

Overlap of diabetic ketoacidosis and hyperosmolar hyperglycemic state

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Abstract

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemia state (HHS) are two life-threatening metabolic complications of diabetes that significantly increase mortality and morbidity. Despite major advances, reaching a uniform consensus regarding the diagnostic criteria and treatment of both conditions has been challenging. A significant overlap between these two extremes of the hyperglycemic crisis spectrum poses an additional hurdle. It has well been noted that a complete biochemical and clinical patient evaluation with timely diagnosis and treatment is vital for symptom resolution. Worldwide, there is a lack of large-scale studies that help define how hyperglycemic crises should be managed. This article

will provide a comprehensive review of the pathophysiology, diagnosis, and management of DKA-HHS overlap.

Key Words: Diabetic ketoacidosis; Hyperosmolar Coma; Diabetes; Metabolic acidosis; Hyponatremia; Hyperosmolar hyperglycemia state

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Core Tip: Diabetes ketoacidosis and hyperosmolar hyperglycemic coma are critical illnesses and medical emergencies associated with diabetes. Diabetic ketoacidosis (DKA) is associated with hyperglycemia and ketoacidosis, whereas hyperosmolar hyperglycemia state (HHS) mainly has severe hyperglycemia and hyperosmolarity. Up to 30% of patients with DKA may also have some features of HHS. Early diagnosis with aggressive management of hyperosmolarity, ketosis, and hyperglycemia can help prevent mortality.

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INTRODUCTION

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the two most commonly seen acute metabolic complications of diabetes mellitus (DM)[1]. DM can cause DKA, a critical condition that can be life-threatening. Type 1 diabetes patients are more likely to experience DKA than type 2 from noncompliance to therapy, but infection, trauma, or acute coronary syndrome can also trigger it [2]. Type 2 diabetes has a 30-d mortality rate of 11.9% compared to type 1 diabetes rate of 2.4%, as patients with type 2 DM are older and have several morbid conditions. T2DM is much more prevalent than T1DM, with a prevalence of 8.5% compared to 0.5% for T1DM[3]. HHS occurs in patients with type 2 DM, causing a severe acute hyperglycemic emergency[4]. A rise in total body ketone concentrations is characteristic of DKA, with metabolic acidosis and uncontrolled hyperglycemia to a lesser degree in comparison to HHS[4]. Patients with HHS tend to have extreme hyperglycemia, usually > 600 mg/dL, hyperosmolality, and dehydration. Although the actual prevalence of HHS is unknown, it is likely to represent less than 1% of hospital admissions in diabetic patients. Most cases are seen in elderly patients with type 2 diabetes. However, it has also been reported in young adults and children[5]. To enhance patient outcomes, early diagnosis and therapeutic interventions are critical. DKA and HHS both present with severe dehydration, necessitating aggressive rehydration, electrolyte replacement, insulin therapy, and treatment of the underlying triggering events. Patients with a hyperglycemic crisis may present with both DKA and HHS. Currently, there is no accepted definition that identifies patients presenting with both DKA and HHS because sufficient data are not available regarding their frequency, clinical characteristics, or prognosis. There is some evidence that up to 30% of patients with DKA have features of both HHS and DKA[5]. They may have ketoacidosis and severe hyperglycemia with glucose greater than 600 mg/dL, which is not usual in DKA patients. Due to overlapping metabolic presentation, they are diagnosed to have DKA/HHS overlap.

HHS patients have been found to have a much higher mortality rate than those with DKA, according to some studies[5]. There is a need to identify the clinical characteristics of patients presenting with isolated hyperglycemic crises, as well as those with DKA and HHS overlap. This will allow us to identify factors associated with poor outcomes and estimate the complications associated with the severity of the disease.

A combination of hyperglycemia (serum glucose more than 250 mg/dL), acidosis (arterial pH < 7.3 and bicarbonate < 15 mEq/L), and ketosis (ketonuria or ketonemia) is referred to as DKA. The term “euglycemic DKA” (euDKA) is DKA without significant hyperglycemia, with serum glucose of less than 250 mg/dL. Partial therapy of DKA, food restriction, alcohol consumption, SGLT2 inhibitors, anorexia, and gastroparesis can cause euDKA[6,7]. Starvation causes a decrease in insulin release and high levels of counterregulatory hormones, especially glucagon and cortisol, resulting in lipolysis and ketone body production.

For the workup of DKA, arterial blood gas, routine chemistry, and serum ketones are obtained, and other causes of metabolic acidosis with a high anion gap are ruled out[8]. The mainstay for diagnosis of HHS is profound hyperglycemia with glucose greater than 600 mg per dL as per American Diabetes Association.

The goal of HHS treatment is to replace lost volume, address hyperosmolality, hyperglycemia, electrolyte imbalances, and manage the underlying condition that caused the metabolic decompensation [9]. Both DKA and HHS are defined by hyperglycemia and absolute or relative insulinopenia. They differ clinically in terms of dehydration, ketosis, and metabolic acidosis[1]. Identifying the variables that caused DKA or HHS during the initial hospitalization should aid in preventing future episodes of hyperglycemia[5]. As diabetes mortality continues to increase, emergency admissions for hyperglycemic crises remain a common occurrence. If left untreated, these illnesses have substantial fatality rates. Patients with HHS patients have a 15% mortality rate, almost tenfold higher than DKA. Elderly patients with DKA, on the other hand, have been observed to have greater fatality rates[10]. Overlap of HHS and DKA was associated with greater mortality (8%) among subjects presenting with hyperglycemic crisis, in comparison to 5% for isolated HHS and 3% for isolated DKA[11]. However, it is important to understand that close similarities between DKA and HHS have not been evaluated rigorously or adjusted for variables and severity of the disease.

