Does Severe Hypokalemia Worsen the Outcome of Diabetic Ketoacidosis?

Pamela Sandhya De Jaka[1], Dias Guita Alantus[1]

1 Balung Regional Hospital, Jember, East Java, Indonesia

Corresponding Author:
Pamela Sandhya De Jaka, MD. Balung Regional Hospital, Jember, East Java, Indonesia
Email: pamelasandhya@gmail.com.

ABSTRACT

Hypokalemia is an uncommon finding in the initial evaluation of patients with DKA before insulin treatment. However, it can complicate the management of DKA and lead to a worse prognosis. Hypokalemia in DKA may result from a combination of factors, including kaliuresis, secondary osmotic diuresis, inadequate oral intake, and gastrointestinal losses such as vomiting. We report the case of a 31-year-old woman who recently experienced diabetic ketoacidosis with severe dehydration, severe hypokalemia, and sepsis. Unfortunately, her condition deteriorated, and she eventually went into cardiac arrest while receiving treatment in the emergency unit. This case highlights the challenges involved in providing therapy and managing complications that arise in patients, presenting a dilemma for healthcare providers.

Keywords: *Diabetes, diabetic ketoacidosis, hypokalemia, sepsis, insulin*

INTRODUCTION

Diabetic ketoacidosis (DKA) is an extreme condition within the spectrum of hyperglycemic crisis, serving as an acute metabolic complication of diabetes. It poses a significant risk of morbidity, mortality, and increased hospital costs. DKA can occur due to delayed diagnosis resulting from a failure to recognize diabetes symptoms. It is characterized by a biochemical triad: hyperglycemia, ketonemia, and metabolic acidosis, leading to a high anion gap. DKA most commonly affects patients with type 1 diabetes but can also occur in individuals with type 2 diabetes who experience extreme stress, such as a severe infection, trauma, cardiovascular disease, or other emergencies.[1]

Abnormal electrolyte levels can complicate the management of DKA and contribute to a worse prognosis. One such electrolyte is potassium. Hypokalemia, defined as a plasma concentration of potassium (K+) < 3.5 mEq/L, is an uncommon finding in the initial evaluation of patients with DKA. Hypokalemia in DKA may result from a combination of factors, including kaliuresis, secondary or prolonged osmotic diuresis, inadequate oral intake, and gastrointestinal losses such as vomiting and diarrhea. In general, potassium levels in DKA patients tend to be normal or slightly elevated. However, rare cases of DKA can present with hypokalemia, occurring in only 5% to 10% of DKA patients, with levels below 2.5 mmol/L.[2] A similar rare occurrence was observed in a patient we treated previously, as described in the case below.

CASE ILLUSTRATION

A 31-year-old woman was referred to the emergency unit of our hospital with hyperglycemia where the blood sugar levels were detected as high index (HI) by a simple glucose meter. The patient complained of feeling weak for about the last 72 hours until she was unable to do some activity. The patient also complained of headaches, tightness on chest, agitation, and a bit nausea and vomiting, with unknown cause. When asked about a history of polyuria, polydipsia, and significant weight loss, the patient denied experiencing these symptoms and explained that she had no complaints of illness. This information was further confirmed by both her mother and husband, who stated that there was no history of diabetes, hypertension, or other diseases, including within the family.

Upon initial examination, the patient was found to be fully conscious, alert with a Glasgow Coma Score (GCS) of E4V5M6. Vital signs measurements were obtained: blood pressure of 140/87 mmHg, heart rate of 100x/minute, respiratory rate of 26x/minute, temperature of 36.1°C and oxygen saturation of 98% without supplemental oxygen. The initial physical examination indicated mild signs of dehydration, with no detectable ketone odor. The blood sugar check conducted in our hospital's emergency unit also showed high levels (HI), necessitating the wait for the results of blood tests, including a complete blood count, biochemical analysis, and blood gas analysis, from the laboratory unit to obtain the specific values. Additionally, an ECG examination was performed, and the results are as follows:

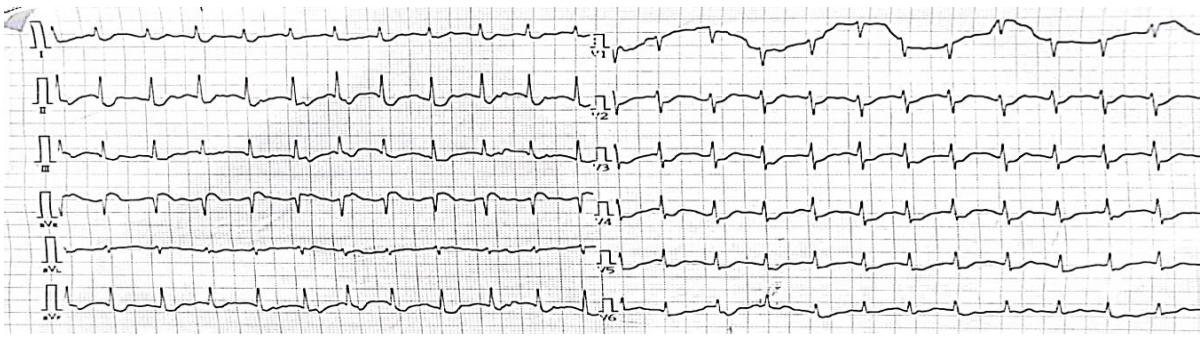

Figure 1: The ECG result showed sinus rhythm with tachycardia HR 120x/minute, predominant depressed ST segment, flattened T wave and prominent U wave suggestive of hypokalemia.

Her blood glucose level is 710.6 mg/dL, potassium level 1.76 mmol/L. pH 7.08, and HCO3 17.7 mmol/L. PCO2 32.0 mmHg. Her leucocyte 34.750/µL.

Following the objective examination, we began considering a diagnosis of hyperglycemia, suspected diabetic ketoacidosis. Initial therapy was initiated based on the principles of managing hyperglycemic crisis. This involved administering 2000 cc of normal saline for resuscitation within the first hour, administering symptomatic medications, and importantly, inserting a urinary catheter. Upon catheter insertion, we observed a urine output of 200 cc, which appeared a brownish tea-like color and highly concentrated. Simultaneously, the laboratory results were released, providing the following data.

However, the patient's experienced reported a decrease of consciousness. Our team immediately confirmed this by checking the patient. The examination of consciousness showed that the patient was at a somnolen level of consciousness with a GCS of E3V3M6, and started showing signs of shock, while the blood pressure was measured at 108/54 mmHg, heart rate at 46x/minute, respiratory rate at 30x/minute with Kussmaul breathing, oxygen saturation dropped to 88% without supplemental oxygen. The patient presented with cold extremities, reduced, and more concentrated urine output, indicating severe dehydration. In addition, the patient also had the impression of ketone odor, which was not present previously. We started resuscitation measures, starting from administering supplemental oxygen, reloading fluids according to the patient's hemodynamic condition, and putting on an ECG monitor.

We gave her therapy instructions, included double iv line, 500 cc/24 hours of NaCl 3%, 50 meq KCl drip in Ringer Acetate 500 cc/12 hours (4 repetitions), intravenous rapid regulation of 6 units of rapid-acting insulin (4 repetitions) followed by 14 units of rapid-acting insulin subcutaneous before every meals, 20 units long-acting insulin subcutaneous in the night, and 2 gram of ceftriaxone once a day, therapy has been well implemented. However, after only approximately 15 minutes of therapy and under strict monitoring, the patient experienced respiratory arrest.

DISCUSION

We report the case of a 31-year-old woman who had diabetic ketoacidosis with severe dehydration, severe hypokalemia and sepsis resulting in cardiac arrest while she was being treated in the emergency unit.

Diabetic ketoacidosis (DKA) is one of the extreme conditions in the hyperglycemic crisis spectrum as an acute metabolic complication of diabetes. Even though DKA happens more often in people with type 1 diabetes, about a third of all cases of DKA happen in people with type 2 diabetes who do not carry out routine therapy followed by extreme stressful conditions, such as serious infections, trauma, cardiovascular disease, or other emergencies. People who have a higher chance of getting DKA are those who have high HbA1c, have had diabetes for a long time, lower socioeconomic status, presence of psychiatric conditions, teenagers, and girls. Newly diagnosed diabetes may also become the most triggering factor of DKA incidence.[1-4] In fact, in this patient, we cannot confirm whether the patient can be included to, type 1 or type 2 diabetes, due to anamnesis data that was not answered with confidence by the patient or the patient's closest family members, such as whether there was a history of illness since childhood and a history of diabetes in her family. This poor initial modal when the patient came to the emergency room was leading the patient to a deteriorating condition very quickly. So, even optimum care and treatment cannot provide the maximum results we wanted because we were also racing against time to handle this very serious condition.

