Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

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KEYWORDS

• Diabetes mellitus • Ketoacidosis • Hyperosmolar state • Hyperglycemic crisis

KEY POINTS

- Diabetic ketoacidosis and the hyperglycemic hyperosmolar state are potentially fatal hyperglycemic crises that occur as acute complications of uncontrolled diabetes mellitus.
- The discovery of insulin in 1921 changed the life expectancy of patients with diabetes.

BACKGROUND AND EPIDEMIOLOGY

Diabetic ketoacidosis (DKA) and the hyperglycemic hyperosmolar state (HHS) are potentially fatal hyperglycemic crises that occur as acute complications of uncontrolled diabetes mellitus.

Because of the improved awareness, prevention, and treatment guidelines, the age-adjusted death rate for hyperglycemic crises in 2009 was less than half the rate in 1980 (7.5 vs 15.3 per 1,000,000 population); however, hyperglycemic crises still caused 2417 deaths in 2009 in the United States.[1] The mortality rate from HHS is much higher than that of DKA and approaches 20%.[2] On the other hand, the incidence of HHS is less than 1 case per 1000 person-years. The annual incidence of DKA varies in different reports and is related to the geographic location.[3–7] It has been reported to be as low as 12.9 per 100,000 in the general population in Denmark[3]; in Malaysia the rate of DKA is high, with 26.3 per 100 patient-years.[4]

The incidence of DKA is increasing in the United States (**Fig. 1**). The National Diabetes Surveillance Program of the Centers for Disease Control and Prevention estimated that from 1988 to 2009, the age-adjusted hospital discharge rate for DKA per 10,000 population consistently increased by 43.8%, so the number of hospital discharges with DKA as the first-listed diagnosis increased from about 80,000 in 1988 to about 140,000 in 2009.[1]

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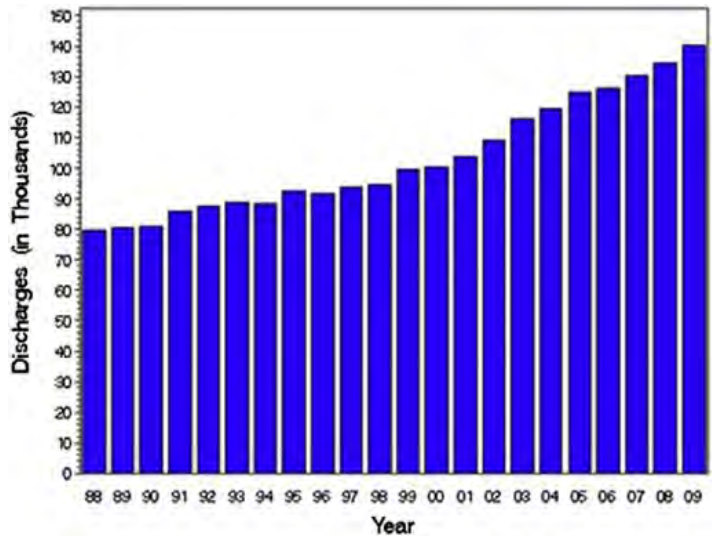

Fig. 1. Number (in thousands) of hospital discharges with DKA as first-listed diagnosis, United States, 1988 to 2009. The number of hospital discharges with DKA as the first-listed diagnosis increased from about 80,000 discharges in 1988 to about 140,000 in 2009. (*From* Centers for Disease Control and Prevention. National hospital discharge survey. Available at: http://www.cdc.gov/nchs/nhds.htm. Accessed April 25, 2013.)

DEFINITION AND DIAGNOSIS

Both DKA and HHS are severe complications of diabetes mellitus and are found to occur simultaneously in about one-third of cases.[8] Although both represent acute hyperglycemic states, DKA is more characterized by ketonemia and anion-gap acidosis and HHS by hyperosmolarity and dehydration.

HHS used to be named *hyperglycemic hyperosmolar nonketotic coma*, but it was found that it frequently presents without coma. It was also named *hyperglycemic hyperosmolar nonketotic state*, but findings of moderate ketonemia in several patients lead to the acceptance of its current term *HHS*. Laboratory findings differ, but some features overlap and are given in **Table 1**:

1. Anion-gap acidosis: Although this is the most important feature of DKA, with serum pH less than 7.3, serum bicarbonate less than 15 mEq/L, and anion gap greater than 10, it is not the finding typical for HHS.

