

## **Diabetic Ketoacidosis**

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### **Article Information**

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### **Abstract :**

*Diabetic ketoacidosis (DKA) is one of the acute complications for diabetics that usually occurs in type 1 DM, but it is possible in type 2 DM. DKA is caused by a decrease in effective insulin circulation associated with an increase in counter-regulatory hormones. The incidence of DKA ranges from 0 to 56 per 1000 people each year. In Indonesia, it is known that 71% of pediatric patients have DKA as the initial clinical presentation of type-1 DM in 2017. To know more about diabetic ketoacidosis. Knowing the characteristics of patients with diabetic ketoacidosis. Know how to treat patients with diabetic ketoacidosis. This research use literatur-review method. DKA is a complication of uncontrolled type 1 diabetes mellitus and has a high risk of being life-threatening. The incidence of DKA in Indonesia is not known for certain, but it is estimated at 76.9% based on data from Riskesdas in 2007. DKA occurs due to insulin deficiency which will result in increased lipolysis and usually occurs due to metabolic stress conditions. Symptoms of DKA are symptoms of hyperglycemia and classic symptoms of hyperglycemia. The key to the diagnosis of DKA is an increase in total circulating ketone bodies. The initial management of DKA is to monitor and secure the airway, breathing, circulation.*

**Keyword : Diabetic Ketoacidosis; Ketoacidosis; Management Of DKA;**

## **Introduction**

Diabetic ketoacidosis (DKA) is one of the acute complications for diabetics that usually occurs in type 1 diabetes, but it is possible that in type 2 diabetes, DKA is caused by a decrease in circulating effective insulin associated with an increase in counter-regulatory hormones. ranged from 0 to 56 per 1000 people annually. (Lizzo, Goyal, and Gupta 2021) In Indonesia, it is known that 71% of pediatric patients have DKA as the initial clinical presentation of type-1 DM in 2017.(Faisal, Adelaine, and Nurhayati 2020)

Mortality due to DKA generally occurs in the first 3-5 days of treatment, therefore treatment of DKA patients is recommended in the intensive care unit. in the first 24-28 hours. Brain edema is the most common cause of mortality in DKA patients, especially in children and adolescents. Hypokalemia, adult respiratory distress syndrome (ARDS)/acute lung injury (ALI) and comorbidities such as pneumonia, acute myocardial infarction, and sepsis are associated with increased mortality in adults (Febrianto and Hindariati 2021). Therefore, this literature review will discuss how to diagnose and manage DKA.

## **Method**

This article was written using various sources from scientific journals and the World Health Organization (WHO). Source searches are carried out on the portal online of journal publications such as Google Scholar (<https://scholar.google.co.id/schhp?hl=id>) and the National Center for Biotechnology Information/NCBI (<https://www.ncbi.nlm.nih.gov/>), with word searches The key used is "Diabetic Ketoacidosis". Literature Review

## **Result and Discussion**

### **Definition**

Diabetic ketoacidosis is a complication of uncontrolled diabetes and has a high risk of being life-threatening. Ketoacidosis is a condition in which the concentration of ketone bodies is high in serum and urine. Diabetes ketoacidosis usually occurs in conditions of hyperglycemia and insulin deficiency which can cause lipolysis and free fatty acid oxidation which can then produce ketone bodies and can result in an increase in metabolic acidosis. (Ghimire and Dhamoon 2021)

### **A. Epidemiology**

Diabetes ketoacidosis can cause mortality and morbidity in patients with type 1 diabetes mellitus. The incidence of diabetes ketoacidosis varies and is influenced by socioeconomic conditions, health services and facilities, and geographical conditions of each region. Therefore the prevalence of DKA varies widely in many countries, the prevalence of DKA is higher in developing countries, ranging from 13-80%. In Indonesia itself, the incidence of DKA does not yet have definite data, but based on a study in Jakarta in 2007, the prevalence of DKA in type 1 diabetes mellitus is 76.9%. Based on medical record data from RSUP dr. Sardjito in Yogyakarta, it was found that the

prevalence of DKA in the 2014-2016 period was 62.5%. (Listianingrum, Patria, and Wibowo 2019)

## B. Pathogenesis

The presence of absolute and relative insulin deficiency and an increase in the increase in counter-regulatory hormones, namely glucagon, catecholamines, cortisol, growth hormone, and somatostatin will lead to an acceleration of catabolic conditions and severe inflammation with the resultant increase in glucose production by the liver and kidneys through glycogenolysis and gluconeogenesis pathways and impaired utilization. peripheral glucose resulting in hyperglycemia and hyperosmolarity. (Setiati et al. 2016)

Insulin deficiency and an increase in counter-regulatory hormones, especially epinephrine, also activates hormone-sensitive lipases in adipose tissue, resulting in increased lipolysis. Increased lipolysis and ketogenesis will trigger ketonemia and metabolic acidosis. Although many ketone bodies have been formed for energy sources, our body cells still feel hungry and will eventually continue to form glucose. (Setiati et al. 2016)

Hyperglycemia and hyperketonemia result in osmotic diuresis, dehydration, and electrolyte loss. These changes will further trigger stress hormones so that hyperglycemia and hyperketonemia will worsen. If this is not treated promptly with insulin and fluids, the consequences are severe dehydration and fatal metabolic acidosis. Ketoacidosis will be exacerbated by lactic acidosis due to poor tissue perfusion. (Setiati et al. 2016)

Relative insulin deficiency occurs due to increased concentrations of counter-regulatory hormones in response to stressful conditions such as trauma, sepsis, myocardial infarction and others. In the presence of certain metabolic stress conditions, the presence of insulin which is normally sufficient to suppress lipolysis becomes relatively insufficient because more insulin is required for metabolism and to suppress lipolysis. (Setiati et al. 2016)

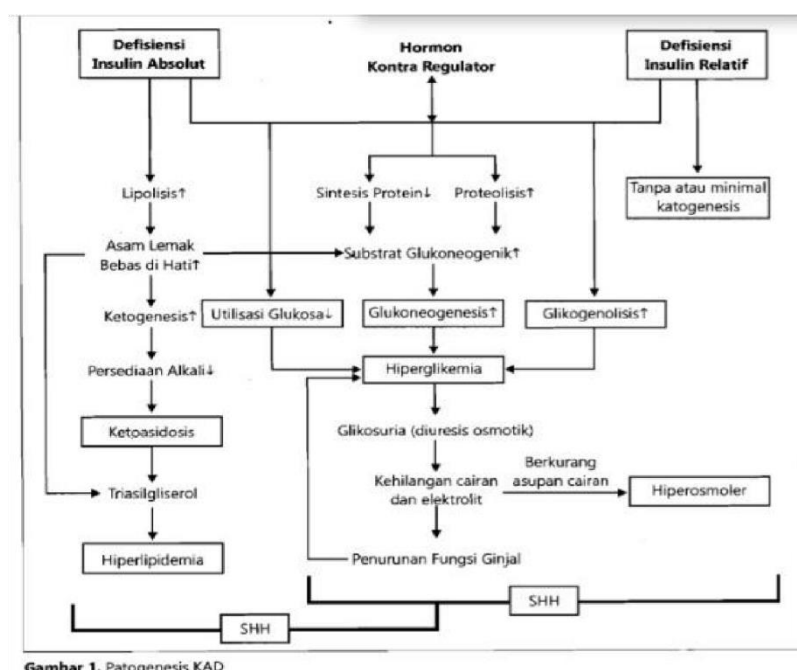


Figure 1. Pathogenesis of DKA. (Setiati et al. 2016)

### **C. Clinical features of diabetic ketoacidosis**

Patients with diabetic ketoacidosis often present with a brief clinical course characterized by fatigue and the classic symptoms of hyperglycemia: polyuria (excessive urine production), polydipsia (excessive thirst), and weight loss. (Fayfman, Pasquel, and Umpierrez 2017) In addition, the classic symptoms of hyperglycemia are also to be found is polyphagia (excessive hunger). Symptoms of polyphagia are relatively rare in adult cases and are more frequently reported in pediatric cases. Gastrointestinal symptoms such as nausea, vomiting, and abdominal pain are commonly reported in >60% of patients. Abdominal pain, sometimes resembling acute abdominal pain, is very common in children and in patients with severe metabolic acidosis. Although the causes of gastrointestinal complaints have not been fully elucidated, delays in gastric emptying, ileus (decreased bowel movements leading to accumulation or blockage of food substances), electrolyte disturbances, and metabolic acidosis are thought to be the causes of these gastrointestinal complaints. (Dhatariya et al. 2020)

On physical examination, the patient often comes with signs of dehydration such as dry mucous membranes and poor skin turgor, tachycardia, or hypotension (Fayfman, Pasquel, and Umpierrez 2017; Westerberg 2013). Hypotension can be observed in adults but is rare in children. The patient's mental status may vary from full awareness to lethargy and stupor, but approximately <20% of hospitalized adults exhibit loss of consciousness (Dhatariya et al. 2020). Metabolic acidosis can cause compensatory deep breathing (Kussmaul), whereas an increase in acetone can be felt as a fruity odor on the patient's breath (Westerberg 2013). Most adults and children appear normothermic or even hypothermic in the presence of infection (Dhatariya et al. 2020).

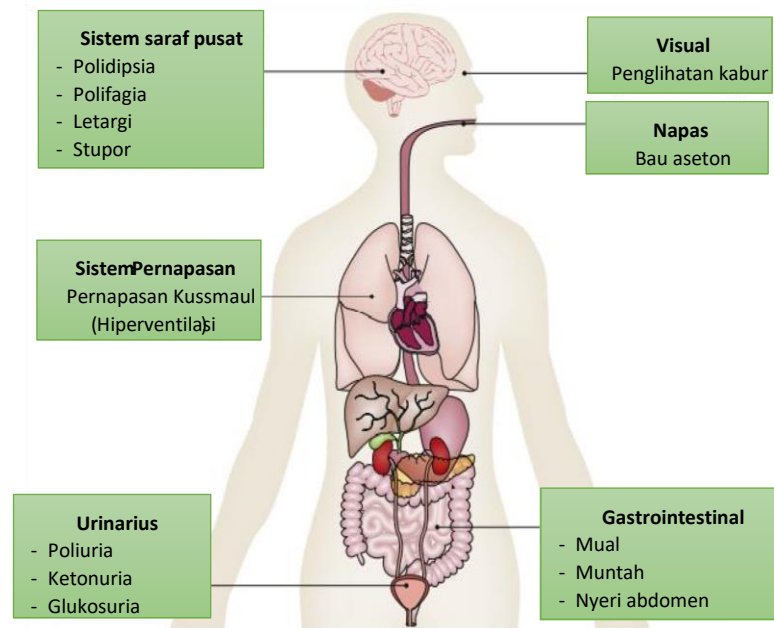


Figure 2. Symptoms and Signs of Diabetic Ketoacidosis

#### D. Diagnosis

Diagnosis of DKA is based on the triad of hyperglycemia, ketosis, and metabolic acidosis (Dhatariya et al. 2020). At the beginning of the evaluation of the needs of investigations are adapted to the clinical situation, it is generally necessary basic examination of blood sugar, electrolytes, blood gases, ketones blood and urine, serum osmolality, peripheral blood complete with differential count, anion gap, ECG and plain chest X-ray. The key to the diagnosis of DKA is an increase in the total circulating ketone bodies. The increase in ketone bodies will result in an increase in the anion gap (Setiati et al. 2016). *The American Diabetes Association* (ADA) classifies diabetic ketoacidosis based on severity as mild, moderate, or severe depending on the degree of acidosis. Most patients present with mild to moderate DKA with blood glucose  $>250$  mg/dL, bicarbonate between 10 and  $<18$  mEq/L, arterial pH  $<7.3$ , high ketones in the urine or blood, and increased anion gap metabolic acidosis  $>12$  (Fayfman, Pasquel, and Umpierrez 2017).

Blood sugar more than 250 mg/dl is considered as the main diagnostic criteria for DKA, thus every diabetic whose blood sugar is more than 250 mg/dl should be considered the possibility of ketosis or DKA if accompanied by appropriate clinical conditions. The degree of blood acidity (pH) which is less than 7.35 is considered the threshold for acidosis, but in compensated conditions the pH often shows normal values. In such circumstances, if the  $\text{HCO}_3^-$  is less than 18 mEq/l plus other appropriate clinical conditions, it is sufficient to establish DKA (Setiati et al. 2016).

	KAD Ringan	KAD Sedang	KAD Berat	HHS
Glukosa Plasma (mg/dL)	>250	>250	>250	>600
pH Arteri	7.25-7.30	7.00-7.24	<7.00	<7.30
Serum Bikarbonat (mEq/L)	15-18	10-15	<10	<15
Keton Urin	Positif	Positif	Positif	Rendah
Keton Serum	Positif	Positif	Positif	Rendah
Beta-Hidroksibutirat	Tinggi	Tinggi	Tinggi	Normal/Tinggi
Osmolalitas Serum (mOsm/kg)	Variasi	Variasi	Variasi	>320
Anion Gap	>10	>12	>12	Variasi
Kesadaran	Sadar	Sadar/Ngantuk	Sopor/Koma	Sopor/Koma

Table 1. KAD Diagnosis Criteria (Setiati et al. 2016)

### E. Management

Successful management of DKA requires correction of dehydration, hyperglycemia, electrolyte disturbances, comorbidities, and monitoring during treatment (Setiati et al. 2016). The principles of DKA management are: (1) Replacement of lost body fluids and salts, (2) Suppress fat cell lipolysis and suppress liver cell gluconeogenesis by administering insulin, (3) Overcoming stress as a trigger for DKA, (4) Restoring physiological state normal and recognizes the importance of monitoring and adjusting treatment (Setyohadi et al. 2012).

#### Management

##### Initial Management

1. Secure airway, breathing, circulation
2. Assess consciousness using GCS (Glasgow Coma Scale)
3. Weigh the patient to calculate fluid requirements and insulin requirements
4. Assess the degree of hydration by observing prolonged capillary refill time, decreased turgor, hyperpnea, and signs of dehydration such as dry mucous membranes, sunken eyes, and no tears
5. Clinical evaluation whether there is an infection or not
6. Measure blood glucose levels and beta-hydroxybutyrate/BOHB (or urine ketones) levels with a bedside device
7. Perform blood sampling for laboratory tests at least plasma glucose, serum electrolytes (anion gap calculation), venous blood gas analysis (pH, HCO<sub>3</sub>, and pCO<sub>2</sub>), BOHB levels, and complete peripheral blood. Other additional tests needed are serum creatinine, plasma osmolality, serum albumin, phosphorus, and magnesium
8. Check HbA1c
9. Perform urinalysis examination
10. If there is a fever or other signs of infection, perform a culture (blood, urine, or other specimen culture) prior to administration of antibiotics

### F. Fluids

The main priority in the management of DKA is fluid therapy (Gotera and DGA 2011). In general fluid management is the first step of KAD after cardiorespiratory resuscitation (Setiati et al. 2016). Insulin therapy is only effective if fluids are given in the early stages of therapy and only fluid therapy can lower blood sugar levels (Gotera and DGA 2011). Fluid therapy is aimed at expansion of intracellular, intravascular, interstitial fluid, and restoration of renal perfusion (Setiati et al. 2016).

Isotonic saline (0.9% NaCl) is given at a dose of 15-20 ml/kg BW/hour the first or one to one and a half liters in the first hour. Follow-up fluid in the following hours depends on the state of hemodynamics, hydration status, electrolytes, and urine production. In general, 0.45% NaCl solution is given if the serum sodium level is high ( $>150$  mEq/l), and is given to correct the increase in serum  $\text{Na}^+$  level (corrected serum sodium) at a rate of 4-14 ml/kg BW/hour or 250-500 ml/hour depending on the patient's hydration status whereas 0.9% NaCl solution is given at a rate of 250-500 ml/hour if the corrected serum sodium is low. When blood sugar reaches 200 mg/dL, fluids are replaced or supplemented with fluids containing dextrose (such as dextrose, dextrose in 0.9% NaCl, or dextrose in 0.45% NaCl) to avoid hypoglycemia and reduce the possibility of cerebral edema due to low blood sugar. too fast blood (Gotera and DGA 2011; Huang 2018; Setiati et al. 2016).

### **G. Insulin**

Insulin is the main causative pharmacotherapy of DKA (Setiati et al. 2016). Insulin therapy should be started immediately after the diagnosis of DKA and adequate rehydration. The use of insulin will reduce levels of the hormone glucagon, thereby suppressing the production of ketone bodies in the liver, the release of free fatty acids from fat tissue, the release of amino acids from muscle tissue, and increasing the utilization of glucose by the tissues (Gotera and DGA 2011).

If there is no hypokalemia ( $\text{K} < 3.3$  mEq/l), regular insulin 0.15 u/kg body weight can be given, followed by a continuous infusion of 0.1 u/kg body weight/hour. If the potassium level is  $<3.3$  mEq/l, it must be corrected first to prevent worsening of hypokalemia which can lead to cardiac arrhythmias. If the blood sugar does not decrease by 50 mg/dl from baseline in the first hour, check the patient's hydration status. If hydration status is adequate, insulin infusion can be increased 2-fold every hour until a constant decrease in blood sugar between 50 - 75 mg/dl/hour is achieved. When blood sugar levels reach 250 mg/dl, reduce insulin infusion to 0.05 - 0.1 u/kg BW/hour and add 5 - 10% dextrose infusion to prevent hypoglycemia (Gotera and DGA 2011; Setiati et al. 2016). Thereafter, the rate of insulin administration or the concentration of dextrose should be adjusted to maintain glucose values until the acidosis improves.

In clinical conditions, intravenous insulin cannot be given, insulin is given at a dose of 0.4 - 0.6 IU/kg BW which is divided into half the dose intravenously and the other half subcutaneously or intramuscularly, then insulin is given intramuscularly or subcutaneously 0.1 IU/kg BW/hour, then the management protocol is the same as for intravenous drip administration.

In mild DKA, regular insulin can be administered subcutaneously or intramuscularly every hour with the same effectiveness as intravenous administration in low blood sugar and low ketone bodies. Patients with mild DKA should receive a baseline dose of regular insulin 0.4-0.6 u/kg body weight, half dose as a bolus, and half dose by subcutaneous or intramuscular injection. Next, insulin is given subcutaneously or intramuscularly 0.1 u/kg BW/hour.

The criteria for resolution of DKA include blood sugar levels  $< 200$  mg/dl, serum bicarbonate 18 mEq/l, venous pH  $> 7.3$  and anion gap 12 mEq/l. Currently, if the patient is NPO (Nothing Per Oral), continue intravenous insulin and fluids and supplement with

subcutaneous regular insulin as needed every 4 hours. When the patient is able to eat, a multiple-dose schedule should be initiated using a combination of short or rapid-acting insulin and intermediate or long-acting insulin as needed to control blood glucose (Gotera and DGA 2011).

#### **H. Potassium**

DKA patients can experience hyperkalemia through the mechanism of acidemia, insulin deficiency, and hypertonicity so that insulin therapy, correction of acidosis, and increasing fluid volume will reduce serum potassium concentrations. Potassium administration is started when potassium levels are around the upper limit of normal values to prevent hypokalemia (Gotera and DGA 2011; Setiati et al. 2016). Total potassium deficiency that occurs during DKA is estimated at 3-5 mEq/kg BW (Setyohadi et al. 2012).

In cases of DKA patients with significant hypokalemia, potassium replacement should be initiated with 40 mEq/l KCl therapy, and insulin therapy should be delayed until potassium levels are  $> 3.3$  mEq/l to avoid arrhythmias and respiratory muscle weakness. To prevent hypokalemia, serum potassium replacement is initiated once the serum potassium level is less than 5 mEq/l. generally, 20-30 mEq of potassium per liter of fluid infusion is sufficient to maintain serum potassium levels in the range of 4-5 mEq / l. Potassium therapy is not performed if there is no urine production, renal abnormalities are present, or the potassium level is  $> 6$  mEq/l (Gotera and DGA 2011).

#### **I. Bicarbonate**

In adult patients with a pH  $< 6.9$ , 100 mmol sodium bicarbonate is added to 400 ml of physiological fluids and administered at a rate of 200 ml/hour. Meanwhile, patients with a pH of 6.9 – 7.0 were given 50 mmol of sodium bicarbonate mixed in 200 ml of physiological fluids at a rate of 200 ml/hour. If the pH is  $> 7.0$ , then sodium bicarbonate is not required. Thereafter, venous blood pH was checked every 2 hours until the pH was 7.0 and therapy could be repeated every 2 hours if necessary.

#### **Conclusion**

DKA is a complication of uncontrolled type 1 diabetes mellitus and has a high risk of being life-threatening. The incidence of DKA in Indonesia is not known with certainty, but it is estimated at 76.9% based on data from Riskesdas in 2007. DKA occurs due to insulin deficiency which will result in increased lipolysis and usually occurs due to metabolic stress conditions. Symptoms of DKA are symptoms of hyperglycemia and classic symptoms of hyperglycemia. The key to the diagnosis of DKA is an increase in the total circulating ketone bodies. The initial management of DKA is to monitor and secure the airway, breathing, circulation.

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