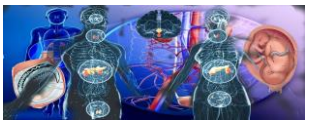
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Acute Metabolic Complications of Diabetes Mellitus: Diabetic Ketoacidosis (Dka) And the Hyperosmolar Hyperglycemic State

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Abstract

Diabetes mellitus (DM) affects the metabolism of primary macronutrients such as proteins, fats, and carbohydrates. Due to the high prevalence of DM, emergency admissions for hyperglycemic crisis, diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are fairly common and represent very challenging clinical management in practice. DKA and HHS are associated with high mortality rates if left not treated. The mortality rate for patients with DKA is < 1% and ~ 15% for HHS. DKA and HHS have similar pathophysiology with some few differences. HHS pathophysiology is not fully understood.

Keywords: Chronic metabolic disorder; hyperglycemia; catecholamines; insulin concentration reduction; gluconeogenesis

Introduction

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) represent two extremes in the spectrum of decompensated diabetes. DKA and HHS remain important causes of morbidity and mortality among diabetic patients despite well-developed diagnostic criteria and treatment protocols. The annual incidence of DKA from population-based studies in 1980s was estimated to range from 4 to 8 episodes per 1,000 patient admissions with diabetes; the annualized incidence remains stable based on the 2017 national inpatient sample analysis. Overall, the incidence of DKA admissions in the US continues to increase, accounting for about 140,000 hospitalizations in 2009.

Decompensated diabetes imposes a heavy burden in terms of economics and patient outcomes. DKA is responsible for more than 500,000 hospital days per year at an estimated annual direct medical expense and indirect cost of 2.4 billion USD in 1997 (CDC). The cost of inpatient DKA care in the US has increased to 5.1 billion USD in 2014, corresponding to approximate charges related to DKA care varying between 20-26 thousand USD per admission and continued to increase in 2017 when DKA admissions costed healthcare about 6.76 billion USD, corresponding to The events leading to hyperglycemia and ketoacidosis. In DKA, reduced effective insulin concentrations and increased concentrations of counterregulatory hormones (catecholamines, cortisol, glucagon, and growth hormone) lead to hyperglycemia and ketosis. Hyperglycemia develops as a result of three processes: increased gluconeogenesis, accelerated glycogenolysis, and impaired glucose utilization by peripheral tissues. This is magnified by transient insulin resistance due to the hormone imbalance itself as well as the elevated free fatty acid concentrations.

Increasing evidence indicates that the hyperglycemia in patients with hyperglycemic crises is associated with a severe inflammatory state characterized by an elevation of proinflammatory cytokines (tumor necrosis factor-α and interleukin-β, -6, and -8), C-reactive protein, reactive oxygen species, and lipid peroxidation, as well as cardiovascular risk factors, plasminogen activator inhibitor-1 and free fatty acids in the absence of obvious infection or cardiovascular pathology. All of these parameters return to near-normal values with insulin therapy and hydration within 24 h.

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. In addition, new-onset type 1 diabetes or discontinuation of insulin in established type 1 diabetes commonly leads to the development of DKA. In young patients with type 1 diabetes, psychological problems complicated by eating disorders may be a contributing factor in 20% of recurrent ketoacidosis. Factors that may lead to insulin omission in younger patients include fear of weight gain with improved metabolic control, fear of hypoglycemia, rebellion against authority, and stress of chronic disease.

about 31 thousand USD per each admission. The mortality rate for DKA and hyperglycemic crises has been falling over the years with estimates of fatality remaining under 1% for DKA; mortality can reach up to 20% in HHS. In 2010, among adults aged 20 years or older, hyperglycemic crisis caused 2,361 deaths.

Epidemiology

Recent epidemiological studies indicate that hospitalizations for DKA in the U.S. are increasing. In the decade from 1996 to 2006, there was a 35% increase in the number of cases, with a total of 136,510 cases with a primary diagnosis of DKA in 2006—a rate of increase perhaps more rapid than the overall increase in the diagnosis of diabetes. Most patients with DKA were between the ages of 18 and 44 years (56%) and 45 and 65 years (24%), with only 18% of patients <20 years of age. Two-thirds of DKA patients were considered to have type 1 diabetes and 34% to have type 2 diabetes; 50% were female, and 45% were nonwhite. 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.

Pathogenesis

Diagnosis

The process of HHS usually evolves over several days to weeks, whereas the evolution of the acute DKA episode in type 1 diabetes or even in type 2 diabetes tends to be much shorter. 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.

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. In addition, 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.

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 absence of cardiac compromise, isotonic saline (0.9% NaCl) is infused at a rate of 15–20 ml · kg body wt^{-1} · h^{-1} or 1–1.5 l during the first hour.

Insulin therapy

The mainstay in the treatment of DKA involves the administration of regular insulin via continuous intravenous infusion or by frequent subcutaneous or intramuscular injections (. Randomized controlled studies in patients with DKA have shown that insulin therapy is effective regardless of the route of administration.

Potassium

Despite total-body potassium depletion, mild-to-moderate hyperkalemia is common in patients with hyperglycemic crises. Insulin therapy, correction of acidosis, and volume expansion decrease serum potassium concentration. 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.

Bicarbonate therapy

The use of bicarbonate in DKA is controversial because most experts believe that during the treatment, as ketone bodies decrease there will be adequate bicarbonate except in severely acidotic patients. Severe metabolic acidosis can lead to impaired myocardial contractility, cerebral vasodilatation and coma, and several gastrointestinal complications. A prospective randomized study in 21 patients failed to show either beneficial or deleterious changes in morbidity or mortality with bicarbonate therapy in DKA patients with an admission arterial pH between 6.9 and 7.1.

Conclusion

DKA and HHS are both life-threatening disorders that carry significant risk of morbidity and mortality. Physicians caring for diabetic patients in the inpatient setting or working in emergent care will likely treat significant numbers of patients with DKA and HHS. Fortunately, most patients recover uneventfully. Care must be taken, however, to not approach treatment of DKA and HHS as "routine," because rare complications such as cerebral edema can be fatal.

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