Table 1
Laboratory findings in DKA and HHS

	DKA	HHS
Anion-gap acidosis	pH <7.3 Bicarbonate <18 Anion gap >10	pH >7.3 Bicarbonate >18 Anion-gap variable
Osmolality	<320	>320
Hyperglycemia	>250	>600
Ketonemia/ketonuria	Present	Rare

2. Ketonemia and ketonuria are more pronounced in DKA but can be present in HHS.
3. Hyperglycemia is elevated in both conditions but more pronounced in HHS, with glucose concentrations frequently greater than 600 mg/dL. Cases of euglycemic DKA have been reported and occur more frequently in pregnancy.[9,10]
4. Osmolality is usually normal in DKA, but may be elevated, and is invariably elevated in hyperosmolar state to above 320 mOsm/kg.

DKA most commonly occurs in patients with type 1 diabetes mellitus although it can occur with type 2 diabetes after serious medical or surgical illness.[11] On the other hand, HHS is more frequently associated with type 2 diabetes, however it has also been reported in type 1 diabetes as a simultaneous occurrence with DKA.[12–14] Many investigators report ketosis-prone type 2 diabetes,[15–17] which is also called Flatbush diabetes after the area in the city of Brooklyn, New York where this type of diabetes was first described and is most frequently diagnosed. These patients are commonly African American and obese with acute defects in insulin secretion and no islet cell autoantibodies.[18–20] Following treatment, some insulin secretory capacity is recovered, and many of them do not require insulin therapy in the future.[21,22]

PRECIPITATING FACTORS

Newly diagnosed individuals with type 1 diabetes mellitus account for 15% of cases of DKA. The frequency of DKA at the diagnosis of type 1 diabetes also varies across different countries,[23] with some extremes, such as United Arab Emirates where it has been reported to be 80%[4] or Sweden where it is 12.8%.[7] Data from Europe reported an inverse correlation between the background incidence of type1 diabetes and the frequency of DKA.[24,25] Most DKA events occur in patients with known diabetes at times of extreme stress, especially infection, such as pneumonia or urinary tract infection, but also myocardial ischemia or any other medical or surgical illness. These cases account for about 40% of all DKA events. The second most important contributor to development of DKA is inadequate insulin treatment, commonly seen as a result of noncompliance, especially in the young population.[26,27] DKA has also been reported with the mismanagement of insulin pumps and undetected leakage of the infusion system or[28] at the time of religious fasting.[29,30] In some cases, medications, such as corticosteroids, pentamidine, and terbutaline, have been identified as triggers for DKA.[31–33] Recent reports from the United States and Canada point to a significant role of atypical antipsychotic medications in the development of fatal cases of DKA.[34–37] Cocaine use is associated with frequent omissions of insulin administration, but it also has significant effects on counter-regulatory hormones. It was found to be an important contributor in the development of DKA and HHS together with alcohol and other abused substances.[27,38–41] In a small number of cases, the workup does not identify any precipitating factor. A rough estimate of most common precipitating factors in development of DKA is given in **Fig. 2**.

In HHS, the most common precipitating events are also inadequate insulin therapy and underlying illness, such as infection, ischemia, or surgery. Because HHS develops more slowly and in a more subtle way, the important contributor to this complication is decreased water intake, especially in elderly patients, that leads to gradual but severe dehydration.[8,42] These patients have either a reduced thirst mechanism or they are unable to access water because of physical or neurologic limitations.

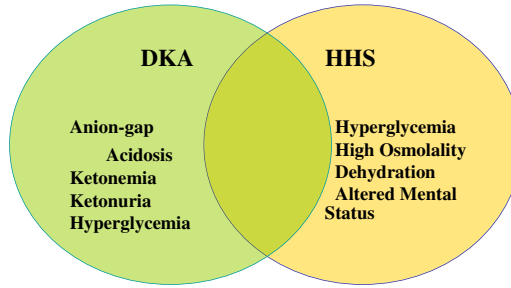

Fig. 2. Major characteristics of DKA and HHS and their estimated overlap.

