RECENT GUIDELINES IN MANAGEMENT OF HYPERGLYCEMIC EMERGENCIES

Essay

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Introduction

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Hyperglycemic crisis, or emergency, encompasses the spectrum of severe metabolic dysfunction of both diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), and the overlap syndrome of hyperosmolar ketoacidosis. DKA and HHS occur in the setting of relative or absolute insulin deficiency in the unique setting of excessive counter regulatory hormone levels, progressive volume depletion, and electrolyte loss ***(Umpierrez et al., 2009).***

In the past, DKA and HHS have been regarded as separate distinct entities, however overlap between the 2 syndromes is now well recognized. Hyperosmolar ketoacidosis has not been as well studied as classic DKA or HHS, although mortality rates have been consistently reported to be highest in this subgroup of patients ***(Ekpebegh et al., 2010).***

In DKA, metabolic acidosis is often the major finding, while the serum glucose concentration is generally below 800 mg/dl. However, serum glucose concentrations may exceed 900 mg/dl in patients with DKA who are comatose.

In HHS, there is little or no ketoacid accumulation, the serum glucose concentration frequently exceeds 1000 mg/dL , the serum osmolality may reach 380 mosmol/kg, and neurologic abnormalities are frequently present (including coma in 25%to 50%of cases) ***(Kitabchi et al., 2009).***

For both DKA and HHS, the classic clinical presentation includes a history of polyuria, polydipsia, weight loss, vomiting, abdominal pain (only in DKA), dehydration, weakness, clouded sensorium, and possibly coma.

The process of HHS usually evolves over several days to weeks, whereas the evolution of the acute DKA episode tends to be hours to days. Although symptoms of poorly controlled diabetes may be present for several days, the acidosis typical of ketoacidosis usually causes symptoms within a short time frame (typically <24 hours, but as short as 6 hours).

Physical findings may include poor skin turgor, Kussmaul respirations (if acidemic), tachycardia, hypotension, alteration in mental status, shock, and ultimately coma- which is more frequent in HHS. In younger patients with HHS, severe altered mental status is commonly seen and explained by the hyperosmolality ***(Bhowmick et al., 2005).***

DKA is distinguished by a blood glucose of >250 mg/dL, moderate ketonuria or ketonemia, arterial pH of <7.3, and a bicarbonate of <15 mEq/L . A diagnosis of HHS may be presumed in a diabetic patient with an altered sensorium, severely elevated glucose (usually >600 mg/dL), minimal or no ketonuria or ketonemia, serum osmolality >320 mOsm/kg, arterial pH (typically) >7.3, and a bicarbonate of >15 mEq/L ***(Kitabchi et al., 2009).***

A patient's history and review of systems should include questions that may point to an infection, the single most common precipitant of hyperglycemic crisis . A recent study suggests that infection more often accounts for severe DKA and that mild to

moderate DKA is associated with missed insulin doses or a change in regimen. Noninfectious precipitants may include prescribed or illicit drugs, MI, cerebrovascular accident, and pancreatitis. Patients with eating disorders may withhold their insulin to avoid weight gain, inadvertently precipitating DKA. Pregnancy is an insulin-resistant state, and gestational diabetes or pregnancy in established diabetics may also provoke hyperglycemic crisis ***(Barski et al., 2012).***

Goals of treatment include uncovering and managing the underlying cause, replacing fluid volume, resolving ketonemia, correcting acidosis, re-establishing euglycemia, improving mental status, optimizing renal perfusion, repleting electrolytes and minerals, and avoiding complications ***(Savage et al., 2011).***

- ***Epidemiology***

DKA is common in type 1 diabetes mellitus (T1DM) while HHS is common in type 2 diabetes mellitus (T2DM). However, there are also reports of ketosis-prone type T2DM where patients are able to discontinue insulin therapy and remain insulin-independent ***(Pinto et al., 2008).***

DKA is more common in young (<65 years) diabetic patients and in women compared to men. DKA mortality per 100,000 diabetic patients declined between 1985 and 2005 with the greatest reduction in mortality among those 65 years of age and older. Mortality in DKA is primarily due to the underlying precipitating illness and only rarely to the metabolic complications of hyperglycemia or ketoacidosis. The prognosis of DKA is substantially worse at the extremes of age and in the presence of coma and hypotension ***(Wang et al., 2006)***.