PRECIPITATING FACTORS AND CAUSES

There is a wide range of precipitating factors that can trigger DKA and HHS, but a recent analysis from a safety net hospital in Atlanta found that insulin cessation was the main cause of DKA in 78% of patients and 56% of patients with recurrent DKA episodes. Infections accounted for 14% of DKA triggers, while 4% were non-infectious causes such as acute myocardial infarction, neurovascular accidents, alcohol usage, and pancreatitis[12,13]. DKA may be the presenting condition in new-onset type 1 diabetic patients. Some medications can cause DKA or HHS, including sympathomimetic drugs (like dobutamine and terbutaline), thiazide diuretics, corticosteroids, lithium, and second-generation antipsychotics[14]. DKA has been associated with two new categories of medications in recent years. SGLT-2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) are known to cause DKA in both type 1 and type 2 diabetic patients. Immune checkpoint inhibitor anti-cancer drugs, including ipilimumab, nivolumab, and pembrolizumab, can lead to new-onset DM in up to 1% of patients, with 50% of these patients initially presenting with DKA[15-17]. Type 1 DM (T1DM) as a side effect of these drugs (Immune checkpoint inhibitors) has only recently been acknowledged, and current guidelines are still following behind this uncommon but potentially fatal condition[11,18]. Fulminant type 1 DM (FT1DM), characterized by markedly elevated glucose, near-normal glycated hemoglobin (HbA1c), ketoacidosis, negative autoantibodies, severe insulin deficiency, and elevated pancreatic enzyme levels, have been documented since the introduction of immune checkpoint medication[11].

Additionally, up to 20% of recurrent DKA cases are caused by insulin omission, chronic disease stress, and eating disorders[19].

It is typical for HHS to be triggered by a UTI, pneumonia, acute cardiovascular event, or other concomitant medical conditions[20,21]. It is less common for HHS to be caused by medical therapy non-adherence or the emergence of new diabetes than it is for DKA[14,22].

PATHOPHYSIOLOGY

While previously considered two distinct conditions, DKA and HHS overlap can occur considerably in clinical practice[23,24]. DKA and HHS overlap to a large extent in the underlying pathophysiology. Reduced insulin production (DKA) or inefficient insulin action (HHS) results in the decreased net effective action of circulating insulin. DKA and HHS are also described as having elevated levels of counterregulatory hormones such as cortisol, catecholamines, glucagon, and growth hormone[25]. In DKA, excessive glucose and fatty acids have been linked to a pro-inflammatory and oxidative state. The pro-inflammatory state is associated with increases in IL-8, IL-6, IL-1B, TNF-alpha, and other cytokines that impair the responsiveness to insulin therapy[26]. Oxidative stress is described as increased production of reactive oxygen species (ROS)[27]. Eventually, these ROS damage lipids, membranes, and proteins in the cells[26]. Furthermore, the oxidative state following the DKA incident raises the chance of acquiring chronic diabetes problems[10]. The absence of ketone bodies in HHS is attributed to the higher levels of insulin in circulation and lower levels of counter-regulatory hormones. The greater insulin secretion appears to be an essential method for preventing ketosis in HHS because insulin has a tenth of the antilipolytic impact of glucose usage[12]. HHS has less well-understood pathogenesis than DKA, although it is distinguished from DKA by a higher degree of dehydration (due to osmotic diuresis) and changes in insulin availability[28]. HHS has a relative insulin shortage, endogenous insulin production (as measured by C-peptide levels) appears to be relatively higher than in DKA[29]. Normalizing this insulin deficiency requires treatment with insulin and adequate hydration (Table 1).

DKA and HHS have many similarities in terms of the presentation of symptoms. Many of the symptoms overlap, making a distinct diagnosis challenging. However, there are a few important differences in presentation and onset[1]. Overlapping symptoms of DKA and HHS include but are not limited to polyuria, polydipsia, and weight loss, usually in the setting of a preceding or current infection

Table 1 Clinical features of diabetic ketoacidosis and hyperosmolar hyperglycemic state

Clinical features	
DKA	HHS
Kussmaul respiration	Dehydration
Fatigue	Stupor
Thirst	Coma
Nausea and vomiting	Unconsciousness
Abdominal pain	Several weeks of polyuria
Sweet breath (acetone)	Hypotension
Hypotension	Tachycardia
Tachycardia	
Confusion	
Drowsiness	

DKA: Diabetic ketoacidosis; HHS: Hyperosmolar hyperglycemia state.

(pneumonia, gastrointestinal infection, UTI)[30]. Polydipsia and polyuria are usually the earliest symptoms identified in DKA patients and occur within hours of onset. However, there are some cases where a patient is euglycemic, like patients taking SGLT-2 inhibitors.