DKA in general, our body is directed to a major catabolic state by breaking down glycogen stores, hydrolyzing triglycerides from adipose tissue, and mobilizing amino acids from muscles or in other words, in DKA, there is an increase in gluconeogenesis, lipolysis, ketogenesis, and a decreased glycolysis.[5]

Triglycerides and amino acids released from peripheral tissues become substrates to produce glucose and ketone bodies by the liver. Hyperglycemia and the production of ketone bodies lead a central role in developing this metabolic decompensation. The osmolar gradient caused by hyperglycemia in DKA results in a displacement of water from the intracellular to the extracellular space, which causes a decrease in cell volume due to loss of water and electrolytes through the urine, so sufferers of DKA tend to fall into cellular dehydration and decreased electrolyte levels, especially sodium and potassium. In addition, potassium decreases due to intracellular migration is also driven by a state of insulin deficiency and metabolic acidosis.[6] Such a thing has happened to our patient, even though at the beginning of the examination, there were no signs of dehydration in our patient, but during observation, suddenly developed signs of severe dehydration and shock, including decreased mental status, bradycardia, tachypnea with Kussmaul breathing, desaturation, cold extremities and obtained concentrated urine output.

The smell of ketones due to hyperglycemia which increases ketogenesis, also appears when the patient is in shock. Ketogenesis, which results in the excretion of ketone bodies through the urine, is also the cause of a decrease in potassium in the blood (hypokalemia), and it's proven by the result of hyponatremia and hypokalemia of electrolyte serum analysis. This is like the theory that loss of potassium in DKA cases occurs because of osmotic diuresis, reduced NaCl reabsorption, and ketonuria.

In DKA treatment, the important things to do are to give lots of fluids, give insulin, replace electrolytes, and find and treat what caused it in the first place. So that is why the main treatment for hyperglycemia is by administering fluid therapy (rehydration). Fluid therapy for acute hyperglycemia patients will have the effect of reducing blood glucose levels in hyperglycemia patients (80% of patients in the first four hours. The principle of fluid therapy is to initially improve the balance of ECF (Extra Cell Fluid) in the body and maintain blood flow to the kidneys, if the fluid balances the body is fulfilled, giving fluid therapy will reduce blood glucose levels without depending on insulin and reduce levels of counter-insulin hormones which will ultimately improve sensitivity to insulin[7].

Hypokalemia may be common in cases of diabetic ketoacidosis, but severe hypokalemia (<2.5 mmol/L) occurring before insulin treatment is extremely rare. Usually, potassium will decrease in greater amounts when followed by insulin treatment because insulin can promote displacements in intracellular potassium and potentially, insulin-like effects of aldosterone on the renal tubules result in increased loss of potassium through the urine (kaliuresis).[8]

Another risk factor that is also closely related to hypokalemia in diabetic individuals is the use of diuretics, especially thiazides and loop diuretics.[9] However, in our patient, it seems to have no effect considering from the anamnesis, the patient has no history of diabetes so there was no previous consumption of any antidiabetic drugs.

Even though we have administered intravenous rapid regulation therapy with insulin, electrolyte serum analysis that showed severe hypokalemia was carried out before insulin was given to the patient. However, based on the theory that insulin can exacerbate hypokalemia, administration of intravenous rapid regulation therapy with insulin aimed at lowering our patient's blood glucose level may exacerbate hypokalemia in these patients. Moreover, it is theorized that when intravenous fluids and insulin are administered to treat hyperglycemia, a rapid decrease in fluid osmolality can cause a reversal of the displacement in intracellular fluid, resulting in cerebral edema.[9]

The most common symptoms of cerebral edema associated with DKA include altered mental status (agitation, confusion, and sleepiness), severe headache, recurrent vomiting, seizures, hypertension, and bradycardia. The incidence of cerebral edema in DKA is closely related to the presence of

factors such as younger patient age, newly diagnosis of diabetes, severity of acidosis, lower pCO2 values, higher urea levels, administration of bicarbonate, intravenous rehydration, use of hypotonic fluids, and rapid correction of hyperglycemia in the first 24 hours.[10,11]

Our patient met some of these criteria, in which the patient complained of headache and seemed agitated at the initial examination that continued to decreased consciousness in the emergency room and was found to have metabolic acidosis, and a history of administration of large volumes of fluid boluses and IV insulin within the first hours. So even though our patient has not had an imaging examination done, the possibility of cerebral edema may occur.

Other than antidiabetic drugs, in various literatures and several researchers have reported the relationship of ceftriaxone which can increase the development of hypokalemia by increasing the excretion of potassium in the urine.[12] Considering the presence of sepsis in our patient, the administration of antimicrobials in its management is also very necessary, but this does not rule out the possibility that this is a driving factor for increasingly severe hypokalemia.