PATHOGENESIS

The pathogenesis of HHS results from disturbances in glucose metabolism and fluid balance. In DKA, a third component, ketogenesis also contributes to the condition. Both conditions present with hyperglycemia and dehydration.

HORMONES

Both DKA and HHS result from diminished or absent insulin levels and elevated counter-regulatory hormone levels. Insulin deficiency causes glycogenolysis, gluconeogenesis, lipolysis, and protein catabolism. The counter-regulatory hormones present in both of these conditions are glucagon, norepinephrine, epinephrine, cortisol, and growth hormone. Glucagon is the most important of these, whereas growth hormone is probably the least important. DKA is much less likely to occur in the absence of glucagon, but cases of DKA have been reported in patients with complete pancreatectomy. Norepinephrine increases ketogenesis not only by stimulating lipolysis but also by increasing intrahepatic ketogenesis. Catecholamines stimulate lipolysis and fatty acid release even in the presence of insulin. Growth hormone has little effect in the presence of insulin but can enhance ketogenesis in insulin deficiency. The difference between DKA and HHS is that in the latter, the insulin levels do not decrease to a level whereby unrestrained ketogenesis occurs.

Hyperglycemia results from increases in glucose levels obtained from 4 sources:

- Intestinal absorption
- Gluconeogenesis (from carbohydrate, protein, fat)
- Glycogenolysis
- Decreased utilization of glucose by cells, primarily muscle and fat cells

The fate of glucose in the cell can be different depending of the current metabolic needs of the body. It can be stored or it can enter glycolysis and form pyruvate. Pyruvate can be reduced to lactate, transaminated to alanine, or converted to acetyl coenzyme A (CoA). Acetyl CoA can be oxidized to carbon dioxide and water, converted to fatty acids, or used for ketone body or cholesterol synthesis.

Insulin deficiency, absolute or relative, is present in both conditions and results in increased gluconeogenesis and glycogenolysis. Insulin deficiency prevents glucose from entering cells and being metabolized. One of the consequences of insulin deficiency is protein, primarily muscle, breakdown with the provision of precursors for gluconeogenesis. Gluconeogenesis is the crucial action in the development of severe hyperglycemia that is found in DKA and HHS.

Gluconeogenic enzymes are stimulated by the actions of glucagon, catecholamines, and cortisol.[43] The lack of inhibitory action of insulin further drives gluconeogenesis

and glycogenolysis and causes increased glucagon activity.[43–45] The end result of insulin deficiency is impairment in carbohydrate utilization, and energy must be obtained from an alternative source, namely, fatty acid metabolism.

Lipid

Lipid mobilization and metabolism are affected by insulin deficiency. In normal subjects, insulin affects fat metabolism by different mechanisms.[46–48] Insulin increases the clearance of triglyceride-rich chylomicrons from the circulation, stimulates creation of triglycerides from free fatty acids (FFA), and inhibits lipolysis of triglycerides.[49–51] In insulin deficiency, fat mobilization is accelerated, resulting in an abundant supply of FFA to the liver. An increase in FFA availability increases ketone production not only by a mass effect but also by a diversion of hepatic fatty acid metabolism toward ketogenesis.[52] FFA levels may be as high in HHS as in DKA.

Ketogenesis

Ketogenesis depends on the amount of FFA supplied to the liver and on the hepatic metabolic fate of fatty acids in the direction of either oxidation and ketogenesis or reesterification.[52] Ketogenesis occurs inside hepatic mitochondria. The glucagon/insulin ratio activates carnitine palmitoyltransferase I, the enzyme that allows FFA in the form of CoA to cross mitochondrial membranes after their esterification with carnitine. In HHS, this ratio does not reach a level whereby unrestrained ketoacidosis occurs. This increase in carnitine palmitoyltransferase I occurs associated with a decrease in malonyl CoA. Fatty acids that are in the mitochondria are converted to acetyl CoA. Most of the acetyl CoA is used in the synthesis of beta-hydroxybutyric acid and acetoacetic acid.[53] Acetoacetate is converted to acetone through nonenzymatic decarboxylation in linear relation to its concentration. Ketones are filtered by the kidney and partially excreted in urine. Progressive volume depletion leads to a reduced glomerular filtration and the shift of acetoacetate to beta-hydroxybutyrate.[54]