In these cases, despite developing ketoacidosis, symptoms of hyperglycemia are often absent[31]. The presentation and onset of DKA tend to occur more rapidly, often within a few hours, in contrast to HHS, which has a more insidious and gradual onset and can take days before clinical signs and symptoms are noted. In both cases, there is evidence of a decrease in intravascular volume with physical signs such as poor skin turgor, dry mucosa, poor capillary refill, tachycardia, and hypotension. Despite the dehydration and state of hypovolemia, patients with DKA can often present with high or normal blood pressure readings. Hypovolemia is much more pronounced in HHS, occurring up to twice as much as DKA, although similarly to DKA can be difficult to assess in some cases because hypertonicity helps maintain volume depletion and delays clinical signs of dehydration[32,33]. More commonly seen in DKA are acetone breath, Kussmaul respirations, nausea, and abdominal pain, primarily due to the accumulation of ketone bodies and subsequent acidosis[34]. In a study designed to evaluate the incidence of abdominal pain in DKA and HHS patients, nearly half of the DKA patients presented with abdominal pain, while none of the HHS patients presented with abdominal pain[35]. The significance of abdominal pain correlated to the severity of metabolic acidosis and not the severity of hyperglycemia, and the pain subsided after ketoacidosis was resolved[35]. The mental status change is another major sign that can present in both DKA and HHS. Mental status in DKA can range from being alert in mild cases to a state of drowsiness and stupor in moderate to severe cases. The mental status of a DKA patient correlates to the level of acidosis[36]. In a significantly high number of patients with HHS, profound alteration in mentation occurs, ranging from stupor to a coma. Unlike DKA, the significantly higher hyperosmolality is thought to have a strong correlation with the severity of mental status change [5]. On occasion, patients can have a combination of both HHS and DKA, presenting with features from both ends of the spectrum. These patients can have a combination of significant ketoacidosis and hyperglycemia with hyperosmolality. A recent retrospective study found that a quarter of patients with diabetes presented with a combination of both HHS and DKA. A two-fold increase in mortality compared to patients with isolated HHS or DKA[37] was noted. There is no clear-cut distinction on the basis of mental status between HHS and overlap of DKA/HHS[38].

KEY INVESTIGATIONS AND FINDINGS

Measurement of serum glucose, blood urea nitrogen (BUN), creatinine, anion gap, serum ketones, serum osmolality, urinalysis, urine ketones, and arterial blood gases (ABG) are vital in the initial assessment of a suspected case of a DKA or HHS in a diabetic patient. The American Diabetes Association's criteria for DKA are serum glucose greater than 250 mg/dL, anion gap metabolic acidosis, and elevated serum ketones[39]. Based on the blood pH, ketones, serum bicarbonate level, and altered mental status, DKA can be classified as mild, moderate, or severe in nature[36]. The ADA criteria state that mild DKA presents with a pH in the range of 7.25-7.30 on ABG, moderate DKA in the range of 7.00-7.25, and in the case of severe DKA, a pH less than 7.00[40]. On the other hand, due to the relative

absence of ketoacidosis caused by ketone bodies, patients diagnosed with HHS tend to have a pH of greater than 7.30. According to current ADA diagnostic criteria, the serum glucose levels in HHS patients exceed 600 mg/dL or 33.3 mmol/L, while serum effective plasma osmolality exceeds 320 mmol/kg[37]. The 320 mmol/kg cutoff was shown to correlate with mental status change, with 74% of patients presenting with impaired cognitive status and 23% of patients in a comatose state directly[41]. One study showed that increased serum urea nitrogen due to prerenal azotemia caused by severe volume depletion was an independent prognostic indicator of mortality in HHS patients. Previous studies have shown other important risk factors, including elevated white blood cell count (WBC) and low serum bicarbonate levels. In this study, elevated markers such as C-reactive protein (CRP) and low fasting C-peptide levels were important predictors of severe levels of DKA[41]. Patients diagnosed with DKA have met the criteria for HHS and vice versa. Numerous cases have shown a mixed picture of patients presenting with significant hyperglycemia and serum osmolality (oftentimes exceeding 1000 mg/dL and 320 mmol/kg, respectively), significant ketoacidosis, and a large anion gap[42]. Overlap in both syndromes in terms of key investigation findings is increasing in incidence. There have been several cases of a mixed picture of DKA and HHS that have gone underreported and instead were often labeled as one or the other based on the diagnostic criteria presented by the ADA. This is seen far more often in pediatric and adolescent patients, particularly obese patients[38]. Young type 1 diabetic patients with DKA have been shown to present with features and laboratory findings suggestive of HHS when high sugar-containing fluids were administered to improve dehydration and fluid loss[38]. It is important to note that patients with HHS who present with severe prolonged dehydration may also present with significant metabolic acidosis due to lactic acidosis that results from prolonged tissue hypoperfusion. Lactic acidosis may add to the metabolic acidosis seen in DKA patients, but the level of serum lactate in these subsets of patients is very low, and the mechanism by which this occurs has been attributed to a different mechanisms of glucose metabolism and not solely due to tissue hypoperfusion. Additionally, lactic acid has been shown to not be a good predictor of mortality and length of stay in the ICU in DKA patients[42]. Before confirming the diagnosis of DKA, it is crucial to exclude the other differential diagnoses that can overlap with DKA or present similarly. In ketoacidosis cases, it is important to explore the clinical history and correlate it with the lab investigations and the patient's clinical picture to identify the cause of ketosis. Especially that ketoacidosis can be easily attributed to DKA, although it is not the only causative factor. In fact, starvation ketosis and alcoholic ketoacidosis are associated with glucose concentrations of plasma ranging from mildly elevated values (rarely > 200 mg/dL) to hypoglycemia[43]. However, the serum glucose in DKA is usually > 250 mg/dL. Additionally, sodium bicarbonate levels can be used to establish a diagnosis. Starvation ketosis is associated with low serum bicarbonate < 18 mEq/L, but alcoholic ketosis has significantly high serum bicarbonate levels. Multiple etiologies can cause high anion gap metabolic acidoses such as lactic acidosis, uremia, or ingestion of drugs like salicylic acid, methanol, ethylene glycol, paraldehyde, and aspirin[36].

