

Evaluation, Diagnosis, and Initial Management of Acute Diabetic Ketoacidosis (DKA)

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Received: January 03, 2021; Published: December 31, 2020

Abstract

Introduction: Diabetic ketoacidosis (DKA) is one of the most common and most serious acute complication of diabetes mellitus. Although diabetic ketoacidosis occurs with type 1 diabetes mellitus (DM), it may occur with type 2 under conditions of extreme stress. DKA could less commonly be the first presentation of type 2 DM; which would be called ketosis-prone diabetes mellitus.

Aim of the Work: This review sheds light on the initial evaluation and management of diabetic ketoacidosis. The management of hyperosmolar hyperglycemic state (HHS) is generally aligns with that of DKA.

Methods: A thorough systematic search and screening of medical literature were conducted by using PubMed and google scholar engines. All relevant article were reviewed and included.

Conclusion: The most common precipitating factors for diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS) are infection and inadequate adherence to insulin therapy. DKA is a triad of hyperglycemia, anion gap metabolic acidosis, and ketonemia. The glucose serum level is commonly less than 800 mg/dL (between 350 to 500 mg/dL. The serum glucose level could be normal or mildly elevated in few setting in such decreased oral intake, pregnancy, insulin use shortly prior to arrival to ED, or use of sodium-glucose co-transporter 2 (SGLT2) inhibitors. The management of diabetic ketoacidosis includes correction of fluid and electrolyte abnormalities and the administration of insulin. Correction of fluids and electrolytes entails the correction of hypovolemia, hyperosmolality, metabolic acidosis, and potassium depletion.

Keywords: DKA; Diabetic Ketoacidosis; Hyperglycemia; Evaluation; Management

Introduction

Diabetic ketoacidosis (DKA) is one of the most common and most serious acute complication of diabetes mellitus. Frequently, DKA and hyperosmolar hyperglycemic state (HHS) are addressed simultaneously due to similar pathogenesis and general approach of management. In addition, one-third of patients may demonstrate overlap between the two conditions [1]. The two conditions differ clinically in the presence of ketoacidosis and, sometimes, the degree of hyperglycemia [2]. Although diabetic ketoacidosis occurs with type 1 diabetes mellitus (DM), it may occur with type 2 under conditions of extreme stress. DKA could less commonly be the first presentation of type 2 DM; which would be called ketosis-prone diabetes mellitus.

DKA is encountered more commonly in patients younger than 65 years of age. On the other hand, older people are more prone to develop HHS [2]. Among patients with DM, the annual rate of hospitalization due to DKA was approximately 6.3 percent. In-hospital mortality rates declined between 2000 and 2014 from 1.1 percent to 0.4 percent [3]. Although HHS admission is less frequent than that of DKA, HHS is responsible for 10 times higher mortality rate; which ranges from 10 to 20 percent [4].

This review sheds light on the initial evaluation and management of diabetic ketoacidosis. The management of hyperosmolar hyperglycemic state (HHS) is generally aligned with that of DKA.

Methods

We have conducted a thorough systematic search and screening of medical literature. The search was conducted on PubMed and Google Scholar engines. No filters were applied and all relevant articles were reviewed. However, newly-published articles were meticulously appraised and used; greatly influencing this review. Terms used in the search process were DKA, diabetic ketoacidosis, hyperglycemia, evaluation and management.

Precipitating factors and suggestive features

The most common precipitating factors for diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS) are infection and inadequate adherence to insulin therapy [1,5]. Pneumonia and urinary tract infection are frequently incriminated types of infection. Inadequate water intake can promote the development of severe dehydration and HHS, especially in old patients with concomitant medical conditions [5]. Other precipitating factors associated with DKA and HHS include acute major illnesses such as myocardial infarction (MI), new-onset type 1 diabetes, drugs that affect carbohydrate, cocaine and psychological problems associated with eating disorders [6,7]. Some patients with type 1 DM wrongly omit insulin based on the belief that they should not use insulin when oral intake is reduced due to gastroenteritis. Examples of drugs that are associated with hyperglycemia include glucocorticoids, high dose of thiazide, sympathomimetic agents such as dobutamine and terbutaline and second-generation "atypical" antipsychotic agents [8]. Some reports suggested episodes of hyperglycemia with sodium-glucose co-transporter 2 (SGLT2) inhibitors, which are used mainly for type 2 DM and often used off-label in type 1 diabetes; the exact mechanism of pathogenesis is complex [9]. Young patients with type 1 diabetes and psychological problems associated with eating disorders are particularly prone to non-adherence to insulin therapy due to psychological problems associated with eating disorders; examples include the fear of weight gain, fear of hypoglycemia, rebellion from authority and the stress of chronic disease.

