REVIEW ARTICLE

Hyperglycemic Crises in Diabetic Patients

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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, 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 counter-regulatory hormones, so treatment consists of water and electrolyte replacement and insulin administration. Recognition and treatment of precipitating factors and frequent monitoring of patients are considered the most crucial aspects of the management.

Key Words: Diabetes, Diabetic ketoacidosis, hyperglycemic state, Nonketotic coma, Hyperosmolar states, Diabetes complications

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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]

Pathogenesis

Carbohydrate metabolism

Both DKA and HHS result from insulin deficiency (relative or absolute) coupled with increased levels of counter-regulatory hormones (glucagon, cathecholamines, cortisol and growth hormone) (Fig.1). 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. The most important hormones in accentuating gluconeogenesis are glucagon

sis are glucagon and cortisol.[1] Glucagon reduces fructose-2,6-bisphophate and as a result, stimulates fructose-1,6-bisphosphatase and inhibits phosphofrucotokinase. The net effect of these processes is a reduction in glycolysis.[1-6] Hence, carbon flux is increased toward gluconeogenic pathway. Furthermore, cortisol increases activity of the gluconeogenic enzymes and cathecholamines 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. Free fatty acids (FFAs) are converted to ketone bodies under the effect of glucagon. Glucagon diminishes malonyl-CoA level through blocking the convertion 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.[4] The net result is ketone body production. In addition, DKA is associated with decreased ketone body clearance.[7]

Table 1. Diagnostic criteria in diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS)[1,2]

	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25-7.30	7.00-<7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15-18	10-<14.9	<10	>15
Urine ketone*	Positive	Positive	Positive	Small
Serum ketone*	Positive	Positive	Positive	Small
Effective Serum Osmolarity†	Variable	Variable	Variable	>320 mOsm/kg
Mental Status	Alert	Alert/Drowsy	Stupor/Coma	Stupor/Coma

*Nitroprusside reaction method; †: Effective serum osmolality= [$2Na^+$ (mEq/L)]+[glucose (mg/dL)]/18

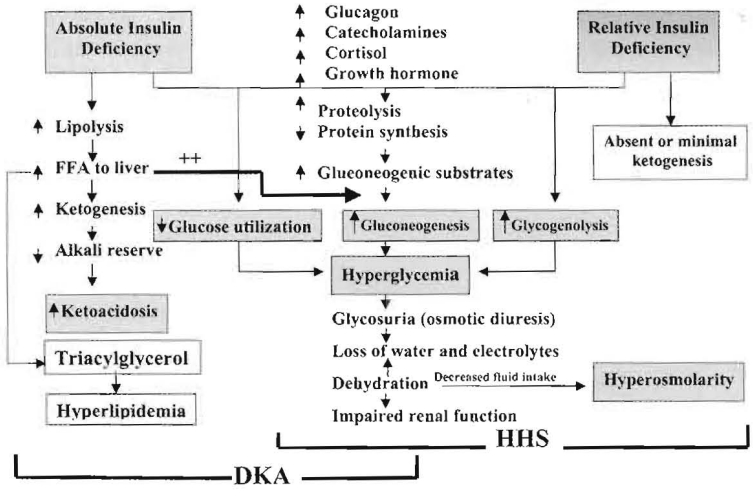

Fig. 1. Pathogenesis of DKA and HHS[10]

Fluid and electrolyte changes

As insulin stimulates salt and H_2O reabsorption in proximal and distal nephrons and phosphate reabsorption in proximal tubule, insulin deficiency in DKA and HHS results in water and electrolytes loss which is exaggerated by hyperglycemia and hyperketonemia.[8] 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 the thirst mechanism is impaired or the patient is unable to drink due to comorbid conditions and a debilitated state. This is the cause of more severe dehydration, prerenal azotemia and higher osmolarity in HHS. Also renal function impairment causes decreased glucose excretion, therefore, hyperglycemia is more severe in HHS.[1,5,9]

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. The reason for this 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 peripheal tissues.[1-5]

Precipitating factors

The most common precipitating factors for DKA and HHS are infections. Even a mild infection such as pharyngitis may precipitate DKA.[2] Occult infections such as furuncle, dental abscess and perirectal infections should be sought.[4] 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.[1-3] 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 glucocorticoids.[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 kaussmaul respiration. Despite volume depletion, patients have warm skin (due to acidosis-induced vasodilatation), and often their 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 comatose 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 kaussmaul 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 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 PO_2, 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/Lt. 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, the so called euglycemic DKA (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. For every 100mg/dL elevation of glucose above 100mg/dL, plasma sodium is decreased by 1.6 mEq/L[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 the 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 count >25,000 signifies infection.[1] Creatinine levels in DKA are falsely elevated due to interference of chemical reaction with ketone bodies.[19] 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] Triglycerides increase due to decreased activity of lipoprotein lipase and elevation of VLDL production (sometimes up to 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 5,000mg/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] 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 (Fig. 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 the 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 includes fluid and electrolyte replacement with adequate potassium, insulin therapy as well as bicarbonate administration, if indicated. Treatment of precipitating factors, particularly infections, is critical for proper recovery from DKA.

