Review Article

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Hyperglycemic Crises: A General Review

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ABSTRACT

The hyperglycemic emergencies, diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are potentially fatal complications of uncontrolled diabetes mellitus. DKA accounts for 8% to 29% of all hospital admissions with a primary diagnosis of diabetes. The incidence of DKA continues to increase. The rate of hospital admissions for HHS is lower than for DKA and is less than 1% of all diabetic-related admissions. The mortality rate for DKA has been falling over the years but contrary to the trend in DKA mortality rate, the mortality rate of HHS has remained alarmingly high. DKA consists of the triad of hyperglycemia, ketonemia, and metabolic acidosis, and HHS consists of hyperglycemia and sensory disturbances that can often be present without coma. Although DKA and HHS often are discussed as separate entities, they represent points along a spectrum of emergencies caused by poorly controlled diabetes. In this article, we present a review of this main complications of diabetes.

ABBREVIATION: DKA: Diabetic Ketoacidosis; HHS: Hyperglycemic Hyperosmolar State; T1DM: Type 1 Diabetes; T2DM: Type 2 Diabetes. KPDM: Ketosis-Prone Diabetes Mellitus; FFAs: Free Fatty Acids; IL-6 interleukin-6; SGLT2: Sodium-Glucose Cotransporter-2 Inhibitors; ICU: Intensive Care Unit; ARDS: Acute Respiratory Distress Syndrome

INTRODUCTION

Diabetes mellitus is a disease with an important impact worldwide. Approximately 9.3% (463 million) of the world's population have the disease [1]. Hyperglycemia is Hyperglycemia is a common diagnosis in emergency department patients. Emergency department physicians are often faced with patients with hyperglycemia and challenges related to their care.

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are acute severe metabolic complications and life-threatening hyperglycemic emergencies in diabetes. They can have devastating consequences. Hospital admission and mortality due to DKA is high in developing countries, with incidence reported of about 80 per 1000 diabetic admissions and mortality rate of 30%. The mortality rate in patients with HHS is also high throughout the world, remaining between 5% and 20% in developed countries. Timely diagnosis and management in the emergency room is very important to improve patient outcomes [2,3].

Both DKA and HHS can occur in patients with type 1 diabetes (T1DM) and type 2 diabetes (T2DM). DKA occurs mainly in T1DM, is more common in young people especially children and adolescents. However, about one-third of DKA cases occur in T2DM under conditions of stress and as a presenting manifestation of a disorder

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called ketosis-prone diabetes mellitus (KPDM) [4]. HHS is more frequent in adult and elderly patients (range 57- 69) with T2DM often nursing home residents but can be seen in T1DM patients with DKA. In these patients, it often presents as a mixed state, DKA-HHS, rather than HHS alone.

The mortality of HHS is due to older age, more severe hyperglycemia, hyperosmolality, dehydration and relevant comorbidities. Features of the 2 disorders with ketoacidosis and hyperosmolality may also coexist [5]. Early diagnosis and management are the key to improving patient outcomes. The bases of treatment in both are aggressive rehydration, electrolyte replacement, insulin therapy, and to find and treat the underlying triggering events.

The first detailed clinical description of a hyperglycemic crisis was reported by August W von Stosch in 1828, including polydipsia, polyuria, very high urine glucose, and altered mental status [6]. There are also many case reports of adult patients with a diagnosis of diabetes who presented an acute clinic of polyuria, polydipsia, coma, deep and frequent respiration (Kussmaul), glycosuria and severe dyspnea and death [7,8]. Kussmaul breathing rapidly became a typical sign of "diabetic coma" [9]. Dr Julius Dreshfeld in 1886 was the first to describe the 2 different categories of "diabetic coma", Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS); [10]. The mortality rate of patients with DKA, before the discovery of insulin in 1921, was greater than 90% [11]. After that, the mortality rate associated with "diabetic coma" dropped significantly and is currently less than 2% in patients for DKA [12,13] and between 5% and 16% in patients with HHS [14].

DKA in patients with T1DM represents one-third of all cases, and the patients with the highest risk are those who have longer diabetes duration, adolescents, and girls [15,16]. HHS regularly occurs in older patients with T2DM with an associated illness such as ischemic events, infection, surgery, and has higher mortality than DKA; however, HHS is recognized as a major problem in children and young adults [17]. The cause of death in patients with DKA and HHS rarely results from the metabolic complications of hyperglycemia or metabolic acidosis, but it is related to the underlying precipitating cause, advanced age and severity of dehydration [18,19].