Hyperosmolar

Hyperosmolar state develops as a result of osmotic diuresis caused by hyperglycemia, which then creates severe fluid loss. The total body deficit of water is usually about 7 to 12 L in HHS, which represents a loss of about 10% to 15% of body weight. Although mild ketosis can be seen with HHS, it is generally absent in this state. It is considered that patients with HHS who are usually older patients with type 2 diabetes still do have enough insulin to be protected from exaggerated lipolysis and the consequent abundance of FFA.[55] They do not, however, have enough insulin to prevent hyperglycemia.[56]

CLINICAL PRESENTATION

DKA and HHS can have similar clinical presentations. There are usually signs and symptoms of hyperglycemia and a general unwell feeling with malaise, fatigue, and anorexia. Patients can present with symptoms of the preceding illness, such as infection (pneumonia, urinary tract infection, and so forth) or myocardial ischemia. DKA will usually develop faster than HHS, sometimes in less than 24 hours. HHS takes days to weeks to develop in most patients.

Some of the differences in the clinical presentations result from the state of metabolic acidosis in DKA. Patients with DKA will frequently have hyperventilation (Kussmaul ventilation) as a compensatory mechanism for acidosis that is rarely seen with HHS. DKA will also present with abdominal pain that is associated with the level of

acidosis.[57] Sometimes the presentation with significant abdominal pain is associated with an underlying abdominal process, such as acute pancreatitis.[58] Abdominal pain is frequently associated with acidosis only and no underlying pathological condition can be identified; however, it always requires a workup for acute abdominal process.

Most patients with HHS will have some degree of neurologic disturbance, whereas only patients with more advanced DKA will be comatose. If they present early in the course of the disease, patients with DKA will frequently have a normal neurologic examination. This difference is caused by greater hyperosmolality in HHS caused by osmotic diuresis and free water loss.[59–62] Hyperosmolar state causes cellular dehydration produced by osmotic shifts of water from the intracellular fluid space to the extracellular space.[63,64] If osmolality is normal and patients show severe neurologic deficit, further workup is indicated to rule out underlying neurologic pathologic condition. Elderly patients are particularly susceptible to these disturbances. Some possible neurologic presentations include irritability, restlessness, stupor, muscular twitching, hyperreflexia, spasticity, seizures, and coma.[65–68] The clinical signs and symptoms reflect both the severity of the hyperosmolality and the rate at which it develops.[69]

Free water deficit is more pronounced in HHS, as compared with DKA; patients with HHS will have more evidence of severe dehydration. An additional source of dehydration is impaired water intake, particularly in elderly patients with ongoing lethargy and confusion.[70] Evaluation of volume status is one of the initial assessments of patients with DKA or HHS. **Table 2** shows some of the important clinical features of DKA and HHS.

INITIAL EVALUATION

Both DKA and HHS are medical emergencies with improved, but high, mortality rates that require careful evaluation. As a first step in evaluating patients who present with a hyperglycemic emergency, the physician should secure the airway and ensure adequate ventilation and oxygenation. Patients should also have secure intravenous (IV) access, with at least 2 ports, and continuous cardiac monitoring. A Foley catheter should be placed for strict monitoring of intake and output.

The initial laboratory investigation should include the following: serum glucose, metabolic panel, serum phosphate and magnesium, arterial blood gas analysis, complete blood count (CBC) with differential, hepatic enzymes, serum ketones, urinalysis, cardiac enzymes, hemoglobin A1C, and coagulation profile. Additional laboratory values that should be considered are infectious workup with urine and blood cultures,

Table 2
Clinical features of DKA and HHS

Clinical Presentation	DKA	HHS
Development of Symptoms	**Hours to Days**	**Days to Weeks**
Polydipsia/polyuria	+	+
Nausea/vomiting	+	+
Abdominal pain	+	–
Anorexia	+	+
Fatigue/malaise	+	+
Neurologic abnormalities	±	+ +
Hyperventilation	+	–
Dehydration	+	+ +

lumbar puncture in selected cases, serum lipase, and amylase. Other investigations should include electrocardiogram and chest radiograph, and selected cases will require additional chest/abdomen/brain or other imaging depending on the clinical presentation. Serum glucose and electrolytes should be repeated every 1 to 2 hours until patients are stable and then every 4 to 6 hours. The most important points in the initial evaluation of DKA and HHS are given in **Table 3**. The initial calculations include serum sodium correction, serum osmolality, anion gap, and free water deficit.

