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# PATHOPHYSIOLOGY AND CLINICAL MANAGEMENT OF DIABETIC KETOACIDOSIS (DKA): ARTICLE REVIEW

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**Abstract:**
Type 1 diabetes mellitus is a medical condition characterized by the absence of proper insulin functioning in the body, leading to the unopposed effects of the glucagon hormone. Diabetic ketoacidosis (DKA) is recognized as a severe and acute life-threatening complication that can arise from type 1 diabetes mellitus. It is important to note that DKA might manifest as the initial presentation of this particular medical condition. Individuals who do not adhere to their insulin therapy regimen or fail to administer insulin as prescribed are at a significantly higher risk of developing DKA. The onset of this condition is often triggered by severe illnesses such as pneumonia or myocardial infarction, which can result in increased levels of hormones that oppose insulin, such as adrenaline and glucocorticoids. Consequently, DKA is closely linked with disturbances in Acid-Base balance and Electrolyte levels within the body, further complicating the individual's overall health status. In this review, we highlight the significance of DKA and its pathophysiology, specifically focusing on suggestions for managing and treating it based on the available evidence.

**Keywords:** Diabetic ketoacidosis (DKA), Pathophysiology, Management.

## Introduction:

Diabetic ketoacidosis (DKA) is seen as a serious acute complication of type 1 diabetes mellitus. However, DKA can sometimes be the first sign of the condition. If patients do not stick to their insulin treatment or fail to take insulin, they are at a high risk of developing DKA. Severe illnesses such as pneumonia and heart attacks can trigger the condition due to increased levels of hormones that counteract insulin, like adrenaline and glucocorticoids. DKA leads to imbalances in Acid-Base and Electrolytes. The American Diabetes Association and the Canadian Diabetes Association guidelines recommend waiting to administer insulin until the initial plasma potassium level reaches 3.3 mmol/L in managing DKA. [1,2] We contend that the current level may be insufficient. Instead, we propose a

more prudent postponement of insulin treatment for individuals with a plasma potassium level of 4 mmol/L. Insulin is known to cause a movement of potassium within cells, which is thought to be more significant in the presence of acidosis - such as that seen in DKA. This process may be attributed to an elevated concentration of hydrogen ions inside cells, which triggers the activation of NHE1 (sodium/hydrogen exchanger 1), increasing sodium entry into cells and the activation of Na1/K1-ATPase. [3] The administration of intravenous potassium chloride should be continued until the monitored plasma potassium level approaches 4 mmol/L. Monitoring potassium levels and administration should be done carefully, as it is hard to predict how much potassium will move into cells. It's important to note that there are no randomized controlled trials to guide decisions in such cases. The intracellular movement of potassium due to insulin happens quickly, within minutes, while the insulin's effect on slowing down ketoacid production may take hours. We strongly believe that the risk of worsening hypokalemia and potential cardiac arrhythmias is more significant than the risk of increased acidemia from a delay of 1 to 2 hours in administering insulin.

**Factors Induce DKA:**

The primary causes of DKA are typically infection and lack of proper adherence to insulin treatment.[4,5] Additional triggers related to DKA are sudden severe health conditions like heart attacks, the onset of type 1 diabetes, medications impacting carbohydrate levels, cocaine use, and mental issues linked to eating disorders.[6,7] Some patients with type 1 diabetes mistakenly skip insulin because they think they don't need it when they eat less due to gastroenteritis. Examples of medications linked to high blood sugar levels are corticosteroids, high doses of thiazides, sympathomimetic drugs like dobutamine and terbutaline, and newer "atypical" antipsychotic medications.[8] Certain reports indicated occurrences of high blood sugar episodes when using sodium-glucose co-transporter 2 (SGLT2) inhibitors, primarily prescribed for type 2 diabetes but also commonly used off-label for type 1 diabetes; the precise pathogenesis mechanism is intricate.[9] Young patients who have type 1 diabetes and psychological issues related to eating disorders are especially likely to not follow their insulin treatment due to psychological challenges linked with eating disorders. These challenges may include concerns about gaining weight, fear of experiencing low blood sugar levels, resistance to following rules, and the burden of dealing with a long-term illness. During a clinical evaluation of patients suspected of having DKA, signs of dehydration can be observed such as reduced skin elasticity, dry armpits, dry mouth lining, decreased jugular venous pressure, rapid heartbeat, and, in severe cases, low blood pressure. Neurological symptoms mentioned earlier may be evident during the examination, particularly in individuals with HHS. A distinct fruity smell in the breath of DKA patients, caused by acetone, similar to that of nail polish remover, can be detected. Another respiratory indicator in these patients is deep breathing.