Height _____
Weight _____
Initially _____
After 24hr _____

SUGGESTED

DKA / HHS FLOWSHEET

	DATE: HOUR:														
	MENTAL STATUS*														
	TEMPERATURE														
	PULSE														
	RESPIRATION/DEPTH**														
	BLOOD PRESSURE														
	SERUM GLUCOSE (MG/DL)														
	SERUM KETONES														
	URINE KETONES														
ELECTROLYTES	SERUM Na^+ (mEq/L)														
	SERUM K^+ (mEq/L)														
	SERUM CL^- (mEq/L)														
	SERUM HCO_3^- (mEq/L)														
	SERUM BUN (mg/dl)														
	EFFECTIVE OSMOLALITY 2 [measured Na (mEq/L)] + Glucose (mg/dl)/18														
	ANION GAP														
ARTERIAL/VENOUS BLOOD GASES	pH VENOUS(V) ARTERIAL (A)														
	pO_2														
	pCO_2														
	O_2 SAT														
INSULIN	UNITS in PAST HOUR														
	ROUTE														
INTAKE FLUID/METABOLITES	0.45% NaCl (ml) PAST HOUR														
	0.9% NaCl (ml) PAST HOUR														
	5% DEXTROSE (ml) PAST HOUR														
	KCL (mEq) PAST HOUR														
	PO_4 (mMOLES) PAST HOUR														
	OTHER														
OUTPUT	URINE (ml)														
	OTHER														

* A-ALERT D-DROWSY S-STUPOROUS C-COMATOSE
** D-DEEP S-SHALLOW N-NORMAL

From: Kitabchi et al

Fig. 2. Suggested DKA/HHS flowsheet[22]

Fluid replacement

Rehydration decreases counter-regulantory hormones, expands extracellular volume and thus diminishes the 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 next 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, increased levels of counterregulatory hormones, electrolyte loss and hyperosmolarity promote insulin resistance.[8,25] In DKA, ketoacidsis 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 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]

When blood glucose reaches 250 mg/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 does not 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 is not use ful for evaluation of recovery. Nitroprusside strip primarily detects acetoacetate, but not β-hydroxybutyrate. Rehydration and insulin stherapy cause betahydroxybutyrate conversion to acetoacetate, hence ketone body lev els are falsely elevated during recovery.[1,10,13] In some centers, tests that directly measure betahydroxybutyrate are available and are in valuable for evaluation of treatment effect on ketonemia.

Table 2. Comparative effects of subcutaneous fast-acting insulin vs IV regular insulin in DKA[28,29]

	Aspart* SC-2hr	Lispro* SC-1hr	Regular† Intravenous
Length of hospital stay (days)	3.9 (1.3)	4 (1)	4.5 (0.8)
Duration of therapy until BG<250 mg/dL (hours)	6.1 (1)	7 (1)	7.1 (1)
Duration of therapy until resolution of DKA (hours)	10.7 (0.8)	10 (1)	11 (0.7)
Amount of insulin until resolution of DKA (units)	94 (8)	92 (9)	82 (9)
Episodes of hypoglycemia	1	1	1

SC: subcutaneous; hr: hour; Data are means±SE
*Treated in general medical wards † Treated in ICU

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 administration of one third of K as potassium phosphate to prevent hyperchloremic acidosis and hypophosphatemia. Rate of potassium administration is 20-40 mEq/hr which should be added to fluids with maximal amount of 40 mEq per hour in severe potassium deficiency.[1,2]

Bicarbonate

Most authorities do not advocate use of bicarbonate unless severe acidosis exists. Alkalinization causes paradoxical CNS acidosis, aggravation of hypokalemia, impairment of oxyhemoglobin dissociation and delay of ketoanion metablism. One prospective randomized study has demonstrated that use of bicarbonate for pH >7.0 provides no improvement in the outcome of patients with DKA.[30] Therefore, it is prudent to give bicarbonate in DKA for pH below 7.0. Once pH is <6.95, 50 mmol bicarbonate is diluted with 200 ml of water and infused over 2 hours. In pH <6.9, 100 mmoL bicarbonate is diluted with 400 mL of H_2O and is infused over 4 hours.[1,2,5,10]

Phosphate therapy

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

Second phase of treatment

Once the patient is able to eat, insulin is injected subcutaneously (SC),[2] but continuation of IV insulin for 1-2 hours 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.[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.[1,2,9,13] One study suggests that low dose insulin (1 U/hr) and slow fluid replacement (slow-motion reequilibration) results in zero mortality.[32] Dose response studies in DKA indicate that 1-2 units of insulin may be adequate for antilipolytic activity of insulin,whereas 3-4 U/hr may be sufficient to inhibit gluconeogenesis.[8]

Other measures

Since signs of infection may be missing or misleading, antibiotic use should be considered less conservatirely 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 325 mg 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 low serum osmolarity, other causes of unconsciousness should be ruled out.[2] In HHS, pateints 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, errosive 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 it was 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 such as excess NaCl during hydration, but 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]

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