DKA is the initial presentation of diabetes in approximately 15% to 20% of adults and in approximately 30% to 40% of children with T1DM. The main triggering causes of DKA reported worldwide are omission or inadequate dosing of insulin, acute illness, and newly diagnosed diabetes mellitus. The second most common cause of DKA are infections, especially urinary tract and pulmonary. Noninfectious acute illnesses such as acute neurovascular accidents, myocardial infarction, trauma, drugs (corticosteroids, thiazides, alcohol abuse, cocaine, cannabis, others) and pancreatitis and unknown cause accounting for up to 4% [20-22]. The lack of adherence to treatment is the leading cause mainly in young patients [23,24]. The main triggering causes of HHS are infection (Urinary tract infection and pneumonia), acute cardiovascular events, poor adherence to medication but it is less common [25].

PATHOPHYSIOLOGY

The characteristic of DKA and HHS is hyperglycemia, which results from insulin resistance or deficiency of insulin secretion from the pancreas. Under normal conditions, blood glucose concentration is controlled by the opposing functions of insulin and glucagon. In the postprandial state blood glucose levels increase and insulin is secreted in the pancreas. Insulin inhibits lipolysis, maintains normoglycemia and inhibits glucagon secretion [26].

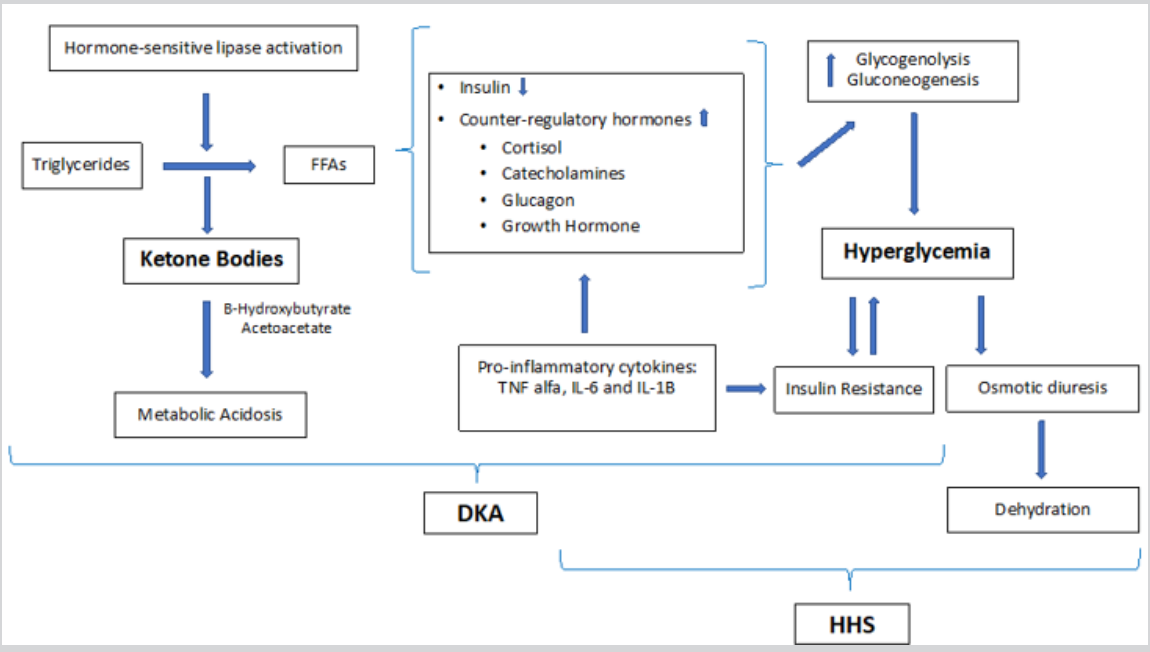

Figure 1: Pathogenesis of hyperglycemic emergencies.