**Manifestations:**

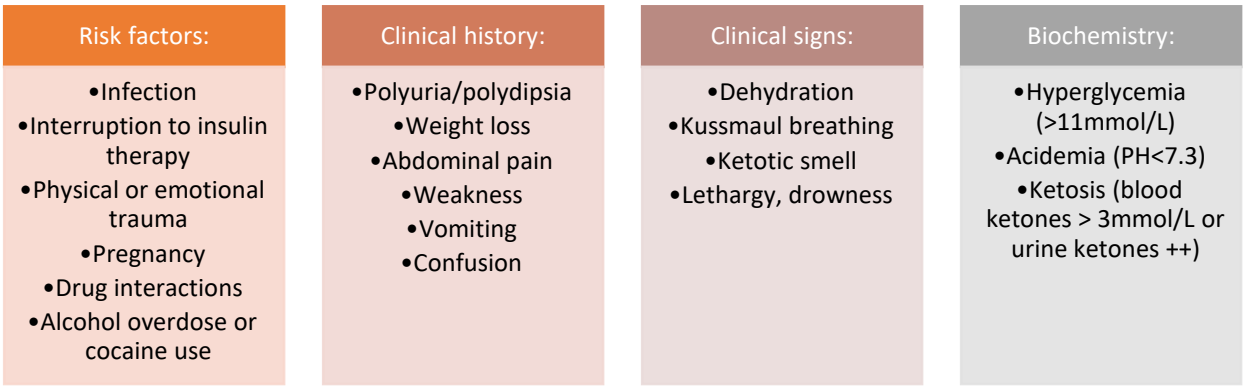
DKA is an urgent DM complication that needs to be identified early and responded to quickly. The first assessment should involve obtaining a thorough medical history, identifying important signs during a clinical examination, and closely monitoring the patient's biochemistry [Figure 1].

Symptoms of significant hyperglycemia typically include polyuria, polydipsia, and weight loss. These symptoms emerge suddenly and progress quickly within a day in DKA, which is mainly characterized by rapid breathing and stomach discomfort. Neurological symptoms like seizures and focal signs such as hemiparesis and hemianopsia can arise. A decrease in mental alertness may occur even with a lower level of hyperosmolality in the presence of severe acidosis. Nonetheless, the presence of significant neurological symptoms along with a low effective Posm (<320 mosmol/kg) necessitates immediate consideration of other potential causes for the change in mental status.[10,11]

Symptoms related to the digestive system like nausea, vomiting, and stomach pain might be the first signs observed in a patient with diabetic ketoacidosis (DKA). These symptoms are typically more prevalent in children and are less likely to occur in adults.[12] Abdominal pain was found to be directly linked to the seriousness of the metabolic acidosis; 86 percent of individuals with a serum bicarbonate level of equal to or less than 5 mEq/L experienced abdominal pain, in contrast to just 13

percent of patients with a serum bicarbonate level of 15 mEq/L or higher. The presence of severe hyperglycemia and/or dehydration does not show any correlation with the occurrence of abdominal pain. Reasons behind abdominal pain may involve acidosis-induced delayed stomach emptying and ileus, as well as related electrolyte imbalances.[4]

**Figure (1):** Risk factors and key signs and symptoms of diabetic ketoacidosis [13]




**Pathophysiology:**

DKA patients commonly exhibit a significant reduction in arterial blood volume caused by osmotic diuresis and natriuresis induced by high blood sugar levels. Administering an appropriate amount of saline solution to achieve stable hemodynamics is important. However, due to the risk of cerebral edema from a large influx of saline, it should only be given in cases of hemodynamic emergency. Besides addressing hypovolemia, fluid therapy also aims to enhance blood flow to muscles to eliminate hydrogen ions by the bicarbonate buffer system.[14] Buffering hydrogen ions decreases their attachment to proteins in essential organs, potentially leading to protein charge, structure, and function changes. The bicarbonate buffer system is mainly found in the intracellular fluid and the space between muscle cells and is influenced by the lower PCO2 in the blood vessels of muscles: H1 1 HCO3 2 / H2CO3/ H2O 1 CO2; this process effectively eliminates hydrogen ions. In cases where blood flow to muscles decreases due to hypovolemia while muscle metabolic rate remains constant, there could be an increase in carbon dioxide in the blood flowing through these poorly perfused muscles. Consequently, despite arterial PCO2 possibly being low due to acidemia-induced hyperventilation, PCO2 in muscles' intracellular and interstitial fluid may be significantly elevated, affecting the bicarbonate buffer system's ability to buffer hydrogen ions efficiently. This could worsen acidemia and more hydrogen ions binding to proteins in various organs, such as the brain. To evaluate this, brachial venous PCO2, which mirrors capillary PCO2 in skeletal muscles, should be assessed in patients with DKA. Administering intravenous fluids is necessary to enhance muscle blood flow and achieve the normal PCO2 difference between brachial and arterial blood under typical blood flow and metabolism rates at rest, around 6 mm Hg. Plasma osmolality needs to be carefully monitored and should not be allowed to decrease during the initial 15 hours of treatment, as this is when most cerebral edema complications occur. [15]

