Hyperglycemic Crises in Diabetic Patients.


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Abstract:
Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are two important causes of mortality and morbidity in patients with diabetes. Mortality rates are <5% in DKA and about 15% in HHS, much of which are avoidable with appropriate management. The prognosis is worsened with aging, hypotension, coma and concomitant life-threatening illnesses. The criteria for DKA and HHS are somewhat arbitrary, although glucose level is higher and ketone body level is minimal in HHS, but they are two extremes in a spectrum of diabetic metabolic decompensation. In general, DKA occurs in type 1 and most often HHS occurs in type 2 diabetes; however, each type of diabetes may be associated with DKA or HHS. Both conditions are associated with marked dehydration, electrolyte disturbances and insulin deficiency and increased counterregulatory hormones, so treatment consists of water and electrolytes replacement and insulin administration. Recognition and treatment of precipitating factors and frequent monitoring of patients are considered the most crucial aspects of the management.

Keywords: Diabetes, Diabetic ketoacidosis, Hyperosmolar hyperglycemic state, Hyperosmolar nonketotic coma, Hyperosmolar states, Diabetes complications.
Learning Objectives:

By completing this continuing medical education offering course, participants should be able to:
1. Recognize the definition and pathogenesis of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS).
2. Differentiate DKA from HHS by recognizing their symptoms, signs and laboratory data.
3. Manage DKA-HHS patients by fluid, insulin, potassium and bicarbonate therapy.
4. Identify the complications of DKA-HHS and their treatment-related complications.

Definition:

The criteria for diagnosis and classification of DKA and HHS are presented in Table 1. Both DKA and HHS are associated with decreased effective concentration of insulin with HHS characteristically having higher serum glucose, more dehydration, higher osmolarity and no acidosis. The mild, moderate and severe classification of DKA is based on serum bicarbonate and arterial pH (1,2).

<table>
<thead>
<tr>
<th></th>
<th>DKA</th>
<th>HHS</th>
</tr>
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<tbody>
<tr>
<td><strong>Mild</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma glucose</td>
<td>&gt; 250</td>
<td>&gt; 250</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.25-7.30</td>
<td>7.00-&lt;7.24</td>
</tr>
<tr>
<td>Serum bicarbonate</td>
<td>15-18</td>
<td>10-&lt;15</td>
</tr>
<tr>
<td>Urine Ketone *</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Serum Ketone *</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Effective Serum Osmolarity**</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Mental Status</td>
<td>Alert</td>
<td>Alert/Drowsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stupor/Coma</td>
</tr>
</tbody>
</table>

*Nitroprusside reaction method*
*Calculation: Effective serum osmolality: 2(measured Na+ (mEq/L)) + glucose (mg/dl)/18

Pathogenesis: Carbohydrate metabolism:

Both DKA and HHS result from insulin deficiency (relative or absolute) coupled with increased levels of counterregulatory hormones (glucagon, catecholamines, cortisol and growth hormone). These hormonal alterations result in hyperglycemia due to three mechanisms: a) increased gluconeogenesis, b) accelerated glycogenolysis and c) impaired glucose utilization by peripheral tissues. When insulin/glucagon ratio is decreased, all substrates for gluconeogenesis (alanine, glutamine, lactate and glycerol) are increased owing to proteolysis muscle glycogenolysis and lipolysis. Most important hormones in accentuating gluconeogenesis are glucagon and cortisol(1). Glucagon reduces fructose-2,6-bisphosphate and as a result, stimulates fructose-1,6-bisphosphatase and inhibits phosphofructokinase. The net effect of these processes is reduction of glycolysis(1-6). Hence, carbon flux is increased toward gluconeogenic pathway. Furthermore, cortisol increases activity of gluconeogenic enzymes and catecholamines induce glycogenolysis.

Fat Metabolism:

In DKA insulin is absent or very low in comparison to HHS. Lack of insulin as an antilipolytic hormone and increased levels of catecholamines, as lipolytic hormones accelerate lipase activity which leads to free
fatty acid increment. FFAs are converted to ketone bodies under effect of glucagon. Glucagon diminishes malonyl-CoA level through blocking of conversion of acetyl-CoA to malonyl-CoA. Low malonyl-CoA level stimulates carnitine-palmitoyl transferase which is required for transferring FFAs into the mitochondria, where FFA conversion to ketone bodies occurs. The net result is ketone body production. In addition, DKA is associated with decreased ketone body clearance.