In DKA, the driving force is insulin insufficiency and a subsequent increase in insulin counterregulatory hormones which prevents the body from metabolizing carbohydrates [27]. Under normal conditions, insulin stimulates the transfer of glucose from the blood to the body's tissues, where it is needed for storage, lipogenesis, glycogen and energy production. Insulin also inhibits hepatic gluconeogenesis, preventing further glucose production by the body [28]. When there is no insulin, hepatic gluconeogenesis continues, yet glucose cannot move into the cells and instead builds up in the bloodstream. The primary pathophysiologic mechanisms

for DKA and HHS are relevant insulin deficiency with insulin resistance created by elevated levels of counterregulatory hormones (cortisol, catecholamines, glucagon, and growth hormone) that oppose insulin and result in hyperglycemia and accumulation of ketone bodies (Figure 1). All contribute, but glucagon is the main responsible for hyperglycemia and ketoacidosis. This produces the activation of hormone sensitive lipase in adipose tissue and converts triglyceride into glycerol and free fatty acids (FFAs); [29]. In DKA, these are oxidized to ketone bodies (beta-hydroxybutyric acid and acetoacetic acid) in the liver by stimulation by glucagon [30,31] and increased glucagon/insulin ratio which reduces the activity of the enzyme (malonyl coenzyme A) that regulates movement of FFA into the hepatic mitochondria where the ketone bodies have the oxidation. The decreased metabolism and clearance of these ketone bodies also contribute to ketoacidosis. All this produces a decrease in serum bicarbonate concentration and metabolic acidosis. The HHS state presents higher insulin levels, lower levels of counterregulatory hormones and FFAs, and inhibition of lipolysis by the hyperosmolar state, which inhibits ketogenesis and limit metabolic acidosis. Also, due to insulin deficiency, gluconeogenesis is increased, glycogenolysis es accelerated, and there is impaired use of glucose by peripheral tissues. Hyperglycemia causes osmotic diuresis that produces electrolyte loss, hypovolemia, and decreased glomerular filtration rate which further worsens hyperglycemia and metabolic acidosis [32]. Respiratory compensation occurs with rapid deep breathing, called Kussmaul respirations.

The presence of hyperglycemia and ketoacidosis produces an inflammatory state characterized by an increase in proinflammatory cytokines and growth of oxidative stress markers. Severe macrophage-induced hyperglycemia produces proinflammatory cytokines such as interleukin (IL)-6 and IL-1, tumor necrosis factor alpha, and C-reactive protein, leading to impaired insulin secretion as well as reduced insulin secretion. of insulin sensitivity [33-35].

KETOSIS-PRONE TYPE 2 DIABETES MELLITUS

DKA occurs predominantly in patients with T1DM, but about one-third of DKA episodes occur in patients with T2DM who have a heterogeneous syndrome known as Ketosis-prone type 2 diabetes mellitus (KPDM). Patients with DKA have clinical and metabolic features of T2DM.

"EUGLYCEMIC" DKA OWING TO SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS (SGLT2)

In DKA, hyperglycemia is defined by a glucose level greater than 250 mg/dl, but there are some cases of DKA with normal or moderately elevated glucose levels, which is called "euglycemic" DKA. This type of DKA has been reported more frequently since the first-in-class SGLT2 inhibitor was introduced in 2013. Has been reported in patients with T2DM, and mainly in T1DM when these medications were used off-label. Diagnosis is often missed due to the absence of marked hyperglycemia [36]. The mechanisms are not clearly understood, it appears that a high glucagon: insulin ratio shifts the use of substrates from carbohydrates to lipids, promoting lipolysis and ketogenesis but far from hyperglycemia [37].

A mixture of DKA-HHS may occur. Additionally, these 2 disorders must be differentiated from other causes of hyperglycemia, metabolic acidosis, ketosis, and metabolic encephalopathy that may also overlap or coexist with DKA or HHS (Table 1).

Table 1: Diagnostic criteria for DKA and HHS.

	DKA			HHS
Measure	**Mild**	**Moderate**	**Severe**	
Plasma Glucose (mg/d)	>250	>250	>250	>600
Arterial pH	7.25 to 7.30	7.00 to <7.24	<7.00	>7.30
Serum Bicarbonate (mEq/L)	15 to 18	10 to< 15	<10	>18
Urine or Serum Ketones	Positive	Positive	Positive	Small
Urine or Scrum b* Hydroxybutyrate (mmol/l)	>3.0	>3.0	>3.0	<3.0
Effective Serum Osmolality	Variable	Variable	Variable	>320 mOsm/kg
Anion Gap	>10	>12	>12	Variable
Mental Status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