Given the major role of potassium in the physiology of various tissues, organs and systems, its deficiency can lead to changes in cardiovascular, skeletal muscle, kidney function, even the release and effects of certain hormones.[9] This certainly does not rule out the possibility that the hypokalemic condition in our patient brought our patient to a drastic deterioration in his condition to the point of cardiac arrest. In this group of patients, cardiovascular disorders are more common due to decreased excitability of myocardial cells and aortic smooth muscle cells and their repolarization which causes atrial and ventricular arrhythmias.[13] Consequently, hypokalemia can affect membrane potential and elicit a decreased response to stressful conditions, such as hypoxia and oxidative stress leading to the cessation of all muscle contractions. The most frequently observed ECG changes include arrhythmias, flattening of the T wave, ST segment depression, prolonged of the QT interval, presence of U waves, and multiple ventricular extrasystoles, which can be seen in up to 20% of patients with severe hypokalemia.[9] We also got the EKG picture clearly from our patient's ECG picture at the initial examination with the findings of sinus tachycardia, predominant depressed ST segment, flattened T wave and prominent U wave.

Our patient case highlights how severe hypokalemia in diabetic ketoacidosis can rapidly worsen a patient's prognosis. Even though all therapies are already given according to the guidelines, the possibility of complications must still be watched out for, especially when one therapy gives adverse effects to each other. For this reason, further research is needed to find the most appropriate combination of therapy that can minimize the occurrence of complications if similar cases are found later.

Table 1. Related Studies

No	Title	Authors	Year Published	Highlights
1.	Diabetic Ketoacidosis with Severe Hypokalemia and Persistent Hypernatremia in an Adolescent Girl with COVID-19 Infection[2]	Badawy MK, Viswanath V, Khetriwal B, Pradhan S, Williams RM, Pathan N, Marcovecchio ML	2022	Hypokalemia in DKA likely results from a combination of kaliuresis, secondary to prolonged osmotic diuresis, inadequate oral intake, and gastrointestinal losses from diarrhea or vomiting. Kaliuresis is also driven by secondary hyperaldosteronism from profound losses of sodium and extracellular volume.
2.	Profound Hypokalemia	Davis SM, Maddux AB, Alonso GT,	2016	Total body potassium depletion is expected in DKA largely due to osmotic renal losses.

	Associated with Severe Diabetic Ketoacidosis[12]	Okada CR, Mourani PM, Maahs DM		Measurement of extracellular serum potassium in DKA patients with severe acidosis greatly underestimates the total body potassium deficit in these patients due to the extracellular potassium shift caused by insulin deficiency and metabolic acidosis. In normal adults, approximate total body content of potassium is 50 mEq/kg and 98% is contained intracellularly. In DKA patients with severe hypokalemia, potassium deficit can reach 10 mEq/kg. Treatment with insulin usually results in a decrease in the measured serum potassium due intracellular potassium shifts and, potentially, an aldosterone-like effect of insulin on the renal tubule that further increases urinary potassium losses.
3.	The Clinical Caveat for Treating Persistent Hypokalemia in Diabetic Ketoacidosis[13]	Khiatah B, Frugoli A, Carlson D	2023	According to a study conducted at the University of Southern California, the prevalence of hypokalemia in patients with DKA is 5.6%. It has been a clinical challenge to treat DKA patients with profound refractory hypokalemia. With the current guideline advising against initiating insulin therapy due to fear of cardiac arrhythmia, many patients face another life-threatening acidosis, cardiac arrhythmia due to hypokalemia, and severe neural complications.

However, the patient's condition is quite complex. There are many conditions that accelerate worsening conditions. Severe dehydration in the patient leads to decreased urine output and increased urine concentration, resulting in reduced tissue perfusion and a rapid decline in the patient's overall condition. Additionally, severe hypokalemia further complicates the management of lowering blood sugar levels, as insulin administration can lower potassium levels by increasing Na-K-ATPase activity. Aggressive insulin therapy aimed at reducing blood sugar levels can exacerbate the patient's hypokalemia, potentially affecting the functioning of the heart. Furthermore, the presence of sepsis in this patient has progressed to septic shock, leading to a significant and rapid deterioration compared to the patient's initial condition.

In cases of suspected diabetic ketoacidosis (DKA), optimal treatment of hypokalemia requires identification of underlying causes and management of associated disorders. Key guidelines for potassium replacement emphasize the importance of blood gas and renal function tests to guide replacement therapy. Initial rehydration with normal saline solution is recommended until serum potassium levels normalize. Insulin administration should be withheld if blood potassium levels are below 3.3 mmol/L to prevent insulin-induced hypokalemia.

CONCLUSION

The management of diabetic ketoacidosis patients with severe hypokalemia indeed poses a serious dilemma. Administration of intravenous fluids and insulin intended to treat hyperglycemia can cause intracellular fluid displacement and produce hypokalemia. Meanwhile, severe hypokalemia can lead to the cessation of all muscle contractions and cerebral edema which ends in cardiac arrest. Therefore, it is crucial to investigate any

potential causes of hypokalemia in patients to prevent the exacerbation of their condition and improve outcomes.

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