**Fluid and electrolyte changes:**

As insulin stimulates salt and H2O reabsorption in proximal and distal nephrons and phosphate reabsorption in proximal tubule, insulin deficiency in DKA and HHS results in loss of water and electrolytes which is exaggerated with hyperglycemia and hyperketonemia. In both DKA and HHS hyperglycemia exceeds kidney threshold, so glycosuria ensues which induces osmotic diuresis resulting in dehydration and loss of fluid and electrolytes concomitant with polyuria and polydipsia. In HHS, fluid intake is also inadequate, because thirst mechanism is impaired or the patient is unable to drink due to comorbid conditions and debilitated state. This is the cause of more severe dehydration, prerenal azotemia and higher osmolarity in HHS. Also renal function impairment causes decrease of glucose excretion, therefore, hyperglycemia is more severe in HHS.

In DKA, ketone body accumulation leads to acidosis. Acidemia contributes to lowering of blood pressure due to its negative inotropic effect on heart and vasodilatation. In HHS, ketosis is mild and there may be mild lactic acidosis. Etiology of lower ketonemia in HHS is not well known but is suggested that insulin level is adequate for inhibiting lipolysis or ketone body formation but not adequate for glucose utilization by peripheral tissues.

**Precipitating factors:**

Most common precipitating factors for DKA and HHS are infections. Even mild infection such as pharyngitis may precipitate DKA. Occult infections such as furuncle, dental abscess and perirectal infections should be sought. Other factors that predispose to DKA include: omission of insulin doses, inaccessibility of medical care, cerebrovascular accident (CVA), myocardial infarction (MI), trauma, cocaine and drugs such as pentamidine, clozapine and beta-sympathomimetics. In nearly 20% of patients, DKA is the first presentation of diabetes. The length of hospital stay of
patients with DKA is apparently correlated with precipitating factors(11). Precipitating factors for HHS are CVA, MI, drugs such as phenytoin, thiazides and lucocorticoids(1,9,12,13).

**Signs and Symptoms:**
DKA usually develops acutely (in less than 24 hours) and presents with abdominal pain, nausea, vomiting and then signs of dehydration (decreased skin turgor, tachycardia, dry mucose membrane and hypotension) appear. Severe DKA is associated with kussmaul respiration. Despite volume depletion, patients have warm skin (due to acidosis-induced vasodilatation). Often breath smells of acetone (nail polish remover). Most patients are normothermic or hypothermic in spite of infection (owing to vasodilatation and diminishing of fuel-substrate)(1). Ten percent of the patients are comatous and in one study about 1/3 of DKA patients were hyperosmolar which was correlated with serum osmolarity(14).

HHS usually develops insidiously with polydipsia, polyuria and weight loss over several days. The patients have marked dehydration and no kussmaul respiration or abdominal pain. Coma is more common in HHS than DKA(20%). Occasionally patients have focal neurologic signs and seizure which should be distinguished from CVA(1,5).

**Diagnosis:**
Prompt recognition and treatment is critical. Special attention should be paid to patency of airways, mental status, cardiovascular and renal status, sources of infection and state of hydration. Blood glucose should be immediately determined by finger stick, and urine and plasma ketone be measured using test strips or tablets. Diagnosis can be made with history and physical examination and these bedside tests. Also blood should be obtained for determination of glucose, urea, electrolytes, creatinine and osmolality. Arterial blood gas is used on admission for both determination of pH and Po2, but subsequent pH should be obtained by venous sampling. Venous pH is usually lower by 0.03 than arterial pH (1). Blood and urine cultures and throat swab should also be obtained, if indicated. Usually in DKA, blood glucose is >250 mg/dl, pH<7.3 and plasma ketone level is >3 mmol/lit. In HHS blood glucose is higher than 600 mg/dl and osmolality is >330mosm/kg and pH>7.3(1,2,13).

