ACUTE COMPLICATIONS OF DIABETES MELLITUS

the two most serious acute metabolic complications of diabetes

- Diabetic ketoacidosis (DKA) a
- hyperosmolar hyperglycemic state (HHS)

- The triad of uncontrolled hyperglycemia, metabolic acidosis, and increased total body ketone concentration characterizes DKA.
- HHS is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis.

- These metabolic derangements result from the combination of absolute or relative insulin deficiency and an increase in counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone).

- Most patients with DKA have autoimmune type 1 diabetes; however, patients with type 2 diabetes are also at risk during the catabolic stress of acute illness such as trauma, surgery, or infections

- DKA is the most common cause of death in children and adolescents with type 1 diabetes and accounts for half of all deaths in diabetic patients younger than 24 years of age

- Insulin levels in HHS are inadequate to facilitate glucose utilization by insulin sensitive tissues but adequate to prevent lipolysis and subsequent ketogenesis

Table 1—*Diagnostic criteria for DKA and HHS*

	DKA			HHS
	Mild (plasma glucose >250 mg/dl)	Moderate (plasma glucose >250 mg/dl)	Severe (plasma glucose >250 mg/dl)	Plasma glucose >600 mg/dl
Arterial pH	7.25–7.30	7.00 to <7.24	<7.00	>7.30
Serum bicarbonate (mEq/l)	15–18	10 to <15	<10	>18
Urine ketone*	Positive	Positive	Positive	Small
Serum ketone*	Positive	Positive	Positive	Small
Effective serum osmolality†	Variable	Variable	Variable	>320 mOsm/kg
Anion gap‡	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

*Nitroprusside reaction method. †Effective serum osmolality: 2[measured Na^+ (mEq/l)] + glucose (mg/dl)/18. ‡Anion gap: $(Na^+) - [(Cl^- + HCO_3^-$ (mEq/l)]. (Data adapted from ref. 13.)