Polyuria, polydipsia, and weight loss are the common symptoms of marked hyperglycemia. These symptoms start acutely and develop rapidly over a 24-hour period in case of diabetic ketoacidosis (DKA). On the other hand, HHS symptoms tend to be more insidious. Neurological symptoms start to appear with prolonged duration and high level of hyperglycemia; these include lethargy, focal signs, and obtundation. These are most commonly seen with HHS and may progress to coma if persisted. DKA, in contrast, is primarily associated with hyperventilation and abdominal pain.

Neurologic manifestation start to appear typically when effective plasma osmolality (Posm) is above 320 mosmol/kg [1]. As HHS is associated with higher degree of effective Posm, mental obtundation and coma are more frequently seen in HHS compared with DKA [10]. Seizures and focal signs such as hemiparesis and hemianopsia may occur [10]. In patient with DKA, mental obtundation may occur with lesser degree of hyperosmolality, when severe acidosis present [11]. However, severe neurologic features with low effective Posm (< 320 mosmol/kg) demand immediate consideration of other causes of the mental status change.

Gastrointestinal symptoms such as nausea, vomiting and abdominal pain could be the initial presentation in patient DKA. These symptoms are more common in children and may be seen less frequently in adults [12]. In contrast, HHS is unusually manifested by abdominal pain. On review of 189 consecutive episodes of DKA and 11 episodes of HHS found no abdominal pain with HHS compared with 46 percent in patients with DKA [13]. Abdominal pain was directly correlated to the severity of the metabolic acidosis; 86 percent of those with a serum bicarbonate ≤ 5 mEq/L had abdominal pain compared with only 13 percent of patients with a serum bicarbonate ≥ 15 mEq/L. The severity of hyperglycemia and/or dehydration is not correlated with incidence of abdominal pain. Explanation of abdominal pain include acidosis-caused delayed gastric emptying and ileus and associated electrolyte abnormalities [1].

Clinical examination of patients suspected to have DKA or HHS yields signs of dehydration; these include decreased skin turgor, dry axillae, dry oral mucosa, low jugular venous pressure, tachycardia and if severe, hypotension. Previously mentioned neurologic findings could be noted in clinical examination, especially in patients with HHS. Characteristic odor (fruity) of DKA patients' exhalation could be noticed due to acetone; the smell is similar to that of nail polish remover. Deep respiration is another respiratory finding in these patient.

Evaluation and diagnosis

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are considered emergency complications of DM that require early recognition and rapid response. The initial evaluation should include hydration, cardiorespiratory, volume, and mental status. Cautious history and examination should be done rapidly and focus on: airway, breathing, and circulation (ABC) status; mental status; possible precipitating events; volume status and the presence of shock. Simultaneously, Laboratory evaluation should be performed. The beneficial initial tests include serum glucose, serum electrolytes, complete blood count (CBC) with differential, urinalysis and urine ketones by dipstick, serum ketone if urine ketone was positive, plasma osmolality (Posm), arterial blood gas (ABG) if bicarbonate is markedly low, and electrocardiogram (ECG). Other possible tests that could be performed on individualized basis include cultures of urine, sputum, and blood, serum lipase and amylase, and chest radiograph. Culture is useful when infection is suspected. It is worth noting that infection may exist without fever in these patients [2].

The fundamental laboratory findings in DKA and HHS are hyperglycemia and hyperosmolality. High anion gap metabolic acidosis is also evident in patient with DKA. Other findings may vary according to the level of hyperglycemia, insulin deficiency, osmotic diuresis, and fluid intake.

