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Diabetic Ketoacidosis – An Ephimeral Review

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Abstract

Diabetes mellitus could be a cluster of metabolic diseases defined by chronic hyperglycemia succeeding from defects in hypoglycemic agent (insulin) secretion, hypoglycemic agent action, or both. Recent epidemiological studies indicate that hospitalizations for diabetic ketoacidosis in the U.S. are increasing. Together the decreased amount insulin concentrations, as well as increased concentrations of counter-regulatory hormones like catecholamines, cortisol, glucagon, and growth hormone, leads to an elevated glucose level [hyperglycemia] and ketosis[ketonebodies] in diabetic ketoacidosis. Assess clinical evaluation to determine the diagnosis and confirm its cause. carefully look for evidence of infection. This article reviews clinical aspects and pathophysiology of diabetic ketoacidosis and its management in emergency conditions.

Keywords: Diabetic ketoacidosis; Hyperglycemia; Ketones; Insulin; Ketonuria; Catecholamines; Cortisol; Glucagon; Growth hormone; Ketonebodies; Infection; Macromolecule; Saccharide; Fat; Macromolecule; Protein; Metabolism

Introduction

Diabetes mellitus could be a cluster of metabolic diseases defined by chronic hyperglycemia succeeding from defects in hypoglycemic agent (insulin) secretion, hypoglycemic agent action, or both. The abnormalities in macromolecule (saccharide), fat, and macromolecule (protein) metabolism that is present in polygenic disorders due to inadequate action of insulin secretion on target tissues. If ketones were found in blood or body waste(urine), treatment imperative as a result of acidosis will evolve rapidly [1,2].

Diabetes is classified into the subsequent general categories:

a) Type-1 Diabetes is caused due to autoimmune beta-cell destruction, sometimes resulting in absolute insulin deficiency.

b) Type-2 diabetes is caused due to a progressive loss of beta-cell insulin secretion often developing insulin resistance.

c) Gestational diabetes mellitus (GDM) is diagnosed within the second or trimester of pregnancy.

d) Specific varieties of Diabetes due to different causes, e.g., monogenic diabetes syndromes.

e) such as diabetes in infants and maturity-onset of diabetes in the young (MODY), diseases of the exocrine duct gland (pancreas)such as cystic fibrosis, and drug or chemical-induced Diabetes mellitus like glucocorticoid use and in the treatment of HIV/AIDS, or post-organ transplantation. [3].

Complication of new-onset IDDM is diabetic ketoacidosis and may be defined as a metabolic unbalance characterized by the triad hyperglycemia (250mg/dl), acidosis (arterial pH 7.3 and/or bicarbonate 1 5mEq/l), and ketonuria. [4,5]. Newly diagnosed diabetics were reported in 20-40% of patients with diabetic ketoacidosis [6], and when unrecognized. This can lead to impairment of consciousness and even death [7].

The most common precipitating factor in the development of diabetic ketoacidosis is an infection. Other co-factors include discontinuation of or inappropriate 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 diabetic ketoacidosis. In young patients with type 1 diabetes, eating disorders may complicate psychological problems which is a contributing factor in 20% of recurrent ketoacidosis. Factors that contribute to insulin depletion in younger patients include fear of weight gain with improved metabolic control, fear of hypoglycemia and stress of chronic disease [8].

Epidemiology

Recent epidemiological studies indicate that hospitalizations for diabetic ketoacidosis 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 diabetic ketoacidosis in 2006 a rate of increase perhaps more rapid than the overall increase in the diagnosis of diabetes [9]. Most patients with diabetic ketoacidosis 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 diabetic ketoacidosis patients were considered to have type 1 diabetes and 34% to have type 2 diabetes; 50% were female, and 45% were non-white. Diabetic ketoacidosis 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 [10,11].