MANAGEMENT

DKA and HHS require urgent medical management to improve the clinical outcome of the patient. Up to 14% of children and 27% of adults hospitalized with acute hyperglycemic crisis presented with DKA complicated by severe hyperglycemia and hyperosmolality[11]. DKA and HHS have high mortality rates and therefore require careful evaluation of any patient presenting in the emergency department (ED) with hyperglycemia[44]. There are some small case series that suggest patients with HHS-DKA overlap have poorer outcomes than those with isolated DKA or HHS; however, no systematic analysis has been done of a large sample of patients presenting with different types of hyperglycemic crises.

For DKA and HHS to be resolved successfully, timely diagnosis, comprehensive clinical evaluation, and effective management are imperative. The location of treating DKA depends upon its severity and precipitating cause. For example, severe DKA due to myocardial infarction or sepsis should be managed in ICU[32]. Mild to moderate DKA can be managed in the ED or within step-down units, but only if close nursing monitoring is utilized. The time to resolve DKA is found to be similar in both ICU and non-ICU settings. HHS has a higher mortality rate in comparison to DKA and should be managed in the ICU[12]. History has profound importance in unveiling the cause of severe hyperglycemia in a patient with a known diagnosis of diabetes. Common precipitating causes of hyperglycemia include skipping insulin or antidiabetic medications, psychiatric illnesses, substance abuse, and infection[41]. The treatment goals for DKA and HHS are similar and include replenishing intravascular fluid levels, bringing hyperglycemia and hyperosmolality to normal levels, correcting ketonemia and electrolyte imbalance, and treatment of precipitating causes[45]. Intravenous fluids, insulin, potassium, and bicarbonate are required for treating both DKA and HHS. In addition, continuous monitoring of IV fluid administration rate, urine output, and insulin dosage is necessary to assess response to medical therapy. Hourly monitoring of vitals, as well as mental and hydration status, is also recommended. Measurement of serum glucose, electrolytes, ketones, venous pH, bicarbonate, and anion gap should be done every 2-4 h. As part of the initial evaluation, hemoglobin A1c, complete blood count with differential, basic metabolic panel, urinalysis, coagulation profile, cardiac enzymes, and hepatic enzymes are

also needed. Chest X-ray, urine and blood cultures, lipase, and ECG can also be performed to identify the precipitating cause. Further testing can be done based on specific cases[44]. The initial therapy for both DKA and HHS is IV fluids. Patient vital signs, electrolyte levels, and urinary output may dictate fluid therapy[46].

IV FLUIDS

Intravenous fluids, especially isotonic saline (0.9% NaCl), are a critical aspect of treating hypertensive emergencies like DKA and HHS. In addition to expanding the intravascular volume and improving renal blood flow, it also reduces insulin resistance by decreasing levels of counter-regulatory hormones. A 500-1000 mL/h of normal saline is recommended to be administered during the first 2-4 h. Depending upon the serum sodium levels and hydration status, the rate of infusion can be reduced to 250 mL/hour. When glucose levels are 200 mg/dL, a fluid containing 5%-10% dextrose should be used to allow insulin to be continued until ketonemia has been corrected without causing hypoglycemia[45]. There is a 3-6-liter fluid deficit in DKA and almost 8 to 10 Liters in HHS. One hundred mL/kg of body weight water is a deficit in DKA and 100-200 mL/kg in HHS. Ringer lactate and 0.9% NaCl have similar efficacy in terms of normalizing pH, but the time to normalize blood glucose takes significantly longer with ringer lactate as compared to 0.9% NaCl[47]. Hence, 0.9% NaCl is the preferred fluid of choice in hyperglycemic emergencies. However, a two-cluster-randomized clinical trial showed that balanced crystalloids resulted in a more rapid resolution of acute DKA[48]. Of note, rapid fluid administration to correct hyperosmolality in the pediatric population may result in cerebral edema, with mortality reaching as high as 24 percent[46].

INSULIN

Insulin administration is the cornerstone of treating hyperglycemic emergencies like DKA and HHS. As insulin inhibits endogenous glucose production and increases peripheral glucose utilization, serum glucose is rapidly lowered. Glucagon secretion, lipolysis, and ketogenesis are also inhibited by insulin. The infusion rate should be modified, so that serum glucose drops by 50 mg/dL/h. In this way, glucose can act as an indicator of insulin action[40]. IV infusion of 0.1 unit (u) regular insulin/kg body weight bolus followed by continuous infusion at 0.1 u/kg/h is the treatment of choice. This regimen is continued until blood glucose is approximately 200 mg/dL. The insulin dose is then reduced by half, and the rate of infusion is maintained at 0.05-0.02 u/kg/h[12]. At this point, the addition of 5% dextrose helps maintain glucose levels while simultaneously resolving ketoacidosis[45]. Subcutaneous administration of rapid-acting insulin analogs like lispro and aspart is an effective replacement for regular insulin. Mild to moderate DKA often responds to subcutaneous insulin. In the ED, subcutaneous insulin is often a better option where one-to-one staffing is often not available[49].