Basic considerations in the evaluation of DKA and HHS laboratory values are given in the following text.

Serum Glucose

Serum glucose is usually more elevated in HHS than in DKA. This elevation is partly caused by the acidosis of DKA leading to an earlier diagnosis of the condition before glucoses levels have increased as high. Also contributing is the fact that about a half of the patients with type 1 diabetes mellitus have glomerular hyperfiltration in the first years in the course of their disease. Patients with type 2 diabetes mellitus also initially have an increased glomerular filtration rate of about 2 standard deviations more than their age-matched nondiabetic and obese controls, but the degree of hyperfiltration is less than that of patients with type 1 diabetes. These differences allow for an increased glucose excretion degree in DKA and less hyperglycemia as compared with HHS.[71] In

Table 3
Initial evaluation of patients with hyperglycemic emergency (DKA/HHS)

First steps	IV line (at least 2 ports, consider central access) Airway and adequate ventilation/oxygenation Cardiac monitor In and out monitoring (Foley catheter)
Initial laboratory test results	Serum glucose Basic metabolic panel with electrolytes Arterial blood gas analysis BUN/creatinine CBC with differential Serum phosphate Liver enzymes Urinalysis Cardiac enzymes Coagulation profile Serum ketones Hemoglobin A1C
Additional laboratory test results (case-by-case basis)	Blood and urine culture Lumbar puncture Amylase and lipase Other laboratory tests based on clinical presentation
Initial imaging	CXR Optional imaging based on clinical presentation (CT head/chest/abdomen)
Initial calculations	Anion gap Corrected serum sodium Free water deficit Serum osmolality

Abbreviations: BUN, serum urea nitrogen; CT, computed tomography; CXR, chest X-ray.

HHS, the glucose level is more than 600 mg/dL and can frequently be more than 1000 mg/dL.[72] The degree of hyperglycemia reflects the degree of dehydration and hyperosmolality.[73] Cases of normoglycemic DKA have been described in pregnant patients.[74,75] Patients with renal failure usually have severe hyperglycemia because of poor renal clearance of glucose. These patients, however, usually do not develop hyperosmolality because of the lack of osmotic diuresis, and their mental status with HHS tends to be less affected than with patients who have preserved renal function.[76–79]

Serum Sodium

Serum sodium levels are affected in both DKA and HHS. In the setting of hyperglycemia, osmotic forces drive water into the vascular space and cause dilution with resulting hyponatremia. Each 100 mg/dL of the glucose level more than normal lowers the serum sodium level by about 1.6 mEq/L. The treatment of DKA and HHS with insulin causes reversal of this process and drives water back into the extravascular space with a subsequent increase in serum sodium level. Corrected serum sodium is calculated with the following formula:

> Corrected sodium = serum sodium (mEq/L) + (1.6 mEq/L for each 100 mg/dL of glucose more than 100 mg/dL)

One study suggested that a more accurate correction factor in extreme hyperglycemic states is 2.4 mEq/L for each 100 mg/dL because of the nonlinear relationship between the glucose and sodium concentration.[80] An additional decrease in serum sodium is present with confounding pseudohyponatremia that occurs with hyperlipidemia or hyperproteinemia with some laboratory assays.[81,82] Thus, most patients will present with hyponatremia. In some cases of HHS, patients may present with hypernatremia secondary to osmotic diuresis and more severe dehydration.[83,84] Hypernatremia indicates a profound degree of water loss. The measured, and not the calculated, serum sodium level should be used to calculate the anion gap.[85]