In adult subjects with diabetic ketoacidosis, the overall mortality is 1% [9], however, a mortality rate of 5% has been reported in the elderly and in patients with concomitant life-threatening illnesses [12,13]. Death in these conditions is rarely due to the metabolic complications of hyperglycemia or ketoacidosis but relates to the underlying precipitating illness [14]. Mortality attributed to hyperosmolar hyperglycemic state is considerably higher than that attributed to diabetic ketoacidosis, with recent mortality rates of 5–20% [15,16]. The prognosis of both conditions is substantially worsened at the extremes of age in the presence of coma, hypotension, and severe comorbidities [8,9,13,17].

Pathogenesis

Together the decreased amount insulin concentrations, as well as increased concentrations of counter-regulatory hormones like catecholamines, cortisol, glucagon, and growth hormone, leads to an elevated glucose level [hyperglycemia] and ketosis[ketonebodies] in diabetic ketoacidosis. Hyperglycemia occurs as a result of increased gluconeogenesis and reduced glucose utilization by peripheral tissues [8,17-22]. This is magnified by transient insulin resistance due to the hormone imbalance itself as well as the elevated free fatty acid concentrations [8]. The combination of both insulin deficiency and increased concentrations counterregulatory hormones in diabetic ketoacidosis also leads to the release of free fatty acids into the blood circulation from adipose tissue [lipolysis] and to unrestrained hepatic fatty acid oxidation in the liver to ketone bodies i.e. hydroxybutyrate and acetoacetate [10], which resulting in ketonemia and metabolic acidosis.

The other precipitating factors include insulin deficiency as the initial primary event in gradual cell failure, its ineffectiveness in a patient with the established disease, or its relative reduced potency when insulin action is antagonized by physiological factors such as sepsis and increased counterregulatory hormone. These hormonal variations enhance glucose production from glycogenolysis and gluconeogenesis and moreover limiting glucose utilization by the cells, resulting in increased glucose levels [11mmol/l [200 mg/dl]], osmotic diuresis, loss of electrolyte, dehydration, decreased glomerular filtration and hyperosmolarity. The clinical symptoms include polyuria, polydipsia, dehydration, deep sighing respirations to reduce pCO2 and buffer acidosis, and gradual obtundation leading to coma. The severity of diabetic ketoacidosis is described by the degree of acidosis: mild ie, pH 7.2-7.3; moderate, ie, pH 7.1-7.2 and severe ie, pH <7.1 [23].

Management of Diabetic Ketoacidosis

Emergency assessment: Assess a clinical evaluation study to confirm the diagnosis and detect its cause. In recurrent diabetic ketoacidosis look for the evidence of infection. Weigh the patient if the body surface area is used for fluid therapy calculations, measure height and length to assess the surface area. Assessment of the clinical severity of dehydration is necessary but accurate clinical assessment of dehydration may be difficult in diabetic ketoacidosis, at least in part due to the hyperosmolar state and polyuria caused by osmotic diuresis. Some findings that may be helpful include: 5%: reduced skin turgor, dry mucous membranes, tachycardia, 10% weak or impalpable peripheral pulses, hypotension, shock, oliguria. Assess level of consciousness [Glasgow coma scale] [24,25] Collect a blood sample for laboratory measurement of serum or plasma glucose; electrolytes including bicarbonate or total carbon dioxide [TCO2]];,urea nitrogen; creatinine, determination of pH in venous; hemoglobin and hematocrit levels, complete blood count, calcium, phosphorus, and magnesium concentrations, HbA1c levels, and blood_ hydroxybutyrate [_-OHB] concentration is also necessary [26]. [An increased white blood cell count in response to stress is characteristic of diabetic ketoacidosis and is not indicative of infection. Perform a urinalysis for determination of ketones. If there are any manifestations of infection is found, obtain appropriate specimens for culture test i.e., blood, urine, and throat. If laboratory measurement of serum potassium is deferred, perform an electrocardiogram for a baseline evaluation of potassium levels [27,28].