An initial bolus of 0.2-0.3 U/kg of rapid-acting insulin followed by 0.1-0.2 U/kg every 1-2 h is also an effective strategy. At < 250 mg/dL glucose levels, the dose of rapid-acting insulin is reduced by half to 0.05 u/kg/h[50]. In patients with HHS, the insulin infusion rate can be decreased at a high glucose level (< 300 mg/dL)[51]. However, the use of rapid-acting insulin analogs is not advised in hypertensive patients, severe DKA, and HHS[5]. In order to resolve DKA, it is necessary to have a serum bicarbonate level of ≥ 18 mEq/L, a blood pH of > 7.30, and a normal anion gap. HHS resolution requires serum osmolality < 310 mOsm/kg. Serum glucose level ≤ 250 mg/dL is required for the resolution of both DKA and HHS. The shorter half-life of insulin necessitates co-administration of subcutaneous basal insulin-like NPH or glargine at a minimum of 2 h before stopping IV insulin infusion[52]. This helps prevent rebound hyperglycemia, ketogenesis, and recurrent metabolic acidosis[52]. After the resolution of an acute hyperglycemic event in a patient with no history of insulin use, a daily insulin dose of 0.5-0.6 units/kg/d is divided into half basal, and the half bolus is started. For patients with an inability to tolerate oral intake, basal insulin alone or continuous insulin drip is recommended until they can eat. Patients with a diagnosis of diabetes can be continued on the previous insulin regimen[53]. However, if they have a history of recurrent hypoglycemia or hyperglycemia, then the insulin dose should be adjusted according to HbA1c. Patients with T1D, DKA, and HHS are most likely to benefit from insulin regimens with basal insulin and rapid-acting insulin analogs[53].

POTASSIUM

Measurement of potassium level is necessary before giving insulin because insulin causes an intracellular shift of potassium resulting in hypokalemia. Patients with both DKA and HHS are potassium depleted even if they have normal serum potassium levels. The potassium level must be > 3.3 mEq/L before insulin therapy is initiated[53]. Giving insulin to a patient with admission potassium <

3.3 mEq/L can result in symptomatic hypokalemia, muscle weakness, and cardiac arrhythmias. To maintain a potassium concentration of 4-5 mEq/L, potassium replacement should begin at < 5.2 mEq/L and > 3.3 mEq/L. Extreme caution is needed while replenishing potassium in anuric patients due to the risk of hyperkalemia. Two hourly monitoring of potassium is needed while administering insulin infusion[54]. Death in the initial phases of hyperglycemic crises is mainly due to hyperkalemia, whereas the most common cause of death in late phases of treatment is hypokalemia. Thus 2-h monitoring of serum potassium is of profound importance during treatment.

pH

Acidosis usually resolves with intravenous fluids and insulin, and routine administration of bicarbonate is not recommended as it has not shown any benefit in improving clinical outcomes[55]. In fact, bicarbonate increases the risk of developing hypokalemia, rebound acidosis, hypoxia, hypernatremia, and cerebral edema[56]. The only case where bicarbonate is recommended is when the blood pH is < 6.9. The use of bicarbonate therapy is not recommended in patients with mild DKA with pH > 7.0 or with HHS because of the lack of therapeutic benefits, bicarbonate therapy is generally avoided[28].

A mild degree of hypophosphatemia is common in hyperglycemic emergencies, and phosphate replacement is only indicated when blood levels are below 1 mg/dL, especially in a patient with respiratory or cardiac distress. There is no beneficial effect of phosphate replacement in DKA[57,58].

CONCLUSION

In summary, DKA and HHS are both hyperglycemic emergencies that have the potential for serious complications if not recognized and treated early and aggressively. The admission number for both hyperglycemic diseases has increased in the past two decades as the incidence of DM has also increased. However, the admission number for DKA is higher than those of HHS, although the mortality rate of HHS remains greater. An overlap in both DKA and HHS is associated with an increased mortality rate than both isolated DKA and HHS. These patients present with a combination of significant hyperglycemia and severe ketosis. Important clinical signs to look for in patients with the hyperglycemic crisis are polydipsia, polyuria, weight loss, signs of intravascular volume loss, mental status change, abdominal pain, evaluation of blood glucose, BUN, creatinine, anion gap, serum ketones, serum osmolality, urinalysis, urine ketones. ABG is important in the initial assessment of DKA, HHS, or a patient presenting with a mixed picture. It is important to recognize the signs and symptoms of DKA and HHS, but it is just as vital to recognize when they overlap as the mortality can increase two-fold when dealing with a case of overlapping disease. DKA and HHS are both medical emergencies that require prompt diagnosis and therapy. Treatment goals for both DKA and HHS involve restoring intravascular volume, normalizing serum glucose and serum osmolality, correcting electrolyte imbalances, reducing serum ketones, and treatment of the underlying infection or cause. The mainstay therapy for both DKA and HHS is insulin administration to inhibit ketogenesis, lipolysis, and gluconeogenesis. As of now, patients presenting with combined features of both DKA and HHS are treated under the same guidelines as isolated DKA patients, as there is no strict consensus for management.

