be regularly checked. Antibiotics may be required in those with an underlying infection. Thromboprophylaxis with low molecular weight heparin is imperative.

Resolution of DKA is defined as general improvement in the symptoms, such as the ability to tolerate oral nutrition and fluids, normalization of blood acidity (pH>7.3) and absence of ketones in blood (<1 mmol/l) or urine. Once this has been achieved, insulin may be switched to the usual subcutaneously administered regimen, one hour after which the intravenous administration can be discontinued.

Attacks of DKA can be prevented in those known to have diabetes to an extent by adherence to "sick day rules"; these are clear-cut instructions to person on how to treat themselves when unwell. Instructions include advice on how much extra insulin to take when sugar levels appear uncontrolled, an easily digestible diet rich in salt and carbohydrates, means to suppress fever and treat infection and recommendations when to call for medical help. People with diabetes can monitor their own ketone levels when unwell and seek help if they are elevated.

There has been a documented increasing trend to hospital admissions due to DKA. It is attributed to changes in case definition, new medications that might increase the risk for DKA (SGLT-2 inhibitors) and higher admission rates because of lower thresholds for hospitalization (i.e., admission of persons with less serious disease). Mortality rates have been declining over the past few years, but remain close to 4%. The decrease in mortality is brought about from a combination of lower incidence of DKA, earlier diagnosis and improved treatment in specialized diabetes clinics.