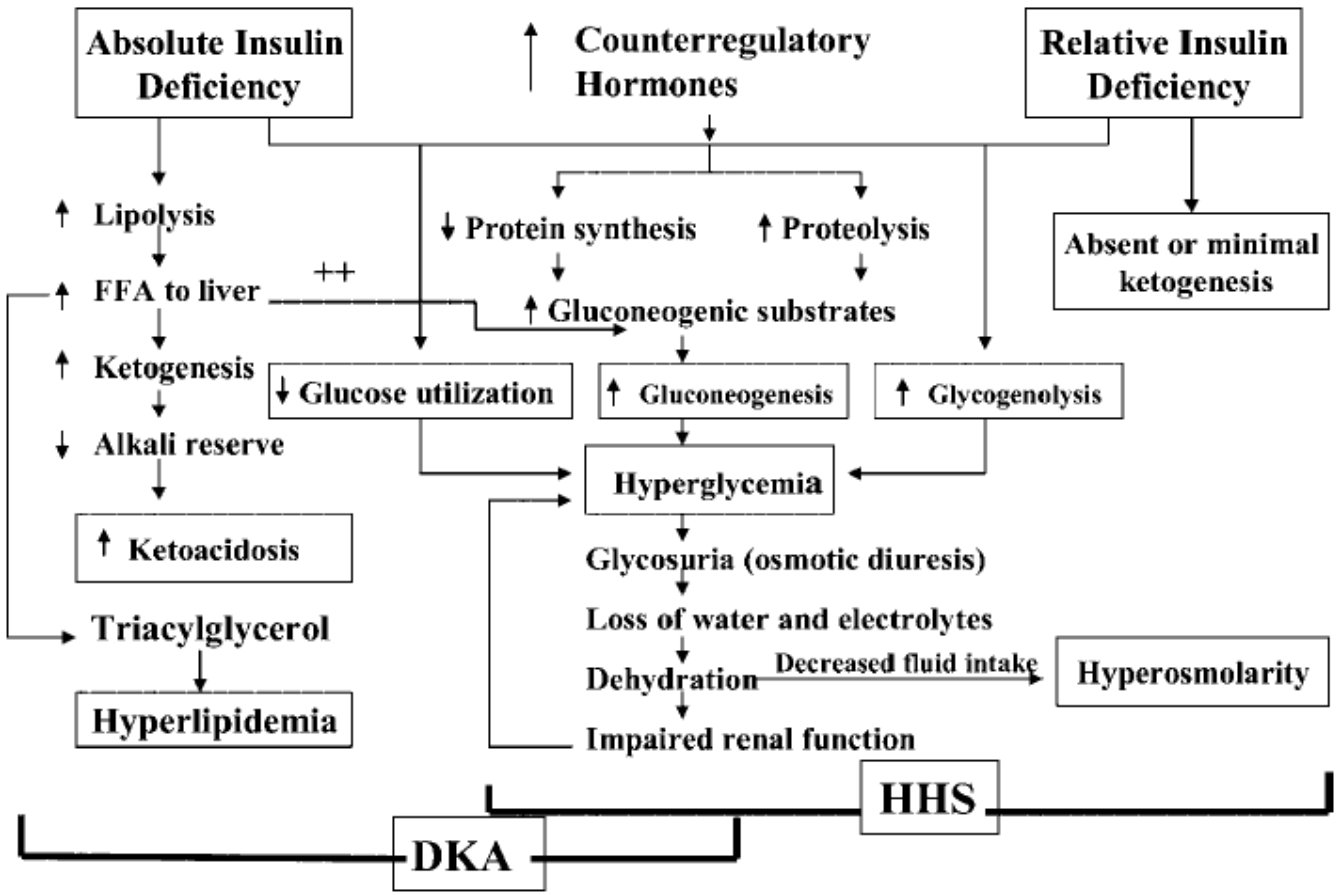
PRECIPITATING FACTORS

- The most common precipitating factor in the
- development of DKA and HHS is infection

- Other precipitating factors include discontinuation of or inadequate insulin therapy, pancreatitis, myocardial infarction, cerebrovascular accident, and drugs (corticosteroids, thiazides,
- sympathomimetic agents, and pentamidine)

- In most patients with HHS, restricted water intake is due to the patient being bedridden and is exacerbated by the altered thirst response of the elderly.

PATHOGENESIS



“Flatbush diabetes/ type 1.5 diabetes/ ketosis-prone type 2 diabetes

- over half of newly diagnosed adult African American and Hispanic subjectswith unprovoked DKA have type 2 diabetes
- The clinical presentation insuch cases is acute (as in classical type 1 diabetes);
- After a short period of insulin therapy, prolonged remission is with eventual cessation of insulin treatment and maintenance of glycemic control with diet or oral antihyperglycemicagents.
- In such patients, clinical and metabolic features of type 2 diabetes include a high rate of obesity, a strongfamily history of diabetes, a measurable pancreatic insulin reserve, a low prevalenceof autoimmune markers of -celldestruction, and the ability to discontinue insulin therapy during follow-up

Clinical

- Although the symptoms of poorly controlled diabetes may be present for several days, the metabolic alterations typical of ketoacidosis usually evolve within a short time frame (typically 24 h).
- Occasionally, the entire symptomatic presentation may evolve or develop more acutely, and the patient may present with DKA with no prior clues or symptoms.
- For both DKA and HHS, the classical clinical picture includes a history of polyuria, polydipsia, weight loss, vomiting, dehydration, weakness, and mental status change.
- Nausea, vomiting, diffuse abdominal pain are frequent in patients with DKA (50%) but are uncommon in HHS

Examination

- Physical findings may include poor skin turgor, Kussmaul respirations
- (in DKA), tachycardia, and hypotension. Mental status can vary from full alertness to profound lethargy or coma, with the latter more frequent in HHS.

- Focal neurologic signs (hemianopia and hemiparesis) and seizures (focal or generalized) may also be features of HHS

- The initial laboratory evaluation of patients include determination of plasma glucose, blood urea nitrogen, creatinine, electrolytes (with calculated anion gap), osmolality, serum and urinary ketones, and urinalysis, as well as initial arterial blood gases and a complete blood count with a differential.
- An electrocardiogram, chest X-ray, and urine, sputum, or blood cultures should also be obtained

- Although the nitroprusside test (both in urine and in serum) is highly sensitive, it can underestimate the severity of ketoacidosis because this assay does not recognize the presence of -hydroxybutyrate, the main metabolic product in ketoacidosis
- If available, measurement of serum - hydroxybutyrate may be useful for diagnosis

- Approximately 10% of the DKA population presents with so-called “euglycemic DKA”—glucose levels 250 mg/dl (38). This could be
- due to a combination of factors, including exogenous insulin injection en route to the hospital, antecedent food restriction , and inhibition of gluconeogenesis.