FOOTNOTES

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REFERENCES

- 1 **Kitabchi AE**, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009; **32**: 1335-1343 [PMID: 19564476 DOI: 10.2337/dc09-9032]
- 2 **Nasa P**, Chaudhary S, Shrivastava PK, Singh A. Euglycemic diabetic ketoacidosis: A missed diagnosis. *World J Diabetes* 2021; **12**: 514-523 [PMID: 33995841 DOI: 10.4239/wjd.v12.i5.514]
- 3 **Puttanna A**, Padinjakara R. Diabetic ketoacidosis in type 2 diabetes mellitus. *Pract Diabetes* 2014; **31**: 155-158 [DOI: 10.1002/pdi.1852]
- 4 **Islam T**, Sherani K, Surani S, Vakil A. Guidelines and controversies in the management of diabetic ketoacidosis - A mini-review. *World J Diabetes* 2018; **9**: 226-229 [PMID: 30588284 DOI: 10.4239/wjd.v9.i12.226]
- 5 **Gosmanov AR**, Gosmanova EO, Kitabchi AE. Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Sperling MA, Stratakis CA, Trencle DL, Wilson DP, editors. *Endotext*. South Dartmouth (MA): MDText.com, Inc., 2000. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK279052/> [DOI: 10.1016/s2352-4642(20)30006-7]
- 6 **Rawla P**, Vellipuram AR, Bandaru SS, Pradeep Raj J. Euglycemic diabetic ketoacidosis: a diagnostic and therapeutic dilemma. *Endocrinol Diabetes Metab Case Rep* 2017; **2017** [PMID: 28924481 DOI: 10.1530/EDM-17-0081]
- 7 **Peters AL**, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. *Diabetes Care* 2015; **38**: 1687-1693 [PMID: 26078479 DOI: 10.2337/dc15-0843]
- 8 **Modi A**, Agrawal A, Morgan F. Euglycemic Diabetic Ketoacidosis: A Review. *Curr Diabetes Rev* 2017; **13**: 315-321 [PMID: 27097605 DOI: 10.2174/1573399812666160421121307]
- 9 **Pasquel FJ**, Umpierrez GE. Hyperosmolar hyperglycemic state: a historic review of the clinical presentation, diagnosis, and treatment. *Diabetes Care* 2014; **37**: 3124-3131 [PMID: 25342831 DOI: 10.2337/dc14-0984]
- 10 **Aldhaefi M**, Aldardeer NF, Alkhani N, Alqarni SM, Alhammad AM, Alshaya AI. Updates in the Management of Hyperglycemic Crisis. *Front Clin Diabetes Healthc* 2022; **2** [DOI: 10.3389/fcdhc.2021.820728]
- 11 **Pasquel FJ**, Tsegka K, Wang H, Cardona S, Galindo RJ, Fayfman M, Davis G, Vellanki P, Migdal A, Gujral U, Narayan KMV, Umpierrez GE. Clinical Outcomes in Patients With Isolated or Combined Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State: A Retrospective, Hospital-Based Cohort Study. *Diabetes Care* 2020; **43**: 349-357 [PMID: 31704689 DOI: 10.2337/dc19-1168]
- 12 **Fayfman M**, Pasquel FJ, Umpierrez GE. Management of Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. *Med Clin North Am* 2017; **101**: 587-606 [PMID: 28372715 DOI: 10.1016/j.mcna.2016.12.011]
- 13 **American Diabetes Associations**. Hyperglycemic Crises in Patients With Diabetes Mellitus. [cited August 10 2022]. Available from: https://diabetesjournals.org/care/article/25/suppl_1/s100/23564/Hyperglycemic-Crises-in-Patients-With-Diabetes
- 14 **Kitabchi AE**, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care* 2006; **29**: 2739-2748 [PMID: 17130218 DOI: 10.2337/dc06-9916]
- 15 **Miyoshi Y**, Ogawa O, Oyama Y. Nivolumab, an Anti-Programmed Cell Death-1 Antibody, Induces Fulminant Type 1 Diabetes. *Tohoku J Exp Med* 2016; **239**: 155-158 [PMID: 27297738 DOI: 10.1620/tjem.239.155]
- 16 **Robert C**, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J, Lorigan P, Neyns B, Blank CU, Hamid O, Mateus C, Shapira-Frommer R, Kosh M, Zhou H, Ibrahim N, Ebbinghaus S, Ribas A; KEYNOTE-006 investigators. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med* 2015; **372**: 2521-2532 [PMID: 25891173 DOI: 10.1056/NEJMoa1503093]
- 17 **Clotman K**, Janssens K, Specenier P, Weets I, De Block CEM. Programmed Cell Death-1 Inhibitor-Induced Type 1 Diabetes Mellitus. *J Clin Endocrinol Metab* 2018; **103**: 3144-3154 [PMID: 29955867 DOI: 10.1210/je.2018-00728]
- 18 **Kyriacou A**, Melson E, Chen W, Kempgowda P. Is immune checkpoint inhibitor-associated diabetes the same as fulminant type 1 diabetes mellitus? *Clin Med (Lond)* 2020; **20**: 417-423 [PMID: 32675150 DOI: 10.7861/clinmed.2020-0054]
- 19 **Fadini GP**, Bonora BM, Avogaro A. SGLT2 inhibitors and diabetic ketoacidosis: data from the FDA Adverse Event