It is estimated that the rate of hospital admissions for HHS is lower than the rate for DKA, and accounts for less than 1 % of all primary diabetic admissions. HHS is most commonly seen in individuals older than 65 years with type 2 diabetes .Mortality attributed to HHS is higher than that of DKA, with rates ranging from 5 to 20 % ; as in DKA, mortality is most often due to the underlying illness or comorbidity ***(Kitabchi et al., 2001).***

DKA remains the most common cause of death in children and adolescents with type 1 diabetes (T1DM), with the vast majority of deaths related to cerebral edema. In adults however, mortality in DKA is considerably lower, although causes of death are not specifically defined in the literature. Cerebral edema is rare in adults being treated for DKA, and death is more likely to be caused by underlying disease states, cardiopulmonary complications, or consequences of hypokalemia ***(Wolfsdorf et al., 2009).***

Traditionally, mortality has been reported to be highest at the extremes of age. One of the major epidemiological shifts over the past 30 years has been the marked decrease in the mortality rates in patients older than 75. Mortality rates in the elderly have declined during the past 10 years to rates persistently lower than those of the youngest patients ***(Pinto et al., 2008).***

HHS mortality far exceeds that of DKA with reported mortality rates of 5 %–20 % in comparison with less than 5 % for DKA in adults, reported as low as <1 % in developed countries. However, the combination of hyperosmolality and ketoacidosis carries the worst prognosis despite the fact that these patients tend to be younger ***(De Vries et al., 2012).***

- ***Precipitating Factors :***

DKA is the initial presentation in 20 to 30% of patients with type 1 DM, whereas major underlying causes of DKA in known diabetic patients are infection and omission or inadequate dosing of insulin ***(Murphy et al., 2004).***

Other causes include:

- Silent myocardial infarction
- Pancreatitis
- Cerebrovascular accident
- Trauma
- Pulmonary embolism
- Medical, surgical, or emotional stress
- Pneumonia
- Pregnancy
- Drugs that affect carbohydrate metabolism such as: corticosteroids, sympathomimetic agents, alcohol and cocaine, antiarrhythmics , antihypertensives, beta blockers, histamine-receptor blockers, total parenteral nutrition (TPN) solutions and fluids that contain dextrose, thiazides, and second generation antipsychotic agents ***(Nyenwe et al., 2006).***

HHS most commonly occurs in patients with T2DM who have some concomitant illness that leads to reduced fluid intake. In general, any illness that predisposes to dehydration or to reduced insulin activity may lead to HHS. Acute febrile illnesses, including infections, account for the largest proportion of HHS cases.

Other conditions and illnesses associated with HHS include the following:

- Acromegaly
- Anesthesia
- Burns
- Cushing syndrome (eg, endogenous, exogenous, ectopic)

A preceding or inter-current infection (in particular, pneumonia or urinary tract infection [UTI]) is the single most common cause, but in a number of patients, the concomitant illness is not identifiable ***(Nugent et al., 2005).***

Table (1): Precipitating factors for diabetic ketoacidosis and hyperosmolar hyperglycemic state .