- On admission, leukocytosis with cell counts in the 10,000 –15,000 mm3 range is the rule in DKA and may not be indicative of an infectious process.
- However, leukocytosis with cell counts 25,000 mm3 may designate infection and require further evaluation (

- The admission serum sodium is usually low because of the osmotic flux of water from the intracellular to the extracellular space in the presence of hyperglycemia. An increased or even normal serum sodium concentration in the presence of hyperglycemia indicates a rather profound degree of free water loss.
- To assess the severity of sodium and water deficit, serum sodium may be corrected by adding 1.6 mg/dl to the measured serum sodium for each 100 mg/dl of glucose above 100 mg/dl

- The occurrence of stupor or coma in a diabetic patient in the absence of definitive elevation of effective osmolality (320 mOsm/ kg) demands immediate consideration of other causes of mental status change.

- Serum potassium concentration may be elevated because of an extracellular shift of potassium caused by insulin deficiency, hypertonicity, and acidemia
- Patients with low normal or low serum potassium concentration on admission have severe total-body potassium deficiency and require careful cardiac monitoring and more vigorous potassium replacement because treatment lowers potassium further and can provoke cardiac dysrhythmia.

- Hyperamylasemia has been reported in 21–79% of patients with DKA however, there is little correlation between the presence, degree, or isoenzyme type of hyperamylasemia and the presence of gastrointestinal symptoms (nausea, vomiting, and abdominal pain) or pancreatic imaging studies
- A serum lipase determination may be beneficial in the differential diagnosis of pancreatitis; however, lipase could also be elevated in DKA in the absence of pancreatitis

Differential diagnosis

- Not all patients with ketoacidosis have DKA.
- Starvation ketosis and alcoholic ketoacidosis are distinguished by clinical history and by plasma glucose concentrations that range from mildly elevated (rarely 200 mg/dl) to hypoglycemia

- although alcoholic ketoacidosis can result in profound acidosis, the serum bicarbonate concentration in starvation ketosis is usually not 18 mEq/l.

- DKA must also be distinguished from other causes of high–anion gap metabolic acidosis, including lactic acidosis; ingestion of drugs such as salicylate, methanol, ethylene glycol, and paraldehyde; and acute /chronic renal failure

- Because lactic acidosis is more common in patients with diabetes than in nondiabetic persons and because elevated lactic acid levels may occur in severely volume contracted pt -plasma lactate should
- be measured on admission

Treatment -Fluid therapy

- Initial fluid therapy is directed toward expansion of the intravascular, interstitial, and intracellular volume, all of which are
- reduced in hyperglycemic crises and restoration of renal perfusion.
- In the absenceof cardiac compromise, isotonic saline(0.9% NaCl) is infused at a rate of 15–20 ml kg body wt1 h1 or 1–1.5 l during the first hour.
- Subsequent choice for fluid replacement depends on hemodynamics, the state of hydration, serum electrolyte levels, and urinary output.
- In general, 0.45% NaCl infused at 250–500 ml/h is appropriate if the corrected serum sodium is normal or elevated; 0.9% NaCl at a similar rate is appropriate if corrected serum sodium is low
- Fluid replacement should correct estimated deficits within the first 24 h

Treatment -Fluid therapy

- Once the plasma glucose is 200 mg/dl, 5% dextrose should be added to replacement fluids to allow continued insulin administration until ketonemia is controlled while at the same time avoiding hypoglycemia.