DIAGNOSIS

Diabetic Ketoacidosis

The signs and symptoms of DKA develop quickly, acute onset (usually over 24 hours or less) with polyuria, polydipsia, asthenia and adynamic, and weight loss (because fluid and electrolyte losses and anorexia). Acidosis also causes diffuse abdominal pain (may be confused with other pathologic conditions e.g., pancreatitis) nausea, vomiting in up to two-thirds of patients and strongly correlated with the severity of acidosis; weakness, and neurologic changes ranging from drowsiness/lethargy to obtundation and coma depending on severity, usually at levels greater than 320 mOsm/kg, in less than 25% of the patients [38]. It usually presents dehydration, hypotension, tachycardia, Kussmaul respirations and breath with a classic fruity odor (acetone). DKA occurs more frequently in T1DM than T2DM. An important clinical complication of DKA that occurs primarily in children is cerebral edema.

Laboratory Findings

There is a triad in the laboratory findings: hyperglycemia, ketonemia and metabolic acidosis. The severity of DKA is determined by the degree of acidemia and extent of neurologic impairment, as mild, moderate, or severe, and not by the severity of hyperglycemia, which may be mild [39]. Most patients with DKA are present with mild to moderate DKA. Some patients show only mild elevations in plasma glucose levels, lower than 250 mg/dl termed "euglycemic DKA". (39). Other key diagnostic criterion is an elevated circulating total blood ketone predominantly beta-hydroxybutyrate

and acetone and high anion gap metabolic acidosis of greater than 12. In DKA, the gap is often greater than 20 mEq/L. [40,41]. Not all patients with ketoacidosis have DKA, for example, the presence of ketoacidosis without hyperglycemia in an alcoholic patient is virtually diagnostic of alcoholic ketoacidosis.

The passage of water from the intracellular to extracellular space due to hyperglycemia reduces the serum sodium concentration, for this reason the correct concentration of sodium must be calculated with a formula (Box 1). There is also a change from intracellular to extracellular compartment of phosphorus and potassium. The latter should also be corrected according to acidosis (Box 1).

Box 1: Formulas for calculate.

- **Effective osmolality:** sodium ion (mEq/L) x 2 + glucose (mg/dL)/18.
- **Serum sodium corrected:** adding 1.6 mg/dL to the measured serum sodium for each 100 mg/dL of glucose greater than 100 mg/dL. (3)
- **Anion gap:** [Na-(Cl+HCO3)]
- **Serum potassium corrected during acidemia:** [K]+(0.6mEq/L per 0.1 drop in pH)

Leukocytosis, usually <15,000/mL, is frequent in DKA in the absence of bacterial infection, attributed to stress and dehydration, and correlates with the degree of ketonemia. Higher levels and/or more than 10% bands suggest an underlying infection. Glucose should be measured every hour (maybe with glucometer) until stabilized, and renal function, electrolytes, and venous pH should be assessed every 2 to 4 hours. The best way to assess the severity of metabolic acidosis is the blood pH arterial or venous.

Hyperglycemic Hyperosmolar State (HHS)

The majority of patients with HHS have an insidious onset of several days to weeks, the longer duration contributes to the more severe hyperosmolality, hyperglycemia and dehydration compared with DKA. Polyuria, polydipsia, weakness, blurred vision, and progressive deterioration of mental status (from drowsiness/lethargy to coma and seizures) also occur. There is a linear relationship between osmolality and the degree of altered state of consciousness. HHS is more frequent in T2DM than T1DM, in geriatric patients average age 60, range 57–69, often institutionalized with an infection or acute illness with delay in seeking medical care. There is often hyperglycemia, hyperosmolarity and dehydration more severe than those seen in CAD, and absence of ketoacidosis [42]. Abdominal pain, nausea, and vomiting are rare, and there is no Kussmaul breathing unlike DKA. The mortality is 10 times higher than the mortality of CAD and is between 5% to 20%. HHS is triggered by many of the same factors as DKA, mainly acute stress and comorbidities, but the main cause is infection [43].

For HHS the diagnostic criteria in laboratories are plasma glucose greater than 600 mg/dL, and effective osmolality greater than 320 mOsm/kg, the absence of acidosis in arterial gases (pH greater than 7.3, bicarbonate of greater than 18 mEq/L), absence of ketones in blood and urine, and variable anion gap. The effective plasma osmolarity is also calculated with a formula (Box 1); [44]. Serum potassium concentration is usually elevated due to increased water losses as in DKA (Box 1). The elevated serum sodium indicates severe dehydration [45]. Management of hyperglycemic crises.