- Reporting System. *Diabetologia* 2017; **60**: 1385-1389 [PMID: 28500396 DOI: 10.1007/s00125-017-4301-8]
- 20 **Umpierrez GE**, Kelly JP, Navarrete JE, Casals MM, Kitabchi AE. Hyperglycemic crises in urban blacks. *Arch Intern Med* 1997; **157**: 669-675 [PMID: 9080921]
- 21 **Wachtel TJ**, Silliman RA, Lambertson P. Prognostic factors in the diabetic hyperosmolar state. *J Am Geriatr Soc* 1987; **35**: 737-741 [PMID: 3611564 DOI: 10.1111/j.1532-5415.1987.tb06351.x]
- 22 **Malone ML**, Gennis V, Goodwin JS. Characteristics of diabetic ketoacidosis in older versus younger adults. *J Am Geriatr Soc* 1992; **40**: 1100-1104 [PMID: 1401693 DOI: 10.1111/j.1532-5415.1992.tb01797.x]
- 23 **Wachtel TJ**. The diabetic hyperosmolar state. *Clin Geriatr Med* 1990; **6**: 797-806 [PMID: 2224747]
- 24 **Canarie MF**, Bogue CW, Banasiak KJ, Weinzimer SA, Tamborlane WV. Decompensated hyperglycemic hyperosmolarity without significant ketoacidosis in the adolescent and young adult population. *J Pediatr Endocrinol Metab* 2007; **20**: 1115-1124 [PMID: 18051930 DOI: 10.1515/jpem.2007.20.10.1115]
- 25 **Alberti KG**. Role of glucagon and other hormones in development of diabetic ketoacidosis. *Lancet* 1975; **1**: 1307-1311 [PMID: 49515 DOI: 10.1016/s0140-6736(75)92315-6]
- 26 **Hoffman WH**, Burek CL, Waller JL, Fisher LE, Khichi M, Mellick LB. Cytokine response to diabetic ketoacidosis and its treatment. *Clin Immunol* 2003; **108**: 175-181 [PMID: 14499240 DOI: 10.1016/s1521-6616(03)00144-x]
- 27 **Rains JL**, Jain SK. Oxidative stress, insulin signaling, and diabetes. *Free Radic Biol Med* 2011; **50**: 567-575 [PMID: 21163346 DOI: 10.1016/j.freeradbiomed.2010.12.006]
- 28 **Natarajan S**, Kulkarni R, Tangri A. Fatal Cerebral Edema in a Young Adult with Diabetic Ketoacidosis: Blame the Bicarbonate-Google Search. Available from: <https://www.google.com/search?q=Natarajan+S%2C+Kulkarni+R%2C+Tangri+A.+Fatal+Cerebral+Edema+in+a+Young+Adult+with+Diabetic+Ketoacidosis%3A+Blame+the+Bicarbonate&oq=Natarajan+S%2C+Kulkarni+R%2C+Tangri+A.+Fatal+Cerebral+Edema+in+a+Young+Adult+with+Diabetic+Ketoacidosis%3A+Blame+the+Bicarbonate&aqs=chrome..69i57.3115j0j4&sourceid=chrome&ie=UTF-8> [DOI: 10.1155/2020/5917459]
- 29 **Dabelea D**, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, Imperatore G, D'Agostino RB Jr, Mayer-Davis EJ, Pihoker C; SEARCH for Diabetes in Youth Study Group. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. *Pediatrics* 2014; **133**: e938-e945 [PMID: 24685959 DOI: 10.1542/peds.2013-2795]
- 30 **Umpierrez GE**, Khajavi M, Kitabchi AE. Review: diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic syndrome. *Am J Med Sci* 1996; **311**: 225-233 [PMID: 8615398 DOI: 10.1097/00000441-199605000-00006]
- 31 **Karslioglu French E**, Donihi AC, Korytkowski MT. Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome: review of acute decompensated diabetes in adult patients. *BMJ* 2019; **365**: 11114 [PMID: 31142480 DOI: 10.1136/bmj.11114]
- 32 **Glaser N**. Pediatric diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Pediatr Clin North Am* 2005; **52**: 1611-1635 [PMID: 16301085 DOI: 10.1016/j.pcl.2005.09.001]
- 33 **Deeter KH**, Roberts JS, Bradford H, Richards T, Shaw D, Marro K, Chiu H, Pihoker C, Lynn A, Vavilala MS. Hypertension despite dehydration during severe pediatric diabetic ketoacidosis. *Pediatr Diabetes* 2011; **12**: 295-301 [PMID: 21443581 DOI: 10.1111/j.1399-5448.2010.00695.x]
- 34 **Matz R**. Hypothermia in diabetic acidosis. *Hormones* 1972; **3**: 36-41 [PMID: 4631908 DOI: 10.1159/000178256]
- 35 **Umpierrez G**, Freire AX. Abdominal pain in patients with hyperglycemic crises. *J Crit Care* 2002; **17**: 63-67 [PMID: 12040551 DOI: 10.1053/jcrc.2002.33030]
- 36 **Kitabchi AE**, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, Wall BM. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care* 2001; **24**: 131-153 [PMID: 11194218 DOI: 10.2337/diacare.24.1.131]
- 37 **Heldeweg M**, Drossaers JR, Berend K. Hyperosmolar Therapy for Diabetic Hyperosmolar Ketoacidosis. *Eur J Case Rep Intern Med* 2022; **9**: 003135 [PMID: 35169581 DOI: 10.12890/2022_003135]
- 38 **Brar PC**, Tell S, Mehta S, Franklin B. Hyperosmolar diabetic ketoacidosis-- review of literature and the shifting paradigm in evaluation and management. *Diabetes Metab Syndr* 2021; **15**: 102313 [PMID: 34731818 DOI: 10.1016/j.dsx.2021.102313]
- 39 **Westerberg DP**. Diabetic ketoacidosis: evaluation and treatment. *Am Fam Physician* 2013; **87**: 337-346 [PMID: 23547550]
- 40 **Dhatariya KK**, Vellanki P. Treatment of Diabetic Ketoacidosis (DKA)/Hyperglycemic Hyperosmolar State (HHS): Novel Advances in the Management of Hyperglycemic Crises (UK Versus USA). *Curr Diab Rep* 2017; **17**: 33 [PMID: 28364357 DOI: 10.1007/s11892-017-0857-4]
- 41 **Wu XY**, She DM, Wang F, Guo G, Li R, Fang P, Li L, Zhou Y, Zhang KQ, Xue Y. Clinical profiles, outcomes and risk factors among type 2 diabetic inpatients with diabetic ketoacidosis and hyperglycemic hyperosmolar state: a hospital-based analysis over a 6-year period. *BMC Endocr Disord* 2020; **20**: 182 [PMID: 33317485 DOI: 10.1186/s12902-020-00659-5]
- 42 **Umpierrez G**, Korytkowski M. Diabetic emergencies - ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. *Nat Rev Endocrinol* 2016; **12**: 222-232 [PMID: 26893262 DOI: 10.1038/nrendo.2016.15]
- 43 **Umpierrez GE**, DiGirolamo M, Tuvlin JA, Isaacs SD, Bhoola SM, Kokko JP. Differences in metabolic and hormonal milieu in diabetic- and alcohol-induced ketoacidosis. *J Crit Care* 2000; **15**: 52-59 [PMID: 10877365 DOI: 10.1053/jcrc.2000.7900]
- 44 **Echouffo-Tcheugui JB**, Garg R. Management of Hyperglycemia and Diabetes in the Emergency Department. *Curr Diab Rep* 2017; **17**: 56 [PMID: 28646357 DOI: 10.1007/s11892-017-0883-2]
- 45 **Kreider KE**, Gabrielski AA, Hammonds FB. Hyperglycemia Syndromes. *Nurs Clin North Am* 2018; **53**: 303-317 [PMID: 30099998 DOI: 10.1016/j.cnur.2018.04.001]
- 46 **Lenahan CM**, Holloway B. Differentiating Between DKA and HHS. *J Emerg Nurs* 2015; **41**: 201-7; quiz 270 [PMID: 25442808 DOI: 10.1016/j.jen.2014.08.015]
- 47 **Van Zyl DG**, Rheeder P, Delpont E. Fluid management in diabetic-acidosis--Ringer's lactate versus normal saline: a randomized controlled trial. *QJM* 2012; **105**: 337-343 [PMID: 22109683 DOI: 10.1093/qjmed/hcr226]
- 48 **Self WH**, Evans CS, Jenkins CA, Brown RM, Casey JD, Collins SP, Coston TD, Felbinger M, Flemmons LN, Hellervik