Insulin

- Regular insulin iv @ the infusion of 0.1 units kg1 h1
- No bolus
- Low-dose insulin infusion protocols decrease plasma glucose concentration at a rate of 50–75 mg dl1 h1 .
- If plasma glucose does not decrease by 50–75 mg from the initial value in the first hour, the insulin infusion should be increased every hour until a steady glucose decline is achieved
- Treatment of patients with mild and moderate DKA with subcutaneous rapid-acting insulin analogs every 1 or 2 h in non–intensive care unit (ICU) settings has been shown to be as safe and effective as the treatment with intravenous regular insulin in the ICU

- To prevent hypokalemia, potassium replacement is initiated after serum levels fall below the upper level of normal for the particular laboratory (5.0 –5.2 mEq/l).
- The treatment goal is to maintain serum potassium levels within the normal range of 4–5 mEq/l.
- Generally, 20–30 mEq potassium in each liter of infusion fluid is sufficient to maintain a serum potassium concentration within the normal range.

- DKA patients may present with significant hypokalemia. In such cases, potassium replacement should begin with fluid therapy, and insulin treatment should be delayed until potassium concentration is restored to 3.3 mEq/l to avoid life-threatening arrhythmias and respiratory muscle weakness

Bicarbonate

- bicarbonate therapy for DKA offers no advantage in improving cardiac or neurologic functions or in the rate of recovery of hyperglycemia and ketoacidosis.
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- several deleterious effects of bicarbonate therapy have been reported, such as increased risk of hypokalemia, decreased tissue oxygen uptake , cerebral edema , and development of paradoxical central nervous system acidosis.

- Because severe acidosis may lead to a numerous adverse vascular effects (63), it is recommended that adult patients
- with a pH 6.9 should receive 100 mmol sodium bicarbonate (two ampules) in 400 ml sterile water (an isotonic solution) with 20 mEq KCI administered at a rate of 200 ml/h for 2 h

Transition to s/c insulin

- Patients with DKA and HHS should be treated with continuous intravenous insulin until the hyperglycemic crisis is resolved. Criteria for resolution of ketoacidosis include a blood glucose 200 mg/dl and two of the following criteria: a serum bicarbonate level 15 mEq/l, a venous pH 7.3, and a calculated anion gap 12 mEq/l. Resolution of HHS is associated with normal osmolality and regain of normal mental status
- it is important to allow an overlap of 1–2 h between discontinuation of intravenous insulin and the administration of subcutaneous insulin

- In insulin-naïve patients, a multidose insulin regimen should be started at a dose of 0.5– 0.8 units kg1 day1 (13). Human insulin (NPH and regular) are usually given in two or three doses per day.
- More recently, basal-bolus regimens with basal (glargine and detemir) and rapid-acting insulin analogs (lispro, aspart, or glulisine) have proposed as a more physiologic insulin regimen in patients with type 1 diabetes.

Complications

- Hypoglycemia and hypokalemia are two common complications with overzealous treatment of DKA with insulin and bicarb

- Hyperchloremic non–anion gap acidosis, which is seen during the recovery phase of DKA, is self-limited with few clinical consequences
- This may be caused by loss of ketoanions, which are metabolized to bicarbonate during the evolution of DKA and excess fluid infusion of chloride containing fluids during treatment
- Cerebral edema, which occurs in 0.3–1.0% of DKA episodes in children, is extremely rare in adult patients during treatment of DKA

- A number of mechanisms have been proposed, which include the role of cerebral ischemia/hypoxia, the generation of various inflammatory mediators, increased cerebral blood flow,disruption of cell membrane ion transport, and a rapid shift in extracellular and intracellular fluids resulting in changes in
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- Prevention might include avoidance of excessive hydration and rapid reduction of plasma osmolarity, a gradual decrease in serum glucose, andnmaintenance of serum glucose between250–300 mg/dl until the patient's serum osmolality is normalized and mental statusis improved.
- Manitol infusion and mechanicalventilation are suggested for treatment of cerebral edema
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PREVENTION

- education regarding sick day management,
- 1) Early contact with the health care provider.
- 2) Emphasizing the importance of insulin insulin during an illness and the reasons never to discontinue without contactingthe health care team.
- 3) Review of blood glucose goals and the use of supplemental short- or rapidacting insulin.
- 4) Having medications available to suppress a fever and treat an infection.
- 5) Initiation of an easily digestible liquid diet containing carbohydrates and salt when nauseated.
- 6) Education of family members on sick day management and record keepingincluding assessing and documentingtemperature, blood glucose, and urine/ blood ketone testing; insulin administration;oral intake; and weight.