Diabetic Ketoacidosis	Hyperosmolar Hyperglycemic State
*Inadequate insulin treatment or noncompliance. *New onset diabetes (20 to 25 percent)	*Inadequate insulin treatment or noncompliance (21 to 41 percent)
➢ **Acute illness** * Infection (30 to 40 percent). * Cerebral vascular accident. * Myocardial infarction. * Acute pancreatitis. ➢ **Drugs:** Clozapine, olanzapine, cocaine, lithium, terbutaline.	➢ **Acute illness** * Infection (32 to 60 percent). * Pneumonia. * Urinary tract infection. * Sepsis, hypothermia. * Cerebral vascular accident. * Myocardial infarction. * Acute pancreatitis. * Acute pulmonary embolus. * Intestinal obstruction. * Dialysis, severe burns. * Mesenteric thrombosis. * Renal failure, heat stroke. * Subdural hematoma. ➢ **Endocrine:** Acromegaly, thyrotoxicosis, cushing's syndrome. ➢ **Drugs/therapy:** Beta-Adrenergic blockers, calcium-channel blockers, chlorpromazine, chlorthalidone cimetidine, clozepine, steroids diazoxide, ethacrynic acid, immunosuppressive agents, L-asparaginase, , phenytoin propranolol, thiazide diuretics, total parenteral nutrition. ➢ **Previously undiagnosed diabetes**

Adapted from :(Kitabchi et al., 2001).

Pathophysiological Consideration Of Hyperglycemic Emergencies

Pathophysiology

The triad of uncontrolled hyperglycemia, moderate to severe metabolic acidosis, and increased total body ketone concentration characterizes DKA .These metabolic derangements result from synergistic factors that include:

(1) Insulin deficiency (with or without impaired insulin action) leading to hyperglycemia.

(2) Insulin deficiency leading to uncontrolled lipolysis, which yields excess ketogenesis in DKA.

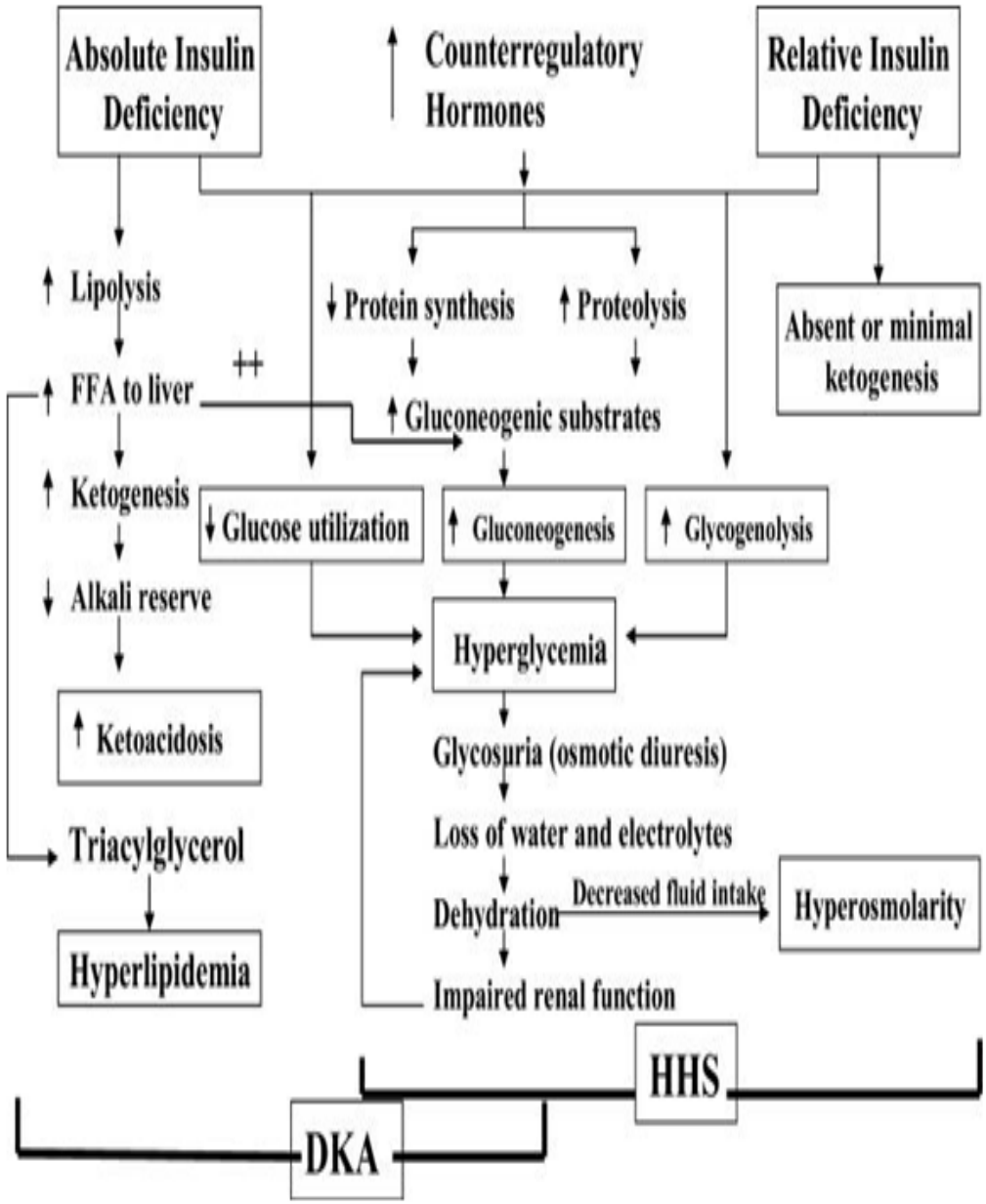
(3) Increased levels of counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) that further elevate glucose levels and promote lipolysis.