There is an algorithm for the management of hyperglycemia crises that is used worldwide. It is the algorithm The American Diabetes Association (Figure 2). Treatment goals include correction of dehydration, hyperglycemia, hyperosmolality, electrolyte imbalance, and increased ketonemia (acidosis), as well as identification and treatment of underlying causes and altered comorbidities.

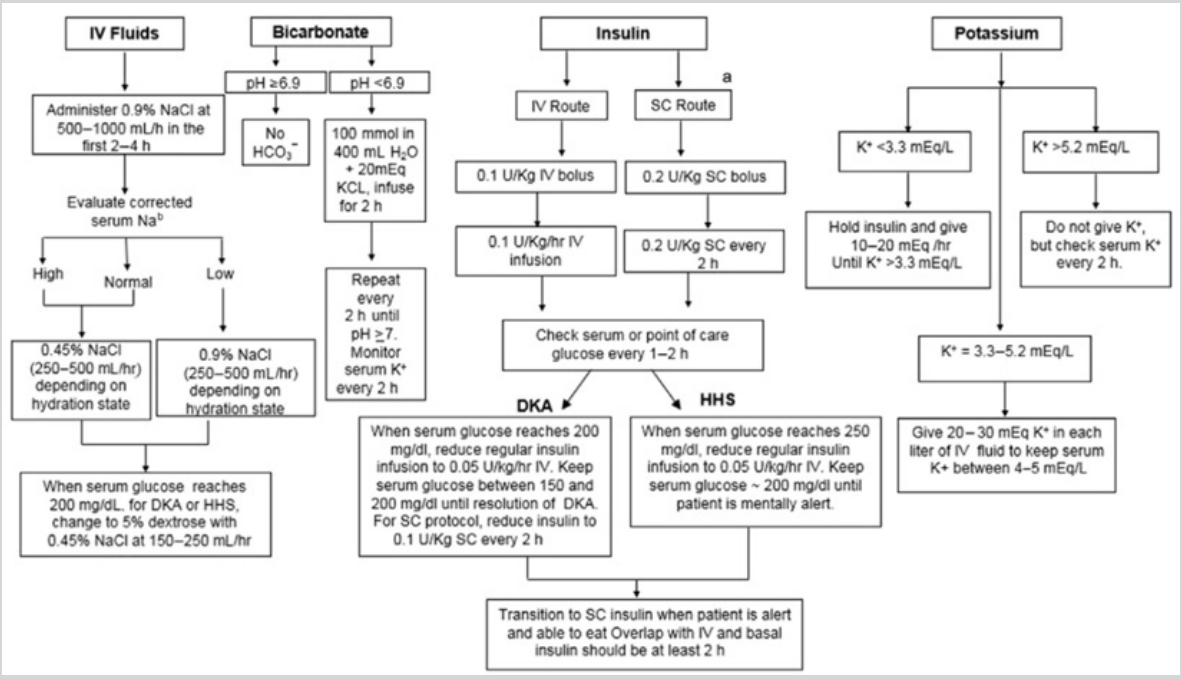

Figure 2: The American diabetes association algorithm for the management of hyperglycemic emergencies.

Most patients with uncomplicated diabetic ketoacidosis can be treated in the emergency room with close nursing supervision and monitoring, or in intermediate care units. Several studies have shown no clear benefit in treating CAD patients in the intensive care unit (ICU) compared to intermediate care units [46,47]. Likewise, admission to the ICU of patients with uncomplicated CAD has been associated with more laboratory tests and higher hospitalization costs [48]. Thus, the recommendation is that only patients with severe or complicated diabetic ketoacidosis, HHS with altered state of consciousness, or those patients with critical illness as a precipitating cause (i.e., sepsis, myocardial infarction, gastrointestinal bleeding, etc.) should be treated in the ICU.