Serum Potassium

Serum potassium is frequently paradoxically elevated despite the total body deficit in DKA and HHS. This elevation is caused by the extracellular shift of potassium in exchange for the hydrogen ions accumulated in acidosis, reduced renal function, release of potassium from cells caused by glycogenolysis, insulin deficiency, and hyperosmolality.[86,87] It is thought that the water deficit from the cells creates passive potassium flux to the extracellular space leading to relative hyperkalemia without having significant acidosis in HHS.[88] The body deficit of potassium occurs with diuresis but also with gastrointestinal losses.[89] Treatment with insulin shifts potassium into the cell and causes a rapid decrease of the serum potassium levels. Hypokalemia is frequently encountered after starting insulin treatment. Careful monitoring and potassium supplementing are required in patients with DKA and HHS, especially if they initially present with a normal or low potassium level.[90–93]

Serum Phosphate

Serum phosphate is lost by diuresis in DKA and HHS, and its typical deficit is usually up to 7 mmol/kg.[94,95] Similarly, as in the case of potassium deficit, patients may present with normal or even high levels of phosphate because insulin deficiency drives phosphate out of the cells. The level of serum phosphate will start decreasing as soon as insulin treatment is established. Hyperphosphatemia, on the first presentation, also

reflects volume depletion. Acidosis is another mechanism that causes falsely normal or high phosphate levels. Patients who present with profound acidosis are at higher risk of developing hypophosphatemia when insulin administration is started. The severity of subsequent hypophosphatemia can be predicted by the degree of metabolic acidosis on presentation.[38] Untreated hypophosphatemia can lead to serious complications, including cardiac arrest.[39–41]

Serum Bicarbonate

Serum bicarbonate is typically more than 18 mEq/L in HHS. Because DKA is characterized by acidosis, the serum bicarbonate is lower than 18 mEq/L and frequently lower than 15 mEq/L. A decrease of bicarbonate to less than 10 mEq/L indicates severe DKA.[96,97]

Serum Ketones

Serum ketones are used as an energy source when glucose is not readily available and are increased in DKA, as a response to low insulin levels and high levels of counterregulatory hormones.[98] Acetoacetate is a ketoacid, whereas beta-hydroxybutyrate represents a hydroxy acid that is formed by the reduction of acetoacetate. The third ketone body, acetone, is the least abundant of all and is formed by decarboxylation of acetic acid. Although ketones are always present, their levels increase in certain conditions, such as starvation, pregnancy, and exercise. DKA causes the most prominent increase in ketone body levels compared with the other common conditions. Serum ketone testing is performed when a urinary dipstick tests positive for urine ketones. The most commonly used test for serum ketones is nitroprusside. However, it detects only acetoacetate and acetone and not hydroxybutyrate. Because beta-hydroxybutyrate is the most prominent ketone body and is disproportionally so in DKA, it is possible to have a negative testing for serum ketones in the presence of severe ketoacidosis.[99] Cases of children who developed DKA, that could have potentially been prevented, as a consequence of false-negative home ketone test-strip readings with nitroprusside have been described.[100]

The initiation of treatment with insulin causes a conversion of beta-hydroxybutyrate to acetoacetate while the overall levels of ketone bodies are decreasing.[101] This effect can potentially create a false observation that DKA is worsening, although, in fact, it is improving; subsequent unnecessary increases in insulin treatment could lead to other complications.[102] Quantitative enzymatic tests have been developed and can be used as point-of-care tests that identify beta-hydroxybutyrate.[99,103,104] On the other hand, false-positive results for serum ketone bodies have been identified in patients using drugs with sulfhydryl groups.[105–109] The risk of inappropriate therapy with insulin caused by false-positive ketones in serum is low but existing.

Anion Gap

Anion gap represents unmeasured anions in serum (ketones) after subtracting the major measured anions from the major measured cation.

$$AG = (\text{serum sodium}) - (\text{chloride} + \text{bicarbonate})$$

where *AG* is anion gap

Measured, not corrected, serum sodium levels should be used to estimate the anion gap.[110] The anion gap is usually more than 20 mEq/L in DKA, and it reflects the production and accumulation of acetoacetate and beta-hydroxybutyrate in the serum. It inversely reflects the rate of excretion of acids that will be impaired with renal

failure.[112] Patients admitted with diabetic ketoacidosis have a mean bicarbonate deficit that is approximately equal to the excess anion gap.