In 15% of DKA patients, blood glucose is below 300mg/dl (Insulin pump users, use of insulin on the way to the hospital, pregnancy, long fasting and alcohol consumption)(15).

**Laboratory tests:**
Plasma sodium level is usually low, because hyperglycemia draws water from intracellular space, diluting the plasma. So that, for every 100mg/dl elevation of glucose above 100mg/dl, plasma sodium is decreased by 1.6mEq/lit(1)(in some reviews: 2.4mEq/lit)(16). In addition severe hyperlipidemia leads to pseudohyponatremia and pseudonormoglycemia in DKA(17,18). On admission plasma potassium may be high, low
or normal, despite total body potassium deficit. This is due to shift of intracellular potassium secondary to acidosis, hyperosmolarity and lack of insulin. The majority of cases with hyperglycemic crises have leukocytosis even in the absence of infection but WBC >25,000 signifies infection\(^1\). Creatinine levels in DKA are falsely elevated due to interference of chemical reaction with ketone bodies\(^{15}\). Amylase level may also be high due to extrapancreatic source of amylase (from parotid)\(^{20}\) and therefore for diagnosis of pancreatitis serum lipase should be measured\(^{1-2}\), although even lipase may be falsely elevated\(^{2,4}\). Triglyceride increase is due to decreased activity of lipoprotein lipase and elevation of VLDL production (sometimes to level of 10,000 mg/dl)\(^4\). Liver function test values are elevated in as many as one-third of the patients because of liver enlargement (fatty liver) and interference by hyperlipidemia in liver enzyme assays\(^{21}\).

In HHS plasma glucose level may be as high as 5,000 mg/dl, serum urea is higher than in DKA and serum sodium may be normal or even high owing to severe dehydration. There may be mild acidosis because of lactic acidosis\(^{1,4}\). Other paraclinical procedure which should be performed is electrocardiogram to rule out MI and changes secondary to hypokalemia or hyperkalemia\(^1\).

**Treatment:**

As noted earlier, frequent monitoring of patient is paramount in overall management of patients in hyperglycemic crises. Using a flow chart for recording vital signs, volume status, state of consciousness, glucose, urea, electrolyte levels, pH and insulin doses is helpful (Figure 2)\(^{22}\). Serum glucose must be checked every 1 to 2 hours. Serum electrolytes and venous pH should be assessed every 2-6 hours. If patient has hypokalemia on admission cardiac monitoring is mandatory and insulin should not be given if serum K is <3.3 mEq/L until hypokalemia is corrected. Treatment include fluid and electrolyte replacement with adequate potassium, insulin therapy as well as bicarbonate administration, if indicated. Treatment of precipitating factors, particularly infection is critical for proper recovery from DKA.

**Fluid replacement:**

Rehydration decreases counterregulantory hormones, expand extracellular volume and so diminishes blood glucose by 23%\(^{23}\). Although in both DKA and HHS fluid loss is hypotonic, the first liter of hydrating solution should be normal saline which is infused as quickly as possible. The following hydrating solution will depend on the patient’s serum Na level (0.9% NaCl for low serum sodium and 0.45% NaCl for normal or high serum sodium, which is administered at rate of 0.5-1 liter per hour). Subsequently, 1 liter of fluid every 4 hours is infused until the patient is well hydrated\(^{1,5,8,13}\). Fluid deficit in HHS is about 7-9 liters and in DKA about 4-6 liters\(^1\). Once blood glucose reaches 250 mg/dl, 5% or 10% dextrose should be added to the replacement
fluid. In all HHS patients and in DKA cases who are unconscious, in shock state or old age with cardiovascular disease, a central venous pressure line should be inserted to prevent volume overload(1).

**Insulin therapy:**

Although fluid administration decreases blood glucose, it does not resolve acidosis, so insulin is necessary(14,24). In both DKA and HHS, increase levels of counterregulatory hormones, electrolyte loss and hyperosmolarity promote insulin resistance(8,25). In DKA, ketoacidosis contributes to this resistance as well. Nonetheless, replacement of fluid alone decreases stress hormones and osmolarity. As a result the insulin resistance is not a major problem. Therefore low dose insulin regimens are as effective as high dose regimens when insulin treatment is preceded with adequate hydration. In addition, incidence of hypokalemia and hypoglycemia is markedly diminished with low dose insulin therapy(1,26).