The principles of treatment of HHS are very similar to those of DKA except for the correction of acidosis. But there are some differences: Fluid resuscitation in HHS must be more aggressive because the average loss is 9 L, compared to less than 6 L in DKA [49]. It is important to replenish intravascular volume prior to insulin administration. The rate of decrease in plasma osmolarity should be slow, with a recommendation to reduce to <3 mOsm/kg/h, because too rapid a reduction can cause cerebral edema. Slow continuous IV infusion of insulin at 0.1 units/kg/h is given as with DKA. The average time to resolution is between 10 and 18 hours for DKA [50,51] and approximately 9 and 11 hours for HHS [52]. During treatment it is important to monitor vital signs, volume, and rate of fluid administration, insulin dosage, and urine output to assess response to medical treatment. Laboratories such as electrolytes, BUN, creatinine, venous pH, bicarbonate, and anion gap should also be repeated every 2 to 4 hours until they stabilize. Glucose (glucometer) should be checked hourly.

Fluid Therapy

Intravenous (IV) fluids are a critical aspect of therapy because they expand intravascular volume, reduce insulin resistance, and restore renal perfusion. Replacement should begin with rapid IV infusion of solution isotonic saline (0.9% NaCl), with an initial rate of 500 to 1000 mL/h during the first 2 to 4 hours.

Subsequent fluid replacement will depend on corrected serum sodium concentration and hydration status of the patient evaluated through diuresis and hemodynamic monitoring. There is no significant difference in time to resolution of DKA with lactate Ringers, but the time to correct hyperglycemia is longer with lactate Ringers [53,54]. When the critical part of intravascular volume depletion is already corrected, the normal saline infusion rate should be reduced to 250 mL/h or changed to 0.45% saline (250 to 500 mL/h), depending on the condition of hydration and corrected serum sodium concentration. When serum glucose reaches 200mg/dL, for DKA or HHS, change to 5% -10% dextrose with 0.45% NaCl at 150-250 mL/hr. to allow continued insulin administration until ketonemia or hyperosmolarity are corrected, while avoiding hypoglycemia.

Insulin

Insulin should be started immediately or after hypokalemia is corrected, if present. Insulin administration is the mainstay of treatment because it helps reduce plasma glucose by inhibiting endogenous glucose production and increasing peripheral glucose use. Insulin also inhibits lipolysis, the formation of ketone bodies and glucagon secretion. With all this, ketoacidosis is reduced. Treatment should be individualized for each patient according to their condition. The treatment of choice is a continuous intravenous infusion of regular insulin.

Previously, most treatment protocols recommended the administration of a bolus of 0.1 U/kg of body weight, but this is not currently considered necessary. It followed by continuous insulin infusion at 0.1 U/kg to 0.2 U/kg per hour until blood glucose is approximately 200 mg/dL in DKA and 250 mg/dL in HHS (Figure 2). Once these blood glucose values are reached, the insulin dose is halved (0.05 U/kg per hour). The rate can be adjusted between 0.02 and 0.05 U/kg per hour, and 5% dextrose is added to maintain the target plasma glucose between 250 and 300 mg/dL until the patient is mentally alert (in HHS) or has resolution of ketoacidosis (in DKA). This more conservative correction of hyperglycemia is done to avoid too rapid a decrease in plasma osmolality that could lead to other complications.

Several studies show that mild to moderate DKA can be treated with subcutaneous rapid-acting insulin analogs, (Lispro and apart). Using programmed subcutaneous insulin allows safe and effective treatment in the emergency department and intermediate care units without the need for ICU care, but severe DKA should be treated with a continuous intravenous infusion of regular insulin at the doses previously described [55,56].

To make the transition from intravenous to subcutaneous insulin, once the glycemic goal has been achieved, subcutaneous basal insulin (NPH, Glargine, Detemir, Degludec) should be administered at least 2 hours before stopping the IV insulin infusion, since an abrupt interruption of insulin can cause rebound hyperglycemia, new formation of ketone bodies and with the respective metabolic acidosis. When using basal insulin analogs (Glargine, Detemir, Degludec), an earlier start should be considered, 3 to 4 hours before the insulin drip is stopped.

Bicarbonate

Correction of metabolic acidosis with sodium bicarbonate is unnecessary in most patients. Its administration is generally only recommended in patients with life-threatening acidosis with a pH below 6.9 because severe acidemia predisposes to cardiac arrhythmias, but its use is controversial. Bicarbonate is not indicated with pH greater than 7.0 or in HHS. Bicarbonate could be administered in patients with severe hyperkalemia (>6.4 mEq/L) because bicarbonate drives potassium into cells but be careful because it can increase the risk of hypokalemia and cerebral edema [57]. Clinical guidelines recommend the administration of 50 to 100 mmol of sodium bicarbonate until pH is greater than 6.9 [58].