Arterial Blood

Arterial blood gas measurement is recommended in all cases of hyperglycemic complications of diabetes mellitus. Acidosis is one of the main features of DKA and is included in the diagnostic criteria, with arterial pH of less than 7.3. Arterial pH in HHS is usually more than 7.3. In order to avoid the painful and more difficult procedure of arterial blood drawing, in patients with normal oxygen saturation on room air, venous blood gas is sometimes used to estimate acidosis. It has been found that there is a high degree of correlation and agreement with the arterial value, with acceptably narrow 95% limits of agreement.[111] Arterial blood gas analysis can, on the other hand, indicate an underlying disease associated with DKA or HHS. Hypoxemia may be found with cardiac or pulmonary trigger diseases, and low carbon dioxide may represent hyperventilation as a compensatory mechanism for metabolic acidosis.

Serum Osmolality

The serum osmolality elevation correlates with the degree of neurologic disturbance.[112] The serum osmolality is determined by the concentrations of the different solutes in the plasma. In normal subjects, sodium salts, glucose, and urea are the primary circulating solutes. Increased serum osmolality to more than 320 mosmol/kg is seen in patients with neurologic abnormalities and is typical for HHS. Rarely, serum osmolality can be more than 400 mOsm/kg. Neurologic deficits ranging from confusion to coma can be seen with DKA, with a less significant increase in serum osmolality, which then reflect the degree of acidosis.[113] The formula for the calculation of serum osmolality is given next[114–116]:

$$\text{Serum osmolality} = (2 \times \text{serum [Na]}) + (\text{glucose, in mg/dL})/18 + (\text{BUN in mg/dL})/2.8$$

where *BUN* is serum urea nitrogen

The formula with all units in millimoles per liter is the following:

$$\text{Serum osmolality} = (2 \times \text{serum [Na]}) + (\text{glucose}) + (\text{urea})$$

The serum osmolal gap represents the difference between the measured and calculated serum osmolality. In normal individuals, the osmolal gap was not significant and was found to be 1.9 ± 3.7 mosmol/kg and -1.7 ± 1.7 mosmol/kg in 2 studies.[117] The measured serum osmolality can be significantly higher than the calculated value in the presence of an additional solute, such as ethylene glycol, methanol, ethanol, formaldehyde, isopropyl alcohol, diethyl ether, glycine, sorbitol, or mannitol, or in presence of significant pseudohyponatremia caused by severe hyperproteinemia or hyperlipidemia.[118–120]

Leukocytosis

Leukocytosis is present in hyperglycemic emergencies even in the absence of infection. This presence is explained by elevated stress hormones, such as cortisol and catecholamines, and cytokines and is proportional to the degree of ketonemia.[121–123] True leukocytosis is also frequent, and a source of infection should be investigated in all cases. White blood cell counts of greater than 25,000/μL were independently associated with altered sensorium in one study.[124]

Amylase and Lipase

Amylase and lipase can be elevated with DKA in the absence of pancreatitis. An increase in lipase correlates with plasma osmolality, and an increase in amylase correlates with plasma osmolality and pH.[125] True pancreatitis is also a frequent precipitating factor for hyperglycemic emergencies and can be confirmed with other clinical characteristics and imaging **Fig. 3**.[59]

TREATMENT

The management of DKA and HHS consists of fluid and electrolyte repletion, insulin administration, and the treatment of the precipitating cause if one can be identified. Patients should be admitted to a monitored unit where close observation of mental status, blood pressure, heart rate and rhythm, and urine output can be done.

Fluid Replacement

Fluid replacement should be the initial therapy in DKA and HHS, with the goal of correcting a fluid deficit in the first 24 hours. The initial fluid should be normal saline. The rate in the first hours should be 10 to 15 mL/kg. Once patients are euvolemic, switching to half-normal saline is appropriate for those with normal sodium or hypernatremia. This change allows for more efficient replacement of the free water deficit induced by the glucose osmotic diuresis. Half-normal saline should be administered at a rate of 4 to 14 mL/kg. Five percent dextrose with half-normal saline should be started when the blood glucose level decreases less than 250 mg/dL in DKA and 300 mg/dL in HHS.[56]

Cerebral edema is a serious complication of DKA treatment with a high mortality of 21% to 24% that is primarily seen in children when hyperosmolality was corrected too rapidly.[126] Symptomatic cerebral edema occurs in 0.5% to 1.0% of pediatric DKA episodes, and 15% to 26% of children remain with permanent neurologic sequelae.[127] Children who presented with higher osmolality and higher serum urea nitrogen (BUN) demonstrated a more severe clinical picture, with the most profound acidosis and hypocapnia.[128]