- SM, Lindsell CJ, Liu D, McCain NS, Niswender KD, Slovis CM, Stollings JL, Wang L, Rice TW, Semler MW; Pragmatic Critical Care Research Group. Clinical Effects of Balanced Crystalloids vs Saline in Adults With Diabetic Ketoacidosis: A Subgroup Analysis of Cluster Randomized Clinical Trials. *JAMA Netw Open* 2020; **3**: e2024596 [PMID: 33196806 DOI: 10.1001/jamanetworkopen.2020.24596]
- 49 **Frid AH**, Kreugel G, Grassi G, Halimi S, Hicks D, Hirsch LJ, Smith MJ, Wellhoener R, Bode BW, Hirsch IB, Kalra S, Ji L, Strauss KW. New Insulin Delivery Recommendations. *Mayo Clin Proc* 2016; **91**: 1231-1255 [PMID: 27594187 DOI: 10.1016/j.mayocp.2016.06.010]
- 50 **Kaser S**, Sourij H, Clodi M, Schneeweiß B, Laggner AN, Luger A. [Correction to: Therapie der akuten diabetischen Stoffwechsellentgleisungen bei Erwachsenen (Update 2019)]. *Wien Klin Wochenschr* 2019; **131**: 389 [PMID: 31388747 DOI: 10.1007/s00508-018-1423-z.]
- 51 **Adeyinka A**, Kondamudi NP. Hyperosmolar Hyperglycemic Syndrome. 2022 May 22. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan- [PMID: 29489232]
- 52 **Hipszer B**, Joseph J, Kam M. Pharmacokinetics of intravenous insulin delivery in humans with type 1 diabetes. *Diabetes Technol Ther* 2005; **7**: 83-93 [PMID: 15738706 DOI: 10.1089/dia.2005.7.83]
- 53 **Dhatariya KK**. Defining and characterising diabetic ketoacidosis in adults. *Diabetes Res Clin Pract* 2019; **155**: 107797 [PMID: 31344382 DOI: 10.1016/j.diabres.2019.107797]
- 54 **Baldrighi M**, Sainaghi PP, Bellan M, Bartoli E, Castello LM. Hyperglycemic Hyperosmolar State: A Pragmatic Approach to Properly Manage Sodium Derangements. *Curr Diabetes Rev* 2018; **14**: 534-541 [PMID: 29557753 DOI: 10.2174/1573399814666180320091451]
- 55 **Lever E**, Jaspan JB. Sodium bicarbonate therapy in severe diabetic ketoacidosis. *Am J Med* 1983; **75**: 263-268 [PMID: 6309004 DOI: 10.1016/0002-9343(83)91203-2]
- 56 **Fraley DS**, Adler S. Correction of hyperkalemia by bicarbonate despite constant blood pH. *Kidney Int* 1977; **12**: 354-360 [PMID: 24132 DOI: 10.1038/ki.1977.122]
- 57 **Wilson HK**, Keuer SP, Lea AS, Boyd AE 3rd, Eknoyan G. Phosphate therapy in diabetic ketoacidosis. *Arch Intern Med* 1982; **142**: 517-520 [PMID: 6802095]
- 58 **Fisher JN**, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. *J Clin Endocrinol Metab* 1983; **57**: 177-180 [PMID: 6406531 DOI: 10.1210/jcem-57-1-177]



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