In patient with HHS, it is usual to detect serum glucose concentration ≥ 1000 mg/dL (≥ 56 mmol/L) [14]. By contrast, the serum level of glucose is generally less than 800 mg/dL (44 mmol/L) in patient with DKA and may even be to the level of 350 mg/dL. Euglycemic diabetic ketoacidosis is term used to indicate DKA with normal or near normal serum glucose. This particularly occurs in patients with poor oral intake, received insulin prior to arrival, in pregnant women, and with sodium-glucose co-transporter 2 (SGLT2) inhibitors [9].

Acetoacetic acid, β -hydroxybutyric acid, and acetone are the 3 types of ketone bodies that accumulate in DKA. Serum testing for ketone is generally performed after positive urine testing. Urine ketone bodies are detected with nitroprusside tests, while serum ketones can be detected with either a nitroprusside test or by direct assay; the latter is preferred for monitoring response to therapy particularly. Nitroprusside test reacts with acetoacetate and acetone but not with beta-hydroxybutyrate. The ratio of latter to the former could be as high as 10:1 in severer ketosis, false-negative nitroprusside test may occur, yet unusual [15]. On the other hand, false-positive urine test for ketone

can be false-positive in case of drugs containing free sulfhydryl groups that react with nitroprusside such as captopril. Recently, measuring serum level of beta-hydroxybutyrate has replaced nitroprusside tests and several instrument are available commercially [15,16]. Although this overcomes the problem of nitroprusside method, it carries a limitation that some of these assays are not quantitated above a level of 6 mEq/L.

Serum anion gap is calculated by measuring the sodium, chloride, and bicarbonate as the following equation: Serum anion gap = Serum sodium - (serum chloride + bicarbonate). Typically, the level of serum bicarbonate is moderately to severely reduced in DKA. On the other hand, the level is normal or slightly reduced in HHS. Hence, DKA usually manifests with a serum anion gap greater than 20 mEq/L mainly due to accumulation of beta-hydroxybutyric and acetoacetic acids. This increase may be affected by many contributors as the rate and duration of ketoacid production, the rate of metabolism and loss, and the volume of distribution of these anions. Hyperventilation occurs to compensate the fall in pH, however, pH may be seen below 7 in severe case of ketoacidosis, especially if hyperventilation is compromised as in pneumonia.

Plasma osmolality (Posm) is largely determined by the level of glucose and sodium in plasma. It is always elevated in hyperosmolar hyperglycemic state (HHS), usually > 320 mosmol/kg (normal 275 to 295 mosmol/kg). In DKA, however, Posm is variable. Water moves across cell membranes to maintain equilibrium in osmolality as the effective osmoles do not penetrate most cell membranes. Ineffective osmoles include urea; urea is rapidly permeable across most cell membranes and its accumulation does not induce major water shifts of water. When Plasma osmolality is measured by a freezing point reduction ohmmeter, the result is the total osmolality and ineffective osmoles should be subtracted to estimate the effective Posm.

The sodium (Na) is typically lower than normal (hyponatremia) in most patients with DKA and HHS [17]. Although physiologic calculations indicate that the serum level of Na should fall by approximately 1.6 mEq/L for each 100 mg/dL increase in glucose concentration, but the marked osmotic diuresis occurs in patients with HHS may lead to a normal or even elevated serum Na concentration, despite a markedly elevated serum glucose concentration [18]. Hence, these patient have a high level of the both effective osmoles and consequently a markedly elevated effective Posm, which, in turn, leads to neurologic symptoms that can include seizures and coma. Inadequate water intake aggravates the problem of hyperosmolality and is a particular problem in hot weather and in older individuals [19].

Similar to Na, patients with DKA and HHS have a potassium (K) deficit that ranges between 3 to 6 mEq/Kg [17]. This is resulted from increased urinary loss and the excretion of potassium ketoacid anion salts. In spite of this deficit, only 5 percent of patients will demonstrate observed hypokalemia [20]; one-third may even show elevated level of potassium concentration due to the shift of intracellular K to extracellular fluid [14,17]. This is due to a shift of potassium from intracellular fluid to extracellular fluid (ECF) caused by hyperosmolality and insulin deficiency [17]. Typically, uncontrolled hyperglycemia is associated with negative phosphate balance. The main causes are decreased phosphate intake, shift of phosphate into the ECF with metabolic acidosis and phosphaturia caused by osmotic diuresis. In a manner that follows that of potassium, the serum phosphate concentration at presentation is frequently normal or even high because insulin deficiency and extracellular shift of phosphate [21]. Once treatment with insulin and fluids is begun, the true state of phosphate and potassium will be unmasked. According to one review of 69 case of DKA, the mean serum phosphate concentration fell from 9.2 mg/dL at presentation to 2.8 mg/dL after 12 hours of admission; some patients even had a level as low as 1 mg/dL [21].

In contrast to serum electrolytes, most cases of uncontrolled hyperglycemia present with acute elevations in the BUN and serum creatinine concentration. This is believed to result from the reduction in glomerular filtration rate induced by hypovolemia. It is been suggested that high acetoacetate levels can also increase the reading of serum creatinine levels with some colorimetric assays devices. As most of laboratories depend now on enzymatic assays, this becomes less encountered. Leukocytosis proportional to the degree of ketonemia is typically seen in the setting of hyperglycemic emergencies. However, a white blood cell (WBCs) count greater than 25,000/microL or >10 percent higher band count should raise the suspicion for infection and should be evaluated. Hyperlipidemia may also present in patients with DKA or HHS.

Diagnostic criteria

The differentiation between Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) could be made by the presence or absence of ketoacidosis and usually greater degree of hyperglycemia in HHS [2,14]. The American Diabetes Association (ADA) has proposed diagnostic criteria for HHS and 3 stages of DKA: for mild, moderate, and severe. Characteristically, DKA is a triad of hyperglycemia, anion gap metabolic acidosis, and ketonemia. The glucose serum level is commonly less than 800 mg/dL (between 350 to 500 mg/dL) [14]. An exception is comatose patient which may show a glucose level higher than 900 mg/dL. The serum glucose level could be normal or mildly elevated in few setting in such decreased oral intake, pregnancy, insulin use shortly prior to arrival to ED, or use of sodium-glucose co-transporter 2 (SGLT2) inhibitors.

Patients with hyperosmolar hyperglycemic state (HHS) have a little or no ketoacid accumulation. In addition, the serum glucose concentration is markedly elevated (more than 1000 mg/dL), the plasma osmolality (Posm) could be as high as 380 mosmol/kg, and neurologic abnormalities are frequently [2,14]. Most patients with HHS have serum pH > 7.30 and a serum bicarbonate > 20 mEq/L on admission.

Treatment

The management of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) follows a very similar pattern. This includes correction of fluid and electrolyte abnormalities and the administration of insulin [2]. Correction of fluids and electrolytes entails the correction of hypovolemia, hyperosmolality, metabolic acidosis (in DKA), and potassium depletion.

Fluids therapy

The initial step in the treatment of DKA or HHS is infusion of fluid to correct hypovolemia and stabilize cardiovascular status. Corrections of hypovolemia increases the response to insulin therapy by lowering the plasma osmolality (Posm), reducing vasoconstriction and improving perfusion, and reducing stress hormone levels [22]. The choice of fluid is determined by the presence and degree of potassium deficit. Isotonic saline is the initial fluid if choice. Dextrose is added to fluids regimen in patient with euglycemic DKA as these patient to avoid hypoglycemia with insulin therapy. Generally, dextrose is added to fluids regimen when the serum glucose declines to 200 mg/dL. The rate of fluids infusion depends on patient's status. When patient presents with hypovolemic shock, saline should be administered very quickly. In hemodynamically stable patients without heart failure, isotonic saline is infused at a rate of 15 to 20 mL/kg per hour for the first couple of hours but at maximum rate of 50 mL/kg in the first four hours [2]. The rate of fluids infusion in the following hours depends on patient status and response.

Potassium replacement

Following fluids, the effort should be directed toward correcting potassium deficit if the serum potassium is lower than 5.3 mEq/L and the urine output is adequate. Typically, almost all patients with DKA or HHS have a marked deficit in total body potassium despite the normal or even mildly elevated level. This is largely due to insulin deficiency and hyperosmolality, each of which cause potassium movement out of the cells [17]. The usual dose of potassium is 20 to 40 mEq/hour added to a liter of saline. This could be repeated until the serum concentration is higher than 3.3 mEq/L [23]. When the level of K ranges between 3.3 and 5.3 mEq/L, a lower dose of potassium (20 to 30 mEq) is added to each liter of fluid and repeated until the measured level is 4 to 5 mEq/L. Potassium should not be added if the first test shows a higher level than 5.3 mEq/L, until it falls with fluids and insulin therapy. Potassium salts affect the osmolality of fluids. Hence, the clinician should be aware of the total amount added and adjust the type of IV fluids accordingly. Additionally, administration of insulin rapidly affects the distribution of potassium and can result in an often dramatic fall in the serum potassium concentration, despite potassium replacement [23]. Patient with limited renal function and/or low urine output should be managed very cautiously with potassium, when necessary.

Insulin

All patient presenting with moderate to severe DKA should receive a low dose of intravenous insulin as long as the serum potassium is 3.3 mEq/L at least. Insulin should be delayed in patient with lower level of serum potassium until potassium replacement has begun and the serum potassium concentration has increased. This is based on the fact that insulin shifts potassium intracellularly which would worsen hypokalemia. Hypokalemia could trigger fatal cardiac arrhythmia, cardiac arrest, and cause respiratory muscle weakness [2]. Both regular insulin and rapid-acting insulin analogs are equally effective in the setting of DKA management [24]. However, the lower cost of regular insulin makes it the commonly preferred choice. Intermediate- and long-acting insulin have no role in the acute management of DKA. Nevertheless, they may be administered prior to discontinuation of IV insulin, to ensure adequate insulin level. The exception from this is with mild case of DKA, due to missed doses of basal insulin, where intermediate- or long-acting insulin can be administered at the initiation of treatment, along with rapid-acting insulin. Regular insulin could be administered an IV bolus of at a dose of 0.1 units/kg body weight, followed within five minutes by a continuous infusion of 0.1 units/kg per hour [25].

Metabolic acidosis

There is no consensus on the exact indication of bicarbonate in the setting of DKA due to lack of strong evidence suggesting benefits [26,27]. However, selected patients may benefit from cautious bicarbonate therapy [28]. First, patients with marked acidosis ($\text{pH} \leq 6.9$) who are prone to impaired tissue perfusion caused by whom decreased cardiac contractility and vasodilatation. Second, patients presenting with markedly-high, life-threatening level of potassium (hyperkalemia) since bicarbonate administration may promote potassium shift into cells. The level of K that justifies bicarbonate administration is > 6.4 mEq/L [29].

Conclusion

The most common precipitating factors for diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS) are infection and inadequate adherence to insulin therapy. Frequently, DKA and hyperosmolar hyperglycemic state (HHS) are addressed simultaneously due to similar pathogenesis and general approach of management. In addition, one-third of patients may demonstrate overlap between the two conditions. The differentiation between Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) could be made by the presence or absence of ketoacidosis and usually greater degree of hyperglycemia in HHS. DKA is a triad of hyperglycemia, anion gap metabolic acidosis, and ketonemia. The glucose serum level is commonly less than 800 mg/dL (between 350 to 500 mg/dL). The serum glucose level could be normal or mildly elevated in few setting in such decreased oral intake, pregnancy, insulin use shortly prior to arrival to ED, or use of sodium-glucose co-transporter 2 (SGLT2) inhibitors.

The management of diabetic ketoacidosis includes correction of fluid and electrolyte abnormalities and the administration of insulin. Correction of fluids and electrolytes entails the correction of hypovolemia, hyperosmolality, metabolic acidosis, and potassium depletion.

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Volume 17 Issue 1 January 2021

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