Insulin therapy is usually initiated with an intravenous(IV) bolus of 10 units of regular insulin followed by IV infusion of 0.1U/kg/hr(6-10 units). If infusion pump is not available or nursing care is inadequate, regular insulin is administered by intramuscular(IM) route and a loading dose of 10 units by IM and 10 units by IV route is given followed by IM injection of 6-10 U/hr(26,27).

Recent studies from the University of Tennessee have demonstrated that fast-acting insulin (lispro or aspartate) given every one to two hours subcutaneously in a general medical ward (with frequent glucose monitoring and adequate nursing care) is as effective as the use of IV regular insulin infusion in an intensive care unit setting(28,29). Table 2 demonstrates the outcome results of lispro and aspart insulins in general works compared to IV regular insulin in ICU. The results were similar but the ICU protocol proved more costly(28,29).

**Table 2. Comparative Effects of Subcutaneous Fast-Acting Insulin vs IV Regular Insulin in DKA (From References 28 and 29)**

<table>
<thead>
<tr>
<th></th>
<th>Aspart* SC-2 hr</th>
<th>Lispro* SC-1 hr</th>
<th>Regular** Intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay</td>
<td>3.9 ± 1.3</td>
<td>4 ± 1</td>
<td>4.5 ± 0.8</td>
</tr>
<tr>
<td>(days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of therapy until BG&lt;250 mg/dl (hours)</td>
<td>6.1 ± 1</td>
<td>7 ± 1</td>
<td>7.1 ± 1</td>
</tr>
<tr>
<td>Duration of therapy until resolution of DKA (hours)</td>
<td>10.7 ±0.8</td>
<td>10 ± 1</td>
<td>11 ± 0.7</td>
</tr>
<tr>
<td>Amount of insulin until resolution of DKA (units)</td>
<td>94 ± 8</td>
<td>92 ± 9</td>
<td>82 ± 9</td>
</tr>
<tr>
<td>Episodes of hypoglycemia</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are means ± SE

* Treated in general medical wards** Treated in ICU

When blood glucose reaches 250mg/dl, insulin infusion is decreased to 0.05U/kg/hr(In IM or SC route, insulin is decreased to 6 units every 2 hours). The dose of insulin is similar in DKA and HHS(1,13). Some authors believe that insulin sensitivity is higher in HHS and recommend lower doses of insulin(12). If four hours after treatment the pH doesn’t rise, or if glucose is not decreased by 10% in one hour after initial hydration, insulin dose should be at least doubled. In HHS where most patients’ mental status are altered, only IV route is used. Ketone body assessment using nitroprusside strips isn’t useful for evaluation of recovery. Nitroprusside strip primarily detects acetocetate, but not β-
hydroxybutyrate. rehydration and insulin therapy cause beta-hydroxybutyrate conversion to acetoacetate, hence ketone body levels is falsely elevated during recovery\textsuperscript{(1,10,13)}. In some centers tests that directly measure beta-hydroxybutyrate are available and are invaluable for evaluation of treatment effect on ketonemia.

**Potassium:**

Insulin therapy and rehydration inevitably may promote hypokalemia in the absence of potassium supplement. Therefore, adding potassium to fluids is necessary. At presentation, if initial serum potassium is $<3.3$ mEq/L, insulin therapy should be delayed until potassium replacement achieves level $>3.5$ mEq/L. If potassium is above $5.5$mEq/L, potassium administration is withheld, but serum K is determined every two hours. The choice of potassium salt is controversial. Some use potassium chloride(KCL) for all of potassium needed, but others recommend to administer one third of K as potassium phosphate to prevent hyperchloremic acidosis and hypophosphatemia. Rate of potassium administration is 20-40mEq/hr which should be added to fluids with maximal concentration of 40mEq per hour in severe potassium deficiency\textsuperscript{(1,2)}.