(4) Progressive dehydration and electrolyte loss from persistent glycosuria (exception here are anuric patients), and vomiting

(5) A decline in the glomerular filtration rate, exacerbating hyperglycemia, ketonemia, and related electrolyte abnormalities. DKA can occur either in patients with type 1 DM who have "absolute" insulin deficiency or with type 2 DM who have "relative" insulin deficiency.

The pathophysiology of hyperosmolality is not well understood, but develops in the setting of a greater degree of dehydration with or without excess ketogenesis ***(MacIsaac et al., 2002).***

Fig (1): Pathogenesis of DKA & HHS



According to: (Kitabchi et al., 2004)

- ***Spectrum of hyperglycemic crises :***

The basic mechanism underlying both DKA and HHS is reduction in the net effective action of circulating insulin, with concomitant elevation of counter-regulatory hormones, primarily glucagon, but also catecholamines, cortisol, and growth hormone ***(Rose et al., 2001).***

- ***Lipid Metabolism:***

Contrary to popular belief deranged lipid 'not carbohydrate' metabolism is the main cause of DKA. In essence DKA is caused by uncontrolled lipolysis in adipose tissue and uncontrolled ketogenesis in liver ***(Koutsari et al., 2006).***

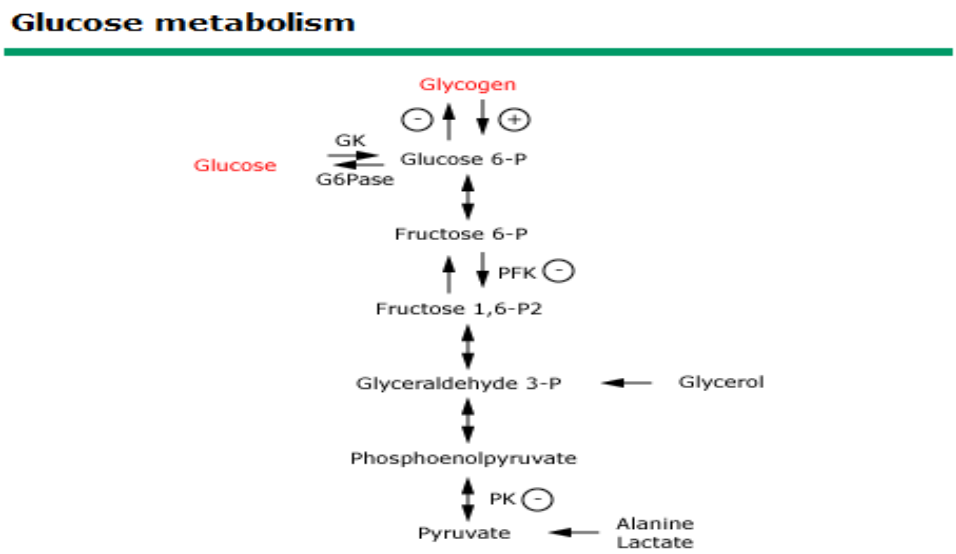
Under physiological conditions lipolysis is tightly controlled by lipases. Hormone-sensitive lipase and probably also adipose triglyceride lipase stimulate release of free fatty acids and glycerol into the circulation. This process is inhibited by insulin and low insulin levels increase lipolysis swiftly. The stress hormones, such as epinephrine, growth hormone and cortisol, stimulate lipolysis. It is plausible that dehydration per-se also participates in the stimulation of lipolysis ***(Keller et al., 2003).***

