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Literature Review: Diabetic Ketoacidosis

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Abstract

Diabetic ketoacidosis (DKA) is a serious complication of type 1 diabetes and sometimes type 2 diabetes, characterized by high blood sugar levels (hyperglycemia) and the buildup of ketones in the body. Ketones are products of the breakdown of fats in the abscense of insulin to use glucose for energy. DKA develops when blood glucose levels are too high and the body begins to break down fat for energy, leading to a buildup of ketones in the blood and urine. This can cause a number of serious symptoms, including extreme thirst, frequent urination, fatigue, nausea, vomiting, confusion, shortness of breath, and in severe cases, even coma. Treatment of diabetic ketoacidosis involves administration of insulin to correct blood sugar levels, as well as rehydration and correction of electrolyte imbalances. CAD is a medical emergency that requires immediate medical attention in a hospital.

Key words:

Introduction

Diabetic ketoacidosis and hyperosmolar hyperglycemic state are acute, life-threatening complications that occur in patients with diabetes mellitus. In addition to early identification, early and effective management of these pathologies leads to a reduction in the dreaded risk of morbidity and mortality to which the patient is exposed, this management includes fundamental pillars ranging from the use of intravenous (IV) insulin, aggressive management of IV fluids, to the correction of hydroelectrolyte and associated acid-base disorders. as the case may be.

Before objectively defining the parameters that make up these entities, the physician must be able to recognize in the first instance the diagnostic criteria for diabetes mellitus, since many times patients debut as diabetics with an acute complication, about 30-40% of people with diabetes are undiagnosed, and between 50% and 70% of cases diagnosed in the Americas are uncontrolled. (1)

Diagnostic Criteria for Diabetes Mellitus
1. Fasting blood glucose ≥126 mg/dL (7.0 mmol/L) (fasting: no caloric intake for 8 hours)

Or
2. Plasma glucose ≥200 mg/dL (11.1 mmol/L), with an oral glucose overload, this test should be performed as described by the WHO, using the equivalent of 75g of anhydrous glucose, dissolved in water.
Or
3. A1C ≥6.5% (48 mmol/mol). This test must be performed using the National Glycosylated Hemoglobin Standardization Program
Or
4. A patient with classic symptoms of hyperglycemia, or hyperglycemia crises, with a random glucose greater than or equal to 200mg/dl (11.1mmol/L).

taken from ADA 2023 (2)

Diabetes can be associated with acute complications that can lead to major alterations, such as precipitation of cardiovascular or cerebrovascular accidents, neurological injuries, coma and life-threatening, if not received urgent treatment. The acute complications of diabetes mellitus that are the subject of this review are: Diabetic Ketoacidosis (DKA), Hyperosmolar Hyperglycemic State (HH), both of which are the result of a decrease or absolute deficiency of insulin along with an increase in circulating concentrations of counterregulatory hormones. (3)

DKA was first described in 1886 by Dr. J. Dreschfeld, who described the symptoms and findings of the physical examination, as well as the presence of glucose, albumin, acetoacetic acid and beta-oxybutyric acid in the urine, as well as the characteristic acetone in both the urine and breath of the patients.(4)

Pathophysiology of diabetic ketoacidosis:

The main pathophysiological mechanism of DKA is based on the imbalance between the amount of insulin and counterregulatory hormones such as glucagon, cortisol, catecholamines, and growth hormone. Absolute or relative insulin insufficiency results in increased hepatic gluconeogenesis and glycogenolysis. An increase in catecholamine and cortisol levels leads to protein catabolism, which causes an increase in gluconeogenic amino acid precursors such as alanine, lactate, and glycerol. (4)

Additionally, there are numerous experimental and clinical studies that reveal how hyperglycemia and ketoacidosis lead to an inflammatory state characterized by the high production of pro-inflammatory cytokines in addition to the increase of markers of oxidative stress, severe hyperglycemia conditions the production of pro-inflammatory cytokines by macrophages, such as: tumor necrosis factor (TNF α), interleukin (IL)-6 and IL--1β, and C-reactive protein, which in turn lead to an alteration in secretion and decreased insulin sensitivity, the elevation of free fatty acids is secondary to an increase in lipolysis and a decrease in lipogenesis, these are converted into ketone bodies: β-hydroxybutyrate (β-HBOT), acetoacetate, and acetone, in addition This accumulation of free fatty acids also causes decreased insulin sensitivity; the altered production of nitric oxide leads to endothelial dysfunction, in conclusion an increased inflammatory response, oxidative stress and the generation of reactive oxygen species condition capillary alteration, cellular damage of lipids, membranes, proteins and DNA. (5)

Euglycemic DKA is another unique presentation of DKA that has been more recently described. The exact pathophysiology of euglycemic DKA is not well established; however, the clinical presentation is similar to DKA, glycemia is < 250 mg/dl. Euglycemic DKA has been linked to many factors, such as the treatment patients receive for diabetes, carbohydrate restriction, high alcohol consumption, and inhibition of gluconeogenesis, it can also be induced by certain medications, most commonly seen with sodium-glucose cotransporter 2 (SGLT-2) inhibitors and insulin.(6)

Precipitating causes:

Poor adherence to insulin treatment is one of the main causes for the development of DKA, followed by infectious processes among which urinary tract infections and pneumonia stand out,

in third order are non-infectious diseases, among which it is convenient to mention cerebrovascular diseases, acute myocardial infarction, alcohol abuse and pancreatitis; some drugs such as atypical antipsychotics, glucocorticoids, and diuretics may predispose to the onset of severe hyperglycemia, DKA, or hyperosmolar hyperglycemic state (HH).(5) (7)

Diagnosis:

Medical history and physical exam:

The clinical presentation includes signs and symptoms related to hyperglycemia, polydipsia, polyuria, polydipsia, weight loss, fatigue, in the most severe cases, alterations in the neurological state can be observed, which may be related to the level of acidosis, such as lethargy, stupor, loss of consciousness, and ventilatory compromise; Gastrointestinal symptoms, such as diffuse abdominal pain, nausea and vomiting, are also common, but usually resolve with established medical treatment.(8)

The physical examination should include the assessment of the neurological status, assessment of the blood volume, in addition to the general examination by apparatus and systems, patients generally present signs of volume depletion, such as hypotension, tachycardia, dysfunction of the turgor in the skin, dry mucous membranes, temperature should be evaluated, which may be altered by the presence of infectious processes, or peripheral vasodilation.(8)

Diagnostic criteria:

Criteria	**ADA**	**UNITED KINGDOM**	**AACE/ACE**
YEAR OF PUBLICATION	**2009***	**2013**	**2016**
Plasma glucose concentration mmol/L	>13.9 mmol/L (250mg/Dl)	>11 mmol/L (> 200mg/dL	N/A
pH	Mild 7.25 – 7.30 Moderate 7.00 – 7.24 Severe <7.00	<7.3 (Severe <7.00)	<7.30
Bicarbonate concentration. mmol/L or mEq/L	Mild 15-18 Moderate 10.14.9 Severe <10	<15(severe <5)	N/A
Anion gap Na^+ - (Cl^-+ HCO_3^-)	Mild >10 Moderate >12 Severe >12	NA (severe >16)	>10
Acetoacetate in Urine	Positive	Positive	Positive
Blood β-hydroxybutyrate. mmol/L	NA	≥3 (severe >6)	≥3.8 (40mg/dl)
State of Mind	Mild: Alert Moderate: alert or drowsy Severe: Stuporous	N/A	Drowsy, stuporous, or coma

AACE/ACE = American Association of Clinical Endocrinologists/American College of Endocrinologists.

ADA American Diabetes Society – *2019 Year Update on 2009 Guideline.

N/A does not apply

Table adapted from BMJ 2019; 365:L1114 DOI:10.1136/BMJ.L1114 (7)

Classification according to severity:

2009 ADA Criteria*	**SLIGHT**	**MODERATE**	**GRAVE**

Plasma glucose concentration mmol/L	>13.9 mmol/L (> 250mg/Dl)	>13.9 mmol/L (> 250mg/Dl)	>13.9 mmol/L (> 250mg/Dl)
pH	7.25 – 7.30	Moderate 7.00 – 7.24	<7.00
Bicarbonate concentration. mmol/L or mEq/L	15-18	10 - 14.9	<10
Anion gap Na^+ - (Cl^-+ HCO_3^-)	>10	>12	>12
Ketone Bodies in Urine	Positive	Positive	Positive
Ketone Bodies in Blood	Positive	Positive	Positive
State of Mind	Alert	Sleepy	Stuporous

From Abbas E. Kitabchi, et al, Hyperglycemic Crises in Adult Patients With Diabetes. Diabetes Care 1 July 2009; 32 (7): 1335–1343. https://doi.org/10.2337/dc09-9032 (9)

Treatment:

Treatment protocols should be flexible and simple to use by healthcare personnel, however, as the management of ketoacidosis is complicated, continuous and close monitoring of the patient is required, in order to make the modifications in medical treatment that are required based on the findings, it is important to know the updated management guidelines that are supported by scientific evidence. and not to substitute clinical judgment for this knowledge.

Successful treatment requires adequate management of blood volume with the consequent correction of dehydration, the use of insulin therapy for the correction of hyperglycemia and also the correction of electrolyte imbalances; All this while the identification of comorbid precipitating events is carried out; and above all, frequent follow-up of the patient; In this sense, we will divide medical treatment into the fundamental pillars that have been previously mentioned.

Volume Correction:

The administration of intravenous fluids is the key point to improve intravascular volume, it also facilitates the resolution of metabolic acidosis and improves peripheral organ perfusion in adults with diabetic ketoacidosis; the American Diabetes Society and UK guidelines recommend the use of saline for initial fluid replacement, administering an initial volume of 15-20 mL/kg per hour, about 1 to 1.5 L/hour in the first 2 to 4 hours (9)(10)

Once glucose reaches a value close to 200mg/dl, it should be rotated to 5% sodium chloride with sodium chloride 0.45%; The use of saline solution after initial fluid resuscitation may result in hyperchloremic metabolic acidosis, and this reduces the sensitivity and specificity of the use of serum bicarbonate as a marker to establish resolution of diabetic ketoacidosis.

Periodic evaluation of serum osmolarity, urinary output, and cardiac function should also be performed to guide aggressive fluid management and avoid iatrogenic fluid overload.

Insulin Use:

The use of insulin is a fundamental pillar in the treatment elements of diabetic ketoacidosis, decreases hepatic glucose production, improves the use of glucose in peripheral tissues, inhibits lipogenesis, ketogenesis, and glucagon secretion.

In adults, many protocols begin with the administration of an intravenous (IV) bolus of insulin, if there is any delay in obtaining peripheral venous access, the dose should be calculated based on the estimated weight 01 U/kg,

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