Diabetic Ketoacidosis: A Review Article

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Received: April 2022 Accepted: May 2022; Published: June 1, 2022.
Citation: Hani Raka Karrar et al. Diabetic Ketoacidosis: A Review Article. World Family Medicine. 2022; 20(6): 66-71
DOI: 10.5742/MEWFM.2022.9525062

Abstract

Type 1 Diabetes Mellitus is the most common chronic disease in childhood and one of its complications is diabetic ketoacidosis. Diabetic ketoacidosis is considered one of the most common causes of death in a patient with type 1 diabetes. Diabetic ketoacidosis is characterized by hyperglycemia, hyperosmolarity, ketosis, and acidosis. The incidence rate of diabetic ketoacidosis has increased globally, annually. Diabetic ketoacidosis may be life-threatening and lead to diabetic coma or death. Diabetic ketoacidosis is defined as metabolic decompensation caused by increasing ketones in the blood. Diabetic ketoacidosis occurs when the body doesn't have enough insulin to allow blood sugar into the cells for use as energy potentiated by glucose counter-regulatory hormone excess. Diabetic ketoacidosis presents with vague symptoms such as nausea, vomiting, and pain in the abdomen. A characteristic symptom of diabetic ketoacidosis, such as Kussmaul breathing, is present in limited patients. Early diagnosis and management are effective to improve patient outcomes. Infections in diabetic patients should be carefully monitored as they are the most common precipitating factors for diabetic ketoacidosis. The diagnosis of diabetic ketoacidosis is based on three major signs which are hyperglycemia, metabolic acidosis, and ketosis. The treatment of diabetic ketoacidosis includes fluid resuscitation, electrolyte replacement, insulin administration, and monitoring of the signs of cerebral edema and fluid overdose. This review article will mainly focus on the epidemiology, pathogenesis, diagnosis, management, and morbidity of diabetic ketoacidosis.

Keywords: Diabetic Ketoacidosis, Review Article, Insulin Therapy, Type one Diabetes mellitus. Type Two Diabetes Mellitus

Introduction

Type 1 Diabetes Mellitus is the most common chronic disease in childhood with significant morbidity and mortality. One of the most common complications of Type 1 Diabetes Mellitus is diabetic ketoacidosis (1, 2). Diabetic ketoacidosis is considered one of the most common causes of death in adults and children with type 1 diabetes and it is characterized by hyperglycemia, hyperosmolality, ketosis, and acidosis. Also, it may affect females with gestational diabetes or patients with type 2 diabetes (3). Since the 2000s, the incidence rate of diabetic ketoacidosis has increased globally (4). Diabetic ketoacidosis is a serious, life-threatening complication of diabetes that leads to diabetic coma or death. Diabetic ketoacidosis is a metabolic decompensation caused by increasing ketones in the blood. Diabetic ketoacidosis occurs when the body doesn't have enough insulin to allow blood sugar into the cells for use as energy potentiated by glucose counter-regulatory hormone excess (5, 6). Early diagnosis and management are effective to improve patient outcomes (7). Diabetic ketoacidosis presents with vague symptoms such as nausea, vomiting, and pain in the abdomen. A characteristic symptom of diabetic ketoacidosis such as Kussmaul breathing is present in limited patients. Infections in diabetic patients should be carefully monitored as they are the most common precipitating factors for diabetic ketoacidosis (8). Mainly diagnosis of Diabetic Ketoacidosis is based on three major signs which are hyperglycemia, metabolic acidosis, and ketosis (9). The treatment of Diabetic ketoacidosis includes fluid resuscitation, electrolyte replacement, insulin administration, and monitoring of the signs of cerebral edema and fluid overdose (10, 11). This review article will mainly focus on the epidemiology, pathogenesis, diagnosis, management, and morbidity of diabetic ketoacidosis.

Epidemiology

Since the 2000s, the incidence rate of diabetic ketoacidosis has increased globally (4). Mainly around two-thirds (2/3) of diabetic ketoacidosis cases occur in a patient with type one diabetes mellitus patients and one-third (1/3) occurs in type two diabetes mellitus (4, 12). In child patients whose age is less than 18 years, the initial diagnosis of diabetic ketoacidosis is type one diabetes mellitus. The differences in the incidence rate along with the population. Mainly the incidence rate ranges from 13% to 80% and the estimated mortality rate of diabetic ketoacidosis is 4% to 10% (13, 14). The onset of diabetic ketoacidosis comes early as the earliest presentation marker at age of 5 years in people who don't have easy access to medical care for social or economic reasons (15, 16). In the United States, Australia, New Zealand, Denmark, and Europe, the need for hospitalization for diabetic ketoacidosis cases has increased especially in adult patients (17-19). Diabetic ketoacidosis in adult patients mainly occurs in type two diabetes mellitus. The incidence rate remains high in adults but not as high as in children (14).

Pathophysiology

Diabetic ketoacidosis is considered the result of a lack of glucose supply at the cellular level. In the absence of absolute or relative deficiency of insulin concentration, cells enter a state of starvation, which in turn activates alternative energy-producing pathways. Glycogen storages are rapidly depleted and the levels of glucagon and epinephrine are elevated, and gluconeogenesis becomes the major metabolic pathway. Furthermore, there is increased lipolysis, which in turn decreases adipocyte storage of free fatty acids (5, 6). Elevation of blood glucose concentration in interstitial space creates an osmotic gradient, resulting in marked diuresis, and this will lead to hypovolemia and dehydration. As a final result, this will lead to exacerbation of the hyperglycemia and acidosis because it promotes the activation of other counter-regulatory stress hormones such as growth hormone, cortisol, glucagon, and catecholamines (20). Furthermore, the level of sodium should be measured because it is affected and can become abnormally low as a result of osmotic diuresis. Also, electrolyte salts containing phosphorus, sodium, and potassium become bound to anions from ketoacids in the bloodstream and are excreted in the urine (20, 21). Finally, there is a decrease in potassium cellular uptake resulting from the lack of insulin concentration (22). There are other ways to cause ketoacidosis such as:

1. Starvation ketosis

Starvation ketosis occurs in any individual who has a prolonged reduction in calorie intake (Less than 500 kcal/day) (23). The mechanism is when the glucose drops in blood because of little or no carbohydrate intake, and the insulin secretion is decreased, leading to two mechanisms to be activated which are lipolysis and ketogenesis (24, 25).

2. Alcoholic Ketoacidosis.

Alcoholic ketoacidosis develops in people with chronic alcohol abuse, and it has a different pathogenesis, and it results in nausea, vomiting, and acute starvation (26). To differentiate between diabetic ketoacidosis and alcohol-induced ketoacidosis we should measure the blood glucose because acute alcohol withdrawal can cause the release of counter-regulatory hormones, and any accompanying starvation will be associated with low insulin secretion, which, in turn, causes lipolysis and ketogenesis. Also, diabetic ketoacidosis is mainly characterized by severe hyperglycemia, but the presence of ketoacidosis without hyperglycemia is mainly a diagnostic marker for alcoholic ketoacidosis (26, 27).

3. Osmotic diuresis

Osmotic diuresis can lead to increase in the risk of ketoacidosis through a decrease in the glomerular filtration rate, thereby reducing the ability to excrete glucose. Also, hypovolemia leads to additional increases in the levels of counter-regulatory hormones. As a result, the low level of circulating volume can lead to generalized hypo-perfusion and this will lead to increase in the level of lactic acid through switching peripheral tissue to anaerobic respiration because of lacking perfusion (1).

Diagnosis

Mainly diagnosis of diabetic ketoacidosis is based on three major signs which are hyperglycemia, metabolic acidosis, and ketosis (9).

1 Glucose
The Joint British Diabetes Societies recommend a glucose cut-off of >11 mmol/L. A higher cut-off is recommended by the American Diabetes Association (>13.9 mmol/L) (28, 29).

2 Ketones
The more recent observational studies show a variation in 3-hydroxybutyrate levels to evaluate the presence of diabetic ketoacidosis (30-32).

3 Bicarbonate
The Joint British Diabetes Societies recommend venous bicarbonate (HCO3) below (15 mmol/l) (29).

4 Venous PH
The Joint British Diabetes Societies recommend a venous pH below (7.3) (29).

Family History

Family history is a useful and inexpensive tool to assess the risks of multifactorial diseases such as diabetes mellitus. It has enabled individualized disease prevention. Family history mainly examines whether these risks are independent of or moderated by sociodemographic factors such as (behavior, health, smoking, weight status, alcohol consumption, physical activity, and depressive symptoms). One study shows a strong relationship between family history and diabetes (33).

Symptoms

Diabetic ketoacidosis presents with vague symptoms such as nausea, vomiting, frequent urination, weakness, fatigue, shortness of breath, and pain in the abdomen. A characteristic symptom of diabetic ketoacidosis such as Kussmaul breathing presents in limited patients. Infections in diabetic patients should be carefully monitored as they are the most common precipitating factors for diabetic ketoacidosis (8).

Management

Diabetic ketoacidosis in an intensive care unit during the first 24-48 hours is always advisable. The management starts with optimizing hydration status, blood glucose concentration, precipitating factors, ketoacidosis, and electrolyte abnormalities such as sodium, chloride, and potassium. The current Guideline for diabetic ketoacidosis is to recommend starting fluid resuscitation with isotonic saline based on corrected serum sodium. Also, there is an option to use insulin either via intravenous or intramuscular, or even the subcutaneous route. This guideline focuses on the correction of electrolytes, especially potassium concentration in blood. Finally, Bicarbonate supplementation is recommended in case of acidosis with pH less than 6.9 (10, 11).

Management

1 Goal of Therapy
The goal of therapy includes identifying and treating the precipitating event, correcting acidosis and reverse ketosis, correcting dehydration, restoring blood glucose to near-normal levels, and avoiding complications of treatment (34)

2 Fluid Therapy
Diabetic ketoacidosis patients mostly will present dehydrated. The water deficit is about 100 mL/kg of body weight. Injectable fluid through an intravenous (IV) will expand the intravascular volume, improve renal perfusion, and reduce peripheral insulin resistance by reducing levels of counter-regulatory hormones such as growth hormone, cortisol, glucagon, and catecholamines. The final result will be a reduction in blood glucose levels (35-37).

3 Insulin Therapy
Insulin therapy will maintain diabetic ketoacidosis because of its effects in reduction of the production of liver glucose, also, its effects increase the utilization of peripheral glucose, and inhibit lipolysis, ketogenesis, and glucagon secretion. Results will be seen in lowering blood glucose concentration and the level of ketoacidosis production. Insulin protocol will be through starting with a bolus of regular insulin at a dose of 0.1 unit/kg body weight. Then within 5 minutes followed by a continuous infusion of regular insulin of 0.1 unit/kg/h. In children, a bolus dose of insulin before starting an intravenous infusion is not recommended, because it may lead to cerebral edema (38-40)

4 Electrolyte Therapy
Electrolyte therapy is considered when there is a deficiency of serum electrolytes in the body, especially, sodium, chloride and potassium. Mainly, the sodium level in the body should be around 7–10 mEq/kg, while potassium level should be in the range of 3–5 mEq/kg, and chloride should be between 3–5 mmol/kg (35, 36).

Monitoring

Close monitoring of blood glucose and potassium level is vital in the management of diabetic ketoacidosis patients, as high insulin doses result in hypoglycemia and hypokalemia whereas low doses may fail to suppress ketogenesis (20).

Complications

The most common complications include hypoglycemia, hypokalemia, hyperglycemia, and hyperchloremia. Less common complications include cerebral edema, fluid overload, acute respiratory distress syndrome, thromboembolism, and acute gastric dilation (41).

1 Hypoglycemia.
Hypoglycemia may occur secondary to an overdose of insulin administration (41).

2 Hypokalemia.
Hypokalemia may develop secondary to treatment with bicarbonate, and insulin. The rate of occurrence of hypokalemia is less common with a low dose of insulin regimens (41, 42).

3 Hyperglycemia
Hyperglycemia may occur if there is no proper administration of subcutaneous doses of insulin (41).

4 Cerebral Edema
Cerebral edema is a rare fatal complication of diabetic ketoacidosis that mainly occurs in pediatric patients (43).

5 Fluid Overload
Patients with cardiac or renal disease who receive rapid administration of fluid as a treatment for diabetic ketoacidosis may develop congestive heart failure. So in patients with a cardiac or renal disease the administration of intravenous fluids should be at a slow rate and more frequent while monitoring the fluid input and fluid output (44).

6 Acute Respiratory Distress Syndrome
Acute Respiratory Distress Syndrome is a rare fatal complication of diabetic ketoacidosis. It occurs from excessive fluid replacement, which may deposit in the lung and lead to pulmonary edema (42, 44).

Prevention

Diabetes Ketoacidosis prevention is a major role in managing diabetes and preventing recurrence. Prevention includes health education and awareness about the diabetes of the first signs and symptoms that will appear in the patient (45). Good hydration is considered one of the most important roles in the prevention of diabetes ketoacidosis. Additionally, blood glucose levels should be measured per hour and ketone concentration in the urine should be measured twice daily. Also, insulin shouldn't be stopped, even if the patient does not consume solid food or fluids (46, 47).

Special cases

1 Pregnancy
Diabetic ketoacidosis is a serious complication and is considered one of the major complications that affects pregnant women and it is associated with increased rates of perinatal morbidity and mortality (48). The onset of diabetic ketoacidosis in pregnancy can be insidious with lower glucose levels and usually progresses more rapidly as compared to non-pregnant patients. The morbidity and mortality rate can be reduced with early detection of precipitating factors such as infection, steroid administration for fetal lung maturation, inappropriate insulin cessation, inadequate insulin management, and intractable vomiting (49). Diabetic ketoacidosis in pregnancy requires targeted therapy with intensive monitoring. Also, the mortality rate increases if the disease is not detected early (50). Management principles include initiation of intravenous insulin therapy, correction of electrolyte abnormalities, correction of acidosis, management of precipitating factors, aggressive volume replacement, and monitoring of maternal-fetal response to treatment (51). The decision for delivery is considered challenging for the physician and must be considered based on gestational age as well as maternal-fetal responses to therapy (52). Prevention strategies for pregnant women should include education about diabetes related to pregnancy, the risks of diabetic ketoacidosis, and the precipitating factors (53).

2 Children
Diabetic ketoacidosis is a common life-threatening condition in children and it is associated mainly with newly diagnosed type 1 diabetes. Diabetic ketoacidosis has many causes but mainly it presents in the presence of type 1 diabetes, which usually appears as the first sign in childhood (54).

3 Chronic Kidney Disease
Diabetic ketoacidosis is considered less frequently in patients with chronic kidney disease, especially those on hemodialysis (55). Chronic kidney dysfunction is associated with improved glucose control because of its effect on the inhibition of kidney gluconeogenesis. Also, it has a role in decreasing insulin clearance and improving insulin sensitivity with dialysis (56).

Conclusion

Diabetic ketoacidosis is considered one of the important causes of hospitalization and mortality in diabetic patients. The most common causes are infections and non-adherence to insulin therapy. Proper management includes starting intravenous fluids, electrolytes replacement, insulin therapy, and treatment of precipitating causes. Also, to ensure better outcomes and prevent complications the patient's condition should be monitored continuously by regular clinical and laboratory analysis and applying management protocols. Finally, prevention includes the identification of risk factors for recurrence and structured educational programs.

Author Contribution:
'H. Karrar' supervised the team and direct the research. 'M. Nouh' wrote the introduction, epidemiology, complication, and Conclusion paragraph. 'R. Alhendi' will revise the article. 'O. Alsaedi' Wrote the introduction paragraphs. 'A. Sadah' Wrote the introduction paragraphs. 'N. Bahri' Wrote the introduction paragraph. 'M. Alharthi' Wrote the introduction paragraph. 'O. Aldhafeeri' Wrote the Epidemiology paragraph. 'S. Razqan' Wrote the Pathogenesis paragraph. 'M. Mojammami' Wrote the Diagnosis paragraph. 'H. Albalawi' Wrote the Management paragraph. 'M. Alsheikh' Wrote the Monitor paragraph. 'N. Abusharhah' Wrote the Management paragraph. 'S. Alzahrani' Wrote the Prevention paragraph. 'S. Seedahmed' Wrote the Special Cases paragraph. The authors had full access to the data and take full responsibility for its integrity of the data. All the authors gave their approval for the submission of the final manuscript.

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