Potassium

Although serum potassium levels may be normal or increased in DKA, patients actually have potassium deficits. Similarly, HHS is associated with total body potassium depletion. If hypokalemia is present, this must be corrected before giving insulin because insulin therapy lowers serum potassium levels and could cause life-threatening cardiac arrhythmias. Potassium replacement should be started when the serum concentration is less than 5.2 mEq/L to maintain a level of 4 to 5 mEq/L. The administration of 20 to 30 mEq of potassium per liter of fluids is sufficient for most patients. With serum potassium levels of less than 3.3 mEq/L the replacement should be at a rate of 10 to 20 mEq/h and insulin therapy should be delayed until the potassium level increases to greater than 3.3 mEq/L. Table 2.

Phosphate deficits also are common. However, replacement is not recommended unless severe hypophosphatemia (<1 mg/dL) develops. Resolution of the crisis is defined:

Table 2: Potassium repletion in DKA and HHS [59].

HHS	OKA
Uremic Encephalopathy	Lactic Acidosis
Hepatic Encephalopathy	Methanol
Sepsis	Salicylate Toxicity
Hyponatremia	Uremic Acidosis
Uncontrolled Diabetes	Acholic Ketoacidosis
Trauma	Starvation
critical Illness (Acute Ml, Stroke)	Renal Failure

In DKA:

a) Glucose levels are lower than 250 mg/dL

b) pH is greater than 7.30

c) Normal anion gap

d) Serum bicarbonate is 18 mEq/L or greater

In HHS:

a) Effective serum osmolality less than 310 mOsm/kg

b) Glucose level is 250 mg/dL or less

c) Recuperation of the mental alertness

Transition to Maintenance Insulin Regimen

Patients with known diabetes can be restarted on their previous insulin regimens. Multidose insulin regimens with basal insulin and prandial rapid-acting insulin analogues are the preferred insulin regimens for patients with T1DM and DKA, and for most patients with HHS.

COMPLICATIONS

Many treatment complications may be the result of improper early management. Hypoglycemia is the most common complication during treatment, reported in 5% to 25% of patients with DKA. Acute adverse outcomes of hypoglycemia include seizures, arrhythmias, and other cardiovascular events. Hypokalemia is the second most common complication during the treatment of DKA and HHS. Less common but significant complications include cerebral edema, volume overload with acute respiratory distress syndrome (ARDS). Rhabdomyolysis can occur in patients with DKA and more commonly with HHS, increasing the risk of acute renal failure.

Cerebral edema is rare in adults but is reported in approximately 1% of children during the resuscitation of DKA patients with a mortality rate between 20% and 40% with no clear pathogenesis and may be due to rupture of the blood-brain barrier. Risk factors are pH less than 7.1, PCO2 less than 20 mm Hg, fluids administered at more than 50 ml/kg within the first 4 hours of treatment. Does not correlate with initial osmolality or osmotic changes during treatment [59,60]. 95% of cases of cerebral edema occur in patients less than 20 years of age. Symptoms may include headache and vomiting, altered mental activity or fluctuating level of consciousness, abnormal motor or verbal response to pain, cranial nerve palsy (mainly III, IV, and VI), decorticate or decerebrate posturing, and an abnormal neurogenic respiratory pattern (e.g., tachypnea, grunting, Cheyne-Stokes respiration). There may also be signs of increased intra-cranial pressure - Cushing triad (hypertension, bradycardia, and irregular respirations).

It is recommended as a treatment to reduce intravenous fluids and elevating the head of the bed. As soon as possible the administration of mannitol, 0.5 to 1 g/kg IV over 20 minutes and repeat in 30 minutes if there is no initial response. An alternative to mannitol could be hypertonic saline (3%), 5 to 10 mL/kg over 30 minutes. After treatment for cerebral edema has been started a cranial computed tomography scan should be obtained to rule out other possible intracerebral causes of neurologic deterioration [61,62]. Therapy should not be delayed obtaining imaging. Cardiogenic pulmonary edema can occur when the amount of fluid administered overwhelms the capabilities of the heart to pump or the kidneys to excrete it. Treatment may require diuretics and oxygen.

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