Treating patients with renal or cardiac compromise is challenging because a fine balance needs to be established between the volume deficit and the volume overload. These patients require frequent monitoring of volume status and parameters of fluid

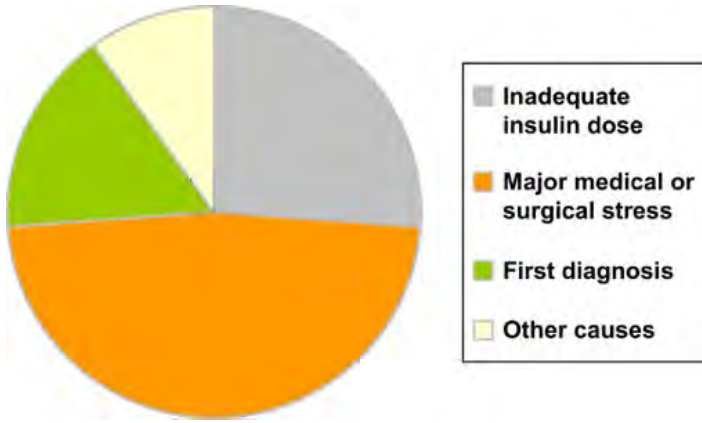

Fig. 3. Estimated prevalence of precipitating factors in development of DKA.

homeostasis, such as osmolality, serum sodium, BUN and creatinine, blood glucose, and urine output, as well as frequent clinical monitoring for signs of respiratory compromise caused by volume overload.

Potassium

Potassium may initially be elevated because of the extracellular shift caused by insulin deficiency, acidosis, and proteolysis.[129] This elevation will rapidly correct with the administration of fluids that create dilution and insulin treatment that will allow for potassium to be shifted back to the cell. Urinary and gastrointestinal loss of potassium also causes an overall deficit in potassium concentration. Glucosuria results in the loss of 70 mEq of sodium and potassium for each liter of fluid lost. The correction of actual deficit of potassium should be started when the potassium level is less than 5.3 mEq/L. The potassium level should be maintained between 4 and 5 mEq/L.

Insulin

Insulin at a low dose should be started approximately 1 hour after the initiation of fluid replacement therapy, with regular insulin as a treatment of choice. This treatment should be further delayed if serum potassium is less than 3.3 mEq/L because of the risk of hypokalemia. The administration of an initial bolus dose of insulin is not associated with a significant benefit to patients with DKA.[130] As an alternative to IV regular insulin, an intramuscular regimen with rapid-acting analogues has been reported to decrease the cost of DKA treatment.[131] When the plasma glucose level is less than 250 mg/dL in DKA or 300 mg/dL in HHS, the insulin rate should be decreased and maintained to keep blood glucose between 150 to 200 mg/dL in DKA and 250 to 300 mg/dL in HHS, until the ketoacidosis and/or hyperosmolar states are resolved.[129,132] It is critical that insulin therapy be based on the correction of the anion gap and not the serum glucose level. In some cases, it may be necessary to give IV 50% dextrose solution to allow adequate insulin therapy.

Bicarbonate therapy is controversial given the potential problems, such as hypokalemia, acidosis, hypoxia, hypernatremia, and the lack of a therapeutic effect.[133,134] There is insufficient data to confirm a benefit of treatment. It should be reserved only for severe cases of ketoacidosis with a very low bicarbonate of less than 10 and severe acidosis. In similar fashion, phosphate repletion is not recommended in all patients. Studies do not show a clear benefit of this treatment, and it may only be of some use in patients who are symptomatic for hypophosphatemia with heart or skeletal muscle involvement.[135–137] The main risk of phosphate therapy is hypocalcemia, especially as the pH normalizes.

SUMMARY

The discovery of insulin in 1921 changed the life expectancy of patients with diabetes mellitus dramatically. Today, almost a century later, DKA and HHS remain a significant economic burden and, most importantly, a significant cause of morbidity and mortality across different countries, ages, races, and socioeconomic groups.

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