**Management:**

During the initial stages of treatment, a significant drop in plasma osmolality can result in cerebral edema due to the reduction in plasma glucose levels.[16] Sodium anions play a role in plasma osmolality, aiming to boost plasma sodium levels by half of the decrease in plasma glucose levels, measured in millimoles per liter. For instance, if the initial plasma glucose measurement was 40 mmol/L and plasma sodium was 130 mmol/L, the effective plasma osmolality would be 300 mmol/kg H2O. In the case of a decrease in plasma glucose to 24 mmol/L (a drop of 16 mmol/L), the goal would be to raise plasma sodium by half of this, or 8 mmol/L, resulting in a target of 138 mmol/L. This adjustment would keep the plasma's effective osmolality constant at 300 mmol/kg H2O. Research suggests that the correlation between an increase in plasma sodium levels and a specific decrease in

plasma glucose levels is foreseeable and is linked to water movement between extracellular fluid (ECF) and intracellular fluid (ICF). However, fluctuations in fluid intake among hyperglycemic patients, alongside glucose-induced osmotic diuresis and natriuresis, mean that assuming a fixed relationship between plasma glucose and sodium levels is unreliable. Therefore, using hypotonic saline based on these calculations to prevent hypernatremia during treatment is incorrect and could lead to cerebral edema. On the other hand, it is advisable to use fluids with an equal or higher effective osmolality of urine (≥400 mmol/kg H2O) in children with diabetic ketoacidosis and polyuria. This can be achieved by supplementing normal saline (0.9% sodium chloride solution) with potassium chloride (30-40 mmol/L) when potassium supplementation is required.[15] Even though there is a risk of developing hypernatremia, we believe it is necessary to prevent a drop in plasma osmolality. In our situation, we are concerned because the patient has consumed a lot of water, which could lower the osmolality in the blood to a dangerous level if absorbed too quickly. To address this, we inserted an arterial line to monitor the osmolality in both arterial and venous blood. If a significant drop in osmolality in the arterial blood is detected, a hypertonic 3% sodium chloride solution should be given to maintain the proper level. This is crucial, especially if symptoms of increased pressure in the brain include headache, nausea, or confusion. The dosage of the hypertonic solution can be calculated based on the current volume of extracellular fluid, considering that the solution has an osmolality of around 1,000 mmol/kg H2O. When the plasma glucose level falls below 14 mmol/L, intravenous glucose should be administered to prevent neuroglycopenia. Instead of the typical 5% dextrose solution, 50g of dextrose (100mL of D50W) can be added to 1 liter of 0.9% sodium chloride solution. To compensate for sodium loss through urine, an adequate amount of sodium should be given initially to stabilize blood flow and slightly increase the PCO2 in brachial venous blood compared to arterial blood by up to 6 mm Hg. Additionally, any remaining sodium deficit should be corrected gradually over several hours to reduce the risk of brain swelling. To prevent overloading with saline and expanding the extracellular fluid too much, the initial sodium deficit should be calculated based on the plasma sodium level and an estimate of the extracellular fluid volume using hematocrit. [17] Generally, the goal is to replenish 30% of the sodium shortage within the initial 4 to 6 hours and address the rest of the deficit within 18 hours, along with the sodium lost in urine due to glucose-induced natriuresis.