Ketogenesis occurs in the liver by oxidation of free fatty acids to ketoacids and ketone bodies. In DKA ketogenesis becomes uncontrolled and circulating levels of ketone bodies rise manifold. This occurs because of both increased supply of fatty acids to the liver and because low levels of insulin and high levels of glucagon in the liver promote ketogenesis. In normal individuals this unrestrained process is prevented by compensatory rises in insulin secretion, but this does not occur in type 1 diabetes ***(Cahill , 2006).***

➢ ***Glucose Metabolism:***

Hyperglycemia is usually present in DKA, but it is important to realise that DKA not infrequently presents with normal or modestly elevated glucose concentrations. Hyperglycemia is caused by a combination of lack of insulin and excess of stress hormones, leading to insulin resistance. In the liver this increases gluconeogenesis and hepatic glucose production ***(Moller et al., 2006).***

Fig(2) : **Normal glucose metabolism.**



Schematic representation of the major regulatory steps in hepatic gluconeogenesis (arrows that point upward) and glycolysis (arrows that point downward). The circles with positive or negative signs represent the reactions that are stimulated or inhibited by glucagon. Glucagon promotes gluconeogenesis and blocks glycolysis by decreasing the activity of phosphofructokinase (PFK) and pyruvate kinase (PK). The sites of entry of the gluconeogenetic precursors - glycerol, alanine, and lactate - are shown. Muscle cells lack glucose 6-phosphatase (G6Pase); they can therefore use glycogen for energy but cannot convert it to glucose for release into the systemic circulation. In pancreatic β-cells, glucokinase (GK) may act as the glucose sensor that regulates insulin release.

According to: (Keller et al., 2003)

➢ ***Normal response to hyperglycemia :***

The hormonal regulation of glucose homeostasis summarized briefly, the extracellular supply of glucose is primarily regulated by two hormones: insulin and glucagon. As the serum glucose concentration rises after a glucose meal, glucose enters the pancreatic beta cells, initiating a sequence of events leading to insulin release.

Insulin acts to restore normoglycemia by diminishing hepatic glucose production, via reductions in both glycogenolysis and gluconeogenesis, and by increasing glucose uptake by skeletal muscle and adipose tissue. Insulin-induced inhibition of glucagon secretion contributes to the decline in hepatic glucose production; this effect is mediated by direct inhibition of glucagon secretion and of the glucagon gene in the pancreatic alpha cells ***(Ahren , 2000)***.

➢ ***Hyperglycemia in DKA & HHS***

Hormonal alterations in DKA and HHS result in hyperglycemia by their impact on three fundamental processes in glucose metabolism:

- Impaired glucose utilization in peripheral tissues
- Increased gluconeogenesis (both hepatic and renal)
- Increased glycogenolysis

Insulin deficiency and/or resistance in diabetic patients impair peripheral glucose utilization in skeletal muscle. However, decreased glucose utilization alone will produce only postprandial hyperglycemia; increased gluconeogenesis is required for the