**Bicarbonate:**

Most authorities don’t advocate use of bicarbonate unless severe acidosis exists. Alkalization causes paradoxical CNS acidosis, aggravation of hypokalemia, impairment of oxyhemoglobin dissociation and delay of ketoanion metabolism. Prospective randomized study has demonstrated that use of bicarbonate for pH $>7.0$ provides no improvement in the outcome of patients with DKA\textsuperscript{(30)}. Therefore, it is prudent to give bicarbonate in DKA for pH below 7.0. Once pH is $<6.95$, 50mmol bicarbonate is diluted with 200ml of water and infused over 2 hours. In pH $<6.9$, 100mmol bicarbonate is diluted with 400ml of H2O and is infused over 4 hours\textsuperscript{(1,2,5,10)}.

**Phosphate Therapy:**

Use of phosphate therapy has been controversial, but a prospective randomized study demonstrated that phosphate therapy does not have influence on outcome in adult patients with DKA except for possible exacerbation of hypocalcemia\textsuperscript{(31)}. Phosphate replacement is however recommended in severe phosphorus depletion (phosphate $<1$mg/dl)\textsuperscript{(1,10)}.

**Second phase of treatment:**

Once the patient is able to eat, insulin is injected subcutaneously(SC)\textsuperscript{(2)}, but continuation of IV insulin for 1-2 hour after first dose of SC insulin is critical to prevent DKA relapse. In patients who are known cases of diabetes, after resolution of DKA insulin may be given in the same dose which they received before DKA\textsuperscript{(2,10)}. All patients with recurrent DKA should receive adequate education to prevent recurrence of DKA. Treatment of HHS is very similar to DKA except no bicarbonate is used and the amount of fluid for hydration is greater\textsuperscript{(1,2,8,13)}. One study suggests that low dose insulin (1U/h) and slow fluid replacement(slow-motion
reequilibration) results in zero mortality (32). Dose response studies in DKA indicate that 1-2U of insulin may be adequate for antilipolytic activity of insulin, whereas 3-4U/h may be sufficient to inhibit gluconeogenesis (8).

Other measures:
Since signs of infection may be missing or misleading, antibiotic use should be considered with less caution than usual. Also, if any invasive procedure is performed, antibiotics should be started (5). Some recommend low dose heparin in patients who are very hyperosmolar, old or unconscious (5) and others administer 325mg of aspirin (4). In patients who are agitated, a small dose of IV lorazepam can be used (5). Because coma in HHS and DKA is related to hyperosmolality, if patient is unconscious despite of low serum osmolarity, other causes of unconsciousness should be ruled out (5). In HHS, patients may be chronically ill and have vitamin B deficiency, thus vitamins particularly vitamin B replacement should be considered.

Complications:
Complications include hypokalemia, hypoglycemia, cerebral edema, acute respiratory distress syndrome, thromboembolic events, gastric dilatation, erosive gastritis, mucormycosis and rhabdomyolysis (1,4,5,10).

Hypokalemia and hypoglycemia are avoidable with judicious use of potassium and dextrose. Cerebral edema is less common in HHS than DKA. Its pathogenesis is not well known. It is suggested that cerebral cells generate idiogenic osmoles during severe hyperglycemia and when extracellular fluid osmolality falls rapidly with treatment, fluid is drawn into the cells. This hypothesis is attractive, but in one study brain swelling was present before initiation of therapy and recommended to reduce the blood glucose slowly (1). Recent study in children with DKA suggests that use of bicarbonate therapy and overhydration may be associated with cerebral edema (33).

It is common for patients recovering from DKA to develop a non-anion gap hyperchloremic metabolic acidosis. Several reasons have been postulated for this phenomenon, the most reasonable one is the decreased amount of bicarbonate in the proximal renal tubules, resulting in greater chloride reabsorption. It may take several days for hyperchloremic metabolic acidosis to resolve (34,35).

Prevention:
As HHS and DKA are associated with significant mortality, prevention is extremely important. This implies intensive patient education and access to healthcare resources. The patient should be informed about "sick-day-rules". It must be emphasized that insulin should never be omitted. The most common etiology of recurrent DKA is insulin omission, so attention to psychiatric condition of patients is important (1,10,36).
References:

30. Morris LR, Murphy MB, Kitabchi AE. Bicarbonate therapy in severe diabetic