Supportive Measures

In the unconscious or severely immobilized patients, secure the airway and clear the stomach by continuous nasogastric suction to prevent pulmonary aspiration. For a comfortable and safe repetitive blood sampling, a peripheral intravenous catheter may be placed. A continuous electrocardiographic monitoring should be performed to assess T waves to detect any evidence of hyper or hypokalemia and to monitor for arrhythmias [29,30]. In case of severe circulatory impairment or shock, oxygen is recommended. After obtaining appropriate cultures of body fluids give antibiotics in febrile patients. Usually, Catheterization of the bladder is not necessary, but if the patient is unconscious or unable to clear on demand in case of, infants and very ill young children, the bladder should be catheterized.

Monitoring of Central venous pressure may be rarely required to guide fluid management in the critically ill, or neurologically compromised patient. Children with diabetic ketoacidosis are frequently associated with thrombosis and should be resorted to only when absolutely necessary. Children with severe diabetic ketoacidosis with longer duration of symptoms, reduced circulation, or depressed level of consciousness or those

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who are at increased risk for cerebral oedema [e.g.5 years of age, low pCO2, high urea nitrogen] should be considered for urgent treatment in an intensive care unit or in a unit that has equivalent resources and supervision, such as a children's ward specializing in diabetes care [29,30].

Fluid Therapy

For expansion of intravascular, interstitial and intracellular volume which are gradually reduced in hyperglycemic patients the initial fluid therapy is indicated [31] and to restore the renal perfusion. Isotonic saline [0.9% NaCl] is infused at a rate of 15–20 ml/ kg body weight should be given in the absence of cardiac comprise patients. The choice for fluid replacement depends on many factors like hemodynamics, the state of hydration, serum electrolyte levels, and urinary output. Normally, 0.45% NaCl infused at a rate of 250–500 ml/hr if the serum sodium is normal or elevated; and 0.9% NaCl at a similar rate is appropriate if corrected serum sodium is low. Hemodynamic monitoring like improvement in blood pressure, measurement of fluid input or output, laboratory values, and clinical examinations are necessary to determine the successful fluid therapy. When the plasma glucose level reaches 200 mg/dl, then add 5% dextrose to replacement fluids in order to allow continued insulin administration until ketonemia is controlled while at the same time avoiding hypoglycemia.

Insulin

Diabetic ketoacidosis is due to decreased effective circulating insulin which is associated with an elevated counterregulatory hormones like glucagon, catecholamines, growth hormone, cortisol. Even though rehydration alone causes some amount of decreased blood glucose level concentration [32,33], but insulin is still essential to normalize blood glucose and suppress lipolysis and ketogenesis [34]. After the patient has received initial volume expansion; i.e., 1–2 h after starting fluid replacement therapy then start insulin infusion [35]. The dose is 0.1unit/kg/hr [50 units regular insulin diluted in 50 ml normal saline; 1 unit/1ml] [36].The dose of insulin should remain at 0.1 unit /kg/hr at least until the resolution of diabetic ketoacidosis [pH 7.30, bicarbonate 15 mmol/l], which invariably takes longer than the normalization of blood glucose concentrations [37].

If the patient manifests any marked sensitivity to insulin in case of some young children with diabetic ketoacidosis or patients with the hyperglycemic hyperosmolar syndrome, the dose may be decreased to 0.05 units/ kg/ hr, or less, provided that metabolic acidosis continues to resolve. If any biochemical parameters of diabetic ketoacidosis like pH, anion gap still do not improve, reassess the patient and review insulin therapy, and determine or consider other possible causes of altered response to insulin e.g., infection, errors in insulin preparation. If no obvious cause is found, increase the insulin infusion rate and adjust the rate of glucose infusion as needed to maintain a glucose concentration of _17 mmol/l [300 mg/dl]. When intravenous administration could not be possible hourly/ 2-hourly in some conditions so subcutaneous or intramuscular administration of a short or rapid-acting insulin analog like insulin lispro or insulin as part is a safe and effective alternative to intravenous regular insulin infