

Complications of Diabetes Mellitus: A Review Article

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ABSTRACT

Introduction: Diabetes Mellitus is a chronic disease that will be suffered for a lifetime so the progressive disease will continue and can cause complications. Diabetes mellitus usually progresses slowly with symptoms that are mild to severe, and can even cause death due to acute or chronic complications.

Content: Hyperglycemic crisis is one of the acute complications that can occur in Diabetes mellitus, both type 1 and type 2. This situation is a serious complication that may occur even in well-controlled diabetes mellitus.

Conclusion: Diabetic ketoacidosis and hyperglycemic Hyperosmolar State are acute complications of Diabetes mellitus. Both of these complications can be triggered due to inadequate insulin therapy and the presence of infection. Diabetic ketoacidosis is a condition characterized by metabolic acidosis due to excessive formation of ketones, while a hyperglycemic hyperosmolar state is characterized by severe hyperosmolality with serum glucose levels which are usually higher than diabetic ketoacidosis.

Keywords: Complications; diabetes mellitus; diabetic ketoacidosis; hyperglycemic hyperosmolar state



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Introduction

Diabetes Mellitus (DM) is a chronic disease caused by metabolic disorders with clinical signs of increased blood sugar levels that exceed normal limits.¹ Indonesia is ranked seventh out of the 10 countries contributing to the highest DM rate in the world in 2019 with a total of 10.7 million sufferers with an estimate that in 2045 it will exceed 16.6 million cases.² The clinical course of DM disease depends on the level of control of blood sugar levels. Based on the International Classification of Diseases (ICD) 10th coding for Diabetes states that uncontrolled blood sugar levels in DM patients can cause damage to various organs including the kidneys, peripheral blood vessels, nerves, eyes, joints and skin.³ This statement is also supported by the study of LeMone et.al., (2016) which describes several complications that often arise due to uncontrolled blood sugar levels in DM patients, namely Diabetic Ketoacidosis (DKA) and Hyperglycemic Hyperosmolar State (HHS).⁴

Definition

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State are emergency cases due to hyperglycemia. Both are acute complications that can occur in patients with Diabetes Mellitus⁵. DKA is a condition characterized by the triad of hyperglycemia, ketonemia, and metabolic acidosis. In DKA, the increase in blood sugar reaches 300-600 mg/dL with an increase in the anion gap and plasma osmolarity (300 - 320 mOs/mL).^{5,6} Whereas HHS is a condition characterized by a very high increase in blood glucose (> 600 mg/dL), increased plasma osmolarity (> 320 mOs/mL), without acidosis. In HHS, the anion gap can be normal or slightly increased, and plasma ketones are minimal.^{6,7}

Epidemiology

DKA and HHS contribute to the mortality and morbidity of DM patients. In the United States, DKA was the cause of 168,000 cases of hospitalization of DM patients in 2014 and increased to 220,340 cases in 2017. The prevalence of DKA is mainly found in patients aged less than 45 years and two-thirds of them are sufferers of type 1 DM. HHS is less common with <1% hospitalization rate in DM patients. However, the mortality rate for HHS is quite high, reaching 10-20%, while DKA is only 1-5%. Most HHS cases are found in patients in their fifth or sixth decade of life and nearly 90% are type 2 DM sufferers⁵.

Etiology and Risk Factor

The main etiologies of DKA and HHS are type 1 DM and type 2 DM. Several factors increase the risk of DKA and HHS occurring. The two main triggering factors are inadequate insulin therapy and the presence of infection. Other precipitating factors include new-onset DM, metabolic stressors, myocardial

infarction, cerebrovascular disease, pulmonary embolism, pancreatitis, alcohol and drug use. The use of drugs such as corticosteroids, diuretics, sympathomimetic agents, and second-generation antipsychotic agents also increases the incidence of DKA and HHS^{5,8,9,10}

Pathophysiology

Diabetic Ketoacidosis (DKA)

Starting from the destruction of pancreatic beta cells in type 1 DM patients. Damage to pancreatic beta cells causes a decrease in insulin secretion. The condition of the body that has decreased insulin secretion causes the body to be unable to process glucose properly so high levels of glucose will accumulate in the blood. As compensation, the body will use fat as an alternative energy reserve. In this process, the body does not need the insulin hormone so most of the glucose will be converted into fat through the process of lipogenesis. Furthermore, the fat will be broken down in the process of lipolysis, the result is an acidic ketone. As a result of the lipolysis process, it causes the accumulation of residues or ketones in large quantities in the body, causing a decrease in blood pH and acidosis.^{5,8}

Hyperglycemic Hyperosmolar State (HHS)

HHS begins with hyperglycemia in patients with type 2 diabetes mellitus. High blood sugar levels cause the body's response to compensate by removing it through the process of urinating. Due to very high blood sugar levels, the body will continue to excrete it through the process of urinating which eventually results in glucosuria. In the process of disposal, the body needs water to help the process of disposing of glucose in the form of urine. Glucosuria that occurs continuously will cause dehydration. This dehydration condition will cause thickening or what is called hyperosmolar. This hyperosmolar condition causes intracellular fluids to be pulled out to extracellular to maintain body fluid homeostasis.^{5, 8,9,11,12,13,14}

Diagnosis

Diabetic Ketoacidosis (DKA).

Clinical manifestations that can be experienced by patients with DKA include polydipsia, polyuria, polyphagia, nausea, vomiting, abdominal pain, and weakness. In a more threatening phase, loss of consciousness, Kussmaul breathing, and ketone-smelling breath can occur. The emergence of symptoms of abdominal pain, nausea and vomiting often makes DKA be mistaken for gastroenteritis. Apart from symptoms, a patient history can be sought that meets risk factors for DKA, such as insulin use, or a previous infection. Laboratory tests were performed to confirm the diagnosis of DKA by assessing blood glucose, urine and serum ketones, arterial blood gas analysis, serum electrolytes and osmolality. In DKA there is an increase in blood glucose (> 250 mg/dL), metabolic acidosis (characterized by an increased

anion gap, bicarbonate levels <15 mEq/L and/or pH <7.30), ketosis (ketonuria and ketoemia). Examination of serum ketones is more often used than urine ketones because of the condition of oliguria associated with dehydration. The severity of DKA is classified based on the level of acidosis as seen from pH, serum bicarbonate and ketones.^{5,16}

Hyperglycemic Hyperosmolar State

The most common clinical manifestation of HHS is a loss of consciousness that will mask other symptoms.⁸ This occurs in HHS patients due to severe dehydration due to hyperglycemia and osmotic diuresis. Laboratory tests for HHS are the same as for DKA, the difference is that acidosis does not occur in HHS patients, resulting in a pH of 7.3 and a bicarbonate level of >18 mEq/L. The hyperosmolar condition of the patient results in a serum osmolality of ≥ 320 mOsm/kg. Hyperglycemia is also found with levels ≥ 600 mg/dL.^{5,16}

Table 1. Diagnostic Criteria and Typical Total Body Deficits of Water and Electrolytes in DKA and HHS

	DKA			HHS
	Mild (plasma glucose >250mg/dl)	Moderate (plasma glucose >250mg/dl)	Severe (plasma glucose >250mg/dl)	Plasma glucose >600mg/dl
Arterial pH	7.25-7.30	7.00 to <7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15-18	10 to <15	<10	>18
Urine ketone	Positive	Positive	Positive	Small
Serum ketone	Positive	Positive	Positive	Small
Effective serum osmolality	Variable	Variable	Variable	>320 mOsm/kg
Anion gap	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

Treatment

NIHL disease is permanent and progressive so that it rarely or even does not require medical therapy. The main strategy that can be done is to prevent the worsening of the patient's condition and carry out rehabilitation in people who have been exposed to NIHL.¹⁴ NIHL management must be done holistically and comprehensively.¹⁶

Fluid Therapy.

Fluid therapy is the initial therapy for DKA and HHS which aims to correct fluid volume depletion in the body. In DKA conditions, the body fluid volume depletion is about 6 L and 9 L in HHS. The first choice of fluid given is normal saline (0.9% NaCl) at a rate of 15-20 ml/kg/hour or 1-1.5 L for the first 1 hour. The choice of fluid for further action depends on hemodynamic status, hydration status, serum electrolyte levels, and urine output. Patients with high or normal sodium levels are given 0.45% NaCl at a rate of 4-14 ml/kg/hour or 250-500 ml/hour depending on the patient's hydration status and 0.9% NaCl

at the same dose in patients with low sodium levels. The goal is to replace half of the estimated water and sodium deficit over 12-24 hours. When blood glucose reaches 200-300 mg/dL, fluid is replaced or added with a dextrose solution (5% dextrose in 0.45% NaCl) to avoid hypoglycemia and reduce the possibility of cerebral edema due to a decrease in blood glucose that is too fast.^{5,15}

Insulin Therapy.

Insulin therapy is given when fluid therapy is adequate. Administration of insulin before fluid therapy can cause intravascular fluid to move into the cells, exacerbating hypotension and leading to collapse (5). In adults, insulin therapy should be started with an intravenous (IV) bolus of 0.1 unit/kg, followed by a continuous infusion of 0.1 unit/kg/hour until blood glucose levels fall to 250-300 mg/dL. Another option is to give a continuous infusion of 0.14 units/kg/hour without a loading dose. If the glucose level does not fall by 10% within the first hour, an IV bolus of 0.14 units/kg/hour should be given, followed by a continuous infusion of 0.1 units/kg/hour. Children should not receive an initial bolus of insulin because it can increase the risk of cerebral edema, so it should be replaced with a continuous infusion of 0.1 unit/kg/hour. Once blood glucose levels are <300 mg/dL in HHS and <200 mg/dL in DKA, 5% dextrose should be added to IV fluids and the continuous infusion insulin dose reduced to 0.02-0.05 units/kg/hour, and blood glucose is maintained between 200-300 mg/dL in HHS and 150-200 mg/dL in DKA until consciousness returns to normal and the DKA condition is resolved.^{5,6,15,18}

If the patient is able to eat consider administering subcutaneous insulin or restarting the previous treatment regimen. In mild DKA, regular insulin can be administered subcutaneously or intramuscularly every hour at a dose of 0.4 – 0.6 u/kg, half the dose as a bolus and half the dose by subcutaneous or intramuscular injection. Then given insulin subcutaneously or intramuscularly 0.1 u/kgBB/hour until the DKA condition is resolved.^{5,15,18}

Potassium Therapy

Patients with DKA may experience mild to moderate hyperkalemia caused by acidosis and insulinopenia so insulin therapy, correction of acidosis, and addition of fluid volume will reduce serum potassium concentration. To prevent hypokalemia, potassium replacement is initiated once the serum level is <5.3 mmol/L (3.3-5.2 mmol/L) by adding 20-30 mmol potassium chloride to each liter of IV fluids to maintain the serum potassium concentration within the normal range. 4-5 mmol/L. In cases of hypokalemia, if the patient's serum potassium level is <3.3 mmol/L, potassium replacement should be initiated with 20-30 mmol potassium chloride fluid therapy and insulin therapy should be delayed until the potassium concentration is >3.3 mmol/L to prevent arrhythmias and respiratory muscle weakness. And if the serum potassium level is >5.2 mmol/L, potassium should be retained until the level is <5.2 mmol/L, with monitoring every two hours.^{5,15}

Bicarbonate Therapy

The use of bicarbonate in the treatment of DKA is controversial. Bicarbonate therapy has several side effects, such as hypokalemia, decreased tissue oxygen uptake, cerebral edema and delay in resolution of ketosis. However, patients with severe DKA may experience a decrease in pH if not treated with bicarbonate. Adult patients with a pH <6.9 should be given 100 mmol of sodium bicarbonate in 400 ml of sterile fluid with 20 mmol of KCL administered at a rate of 200 ml/hour for two hours. Whereas patients with a pH between 6.9-7.0 can be given 50 mmol bicarbonate in 200 ml of sterile fluid with 10 mmol KCL for two hours to maintain a pH > 7.0. If the pH is >7.0, sodium bicarbonate is not needed. After that, the pH of the venous blood is checked every 2 hours until the pH is 7.0 and the therapy can be repeated every 2 hours if necessary. For HHS conditions, bicarbonate therapy is not necessary.^{5,18}

Phosphate Therapy.

There is no evidence that phosphate therapy is necessary for the treatment of DKA or better HHS. However, in patients with potential complications of hypophosphatemia, including cardiac and skeletal muscle weakness, the use of phosphates may be considered. However, administration of phosphate can cause hypocalcemia when used in high doses.⁵

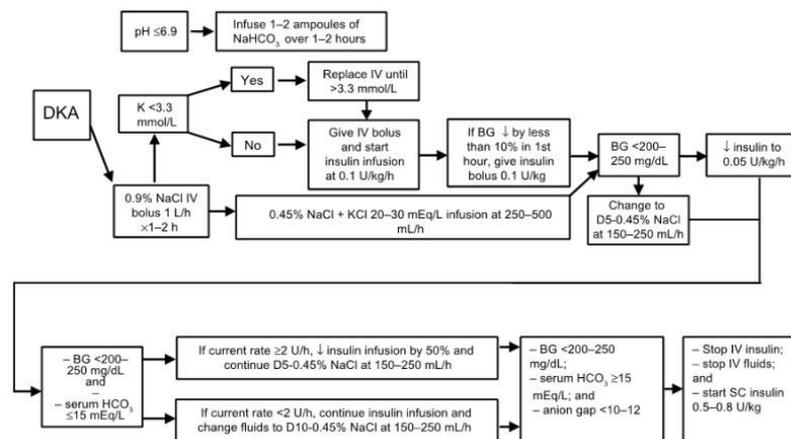


Figure 1. Protocol for the management of adult patients with DKA⁵

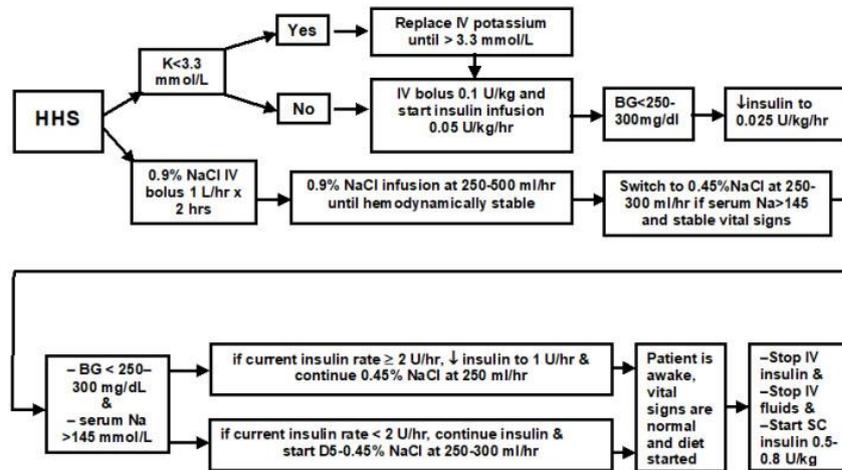


Figure 2. Protocol for the management of adult patients with HHS⁵

The simplest prevention that can be done is measuring noise. This procedure was carried out with the aim of assessing the maximum, average, minimum, intermittent type fluctuation and noise steadiness. The frequencies that are prone to causing damage to the organ of Corti in the cochlea are 3000 Hz - 8000 Hz. If exposure to high-intensity noise continues for a long time, it can cause hearing loss. After finding the source of the noise, this must be recorded and followed by measuring the time of exposure to noise. The higher the noise intensity, the relatively safe exposure time becomes shorter. This has been regulated in the Decree of the Minister of Manpower of the Republic of Indonesia no. KEP51/MEN/1999 concerning the threshold value of physical factors in the workplace. After taking the noise measurement, can be continued with noise control. This management can be done by minimizing the amount of noise at noise sources such as noise reduction at the engineering control program stage (engineering control program), installation of silencers, engine insulation and sound-absorbing materials.¹⁶

Referral System

The referral system is a reciprocal process between the team and the referring facility and the recipient. Based on the 2021 Guidelines for Treatment and Prevention of Type 2 Diabetes mellitus in Indonesia, DKA and HHS are emergency conditions in the internal sector if they are found in a primary health facility or level I health service provider who must be referred immediately to a specialist in internal medicine. A referral should be made after the patient has received initial treatment and is in a stable condition. If after taking action by a specialist in internal medicine, the conditions of DKA and HHS still cannot be resolved, then the patient must be referred to a diabetic metabolism endocrinology subspecialist doctor. After the hyperglycemia crisis is handled and blood sugar levels have been controlled, the patient

can be referred back to the referring health facility or health service provider. Controlled blood sugar levels can be seen through the criteria of fasting blood glucose (FBG) <130 mg/dL, 2 hours postprandial blood glucose (2hPBG) <180 mg/dL, and/or HbA1c <7%.⁶

Complications

Most of the complications of DKA and HHS are related to inadequate management. Hypoglycemia and hypokalemia are the most common complications of DKA and HHS caused by excessive administration of insulin and bicarbonate and are not accompanied by close monitoring. Other complications of DKA and HHS are electrolyte imbalance, cerebral edema, respiratory distress syndrome, seizures, myocardial infarction, mesenteric artery thrombosis, decreased consciousness to coma, acute renal failure, and rhabdomyolysis.^{5,15,21}

Prognosis

DKA and HHS which are treated quickly and appropriately have a fairly good prognosis.⁷ The mortality rate for DKA in adults ranges from 0.2-2.5%.¹⁹ This mortality rate is increased by 15-20% in HHS patients (20). However, the recurrence rate of DKA tends to be higher, where 1 in 5 patients with type 1 DM with DKA will be re-admitted to the hospital because of DKA within 30 days after the last incident of DKA experienced.⁵

Conclusion

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State are acute complications of Diabetes Mellitus. Both of these complications can be triggered due to inadequate insulin therapy and the presence of infection. Diabetic Ketoacidosis is a condition characterized by metabolic acidosis due to excessive formation of ketones, while a hyperglycemic hyperosmolar State is characterized by severe hyperosmolality with serum glucose levels which are usually higher than Diabetic Ketoacidosis.

Conflict of Interest

There is no conflict of interest

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