The goal of administering insulin is to prevent the production of ketone acids, though it may require a significant amount of time to take effect. It is not recommended to give a bolus of insulin to children due to the potential risk of causing cerebral edema.[18] Despite this, the effect of insulin on high blood sugar levels at the beginning of treatment is minimal as the plasma glucose level decreases primarily due to dilution and the presence of glucose in urine. In most cases of diabetic ketoacidosis (DKA), using sodium bicarbonate is unnecessary because insulin helps reduce the production of ketoacids, and bicarbonate is naturally produced when ketoacid anions are broken down. Guidelines generally advise against giving sodium bicarbonate to DKA patients, except in cases where the plasma pH drops to 6.90 or lower.[19] Only three randomized controlled trials involving a total of 73 patients have investigated the impact of sodium bicarbonate in adults with DKA, excluding those with serious illnesses. The results showed that sodium bicarbonate did not provide any benefits regarding various measured outcomes, such as changes in arterial pH, plasma bicarbonate, and metabolites. However, one study did suggest a potential effect on mean arterial blood pressure. Personalizing the decision to administer sodium bicarbonate is recommended, rather than relying on specific plasma pH values. Factors that may necessitate the use of sodium bicarbonate include patients with significant hyperchloremic metabolic acidosis. These patients experience excessive loss of ketoacid anions in urine, leading to a lack of circulating anions for metabolization into bicarbonate. Rapid saline infusion could worsen acidemia by diluting and titrating bicarbonate with hydrogen ions bound to intracellular proteins as muscle capillary PCO2 decreases. Initial treatment with sodium bicarbonate may be considered for patients with moderate to severe acidemia (pH 7.20 and plasma bicarbonate 12 mmol/L) if there is a risk of slower ketoacid removal, indicated by a significant decline in consciousness or pre-existing chronic kidney disease with a GFR of 30 mL/min. Aggravation of acidemia can result in more severe hemodynamic instability in DKA patients. The use of sodium

bicarbonate in these cases can help prevent a significant drop in plasma bicarbonate levels by administering it at a rate similar to the expected liver production of ketoacids, estimated at approximately 60 mmol per hour based on data from individuals with starvation ketosis.[20] This approach should undergo a re-evaluation through serial monitoring of plasma bicarbonate levels. It is important to note that there have been no clinical trials conducted to assess the potential advantages of this method on various outcome measures, such as restoring hemodynamic stability and reducing the occurrence of complications like stroke, myocardial infarction (MI), and acute kidney injury. A retrospective case-control study involving pediatric patients with DKA revealed that individuals treated with sodium bicarbonate faced a notably higher risk of developing cerebral edema.[21] We believe sodium bicarbonate should not be administered to children with DKA unless the negative effects are greater than the positive ones. The exception is when acidemia is extremely severe (pH 6.90 and plasma bicarbonate 5 mmol/L) and if hemodynamic instability does not respond to intravenous saline.[22] Patients experiencing diabetic ketoacidosis (DKA) typically find themselves in a catabolic state and could be facing significant phosphate deficiencies. The levels of plasma phosphate drop significantly once insulin therapy commences. Despite this, there is no clear evidence supporting the use of phosphate supplementation to aid in the recovery process. However, it is crucial to steer clear of hypocalcemia, a hazardous complication that can arise from the precipitation of ionized calcium with phosphate.[23] Current evidence suggests that addressing severe hypophosphatemia (serum phosphate levels of 0.32 mmol/L or below) is advisable, especially when other conditions such as cardiac dysfunction, respiratory muscle weakness, or hemolytic anemia are also present.

**Conclusions:**

Diabetic ketoacidosis (DKA) is a frequent cause of severe metabolic acidosis. Despite advancements in treatments, it remains a dangerous condition due to complications related to both the disease itself and its treatment. This instructional case focuses on managing DKA, with a particular emphasis on the potential treatment complications. Cerebral edema is a critical complication that poses a significant risk to patients and is a leading cause of both mortality and morbidity. Therefore, we thoroughly examine its underlying mechanisms and the preventive strategies that can be implemented. To reduce the risk of cerebral edema, it is crucial to avoid giving a sudden large dose of insulin, excessive saline fluids, and an early decrease in effective plasma osmolality during treatment. The primary goal of fluid therapy is to lower the PCO2 in the muscular veins, ensuring the efficient removal of hydrogen ions by the bicarbonate buffer in the muscles. This, in turn, diminishes the binding of hydrogen ions to intracellular proteins in vital organs, including the brain. In cases where patients have low plasma potassium levels, immediate administration of insulin can lead to hypokalemia and potentially dangerous cardiac arrhythmias. It is recommended that insulin administration be delayed and intravenous potassium chloride initially provided to these individuals, to normalize the plasma potassium level to around 4 mmol/L. The use of sodium bicarbonate in adult patients should be tailored to the individual, considering specific circumstances such as moderately severe acidemia in patients at risk of worsening acidemia, especially if they are hemodynamically unstable. However, it is important to note that sodium bicarbonate should not be used in children with DKA except in cases of severe acidemia or refractory hemodynamic instability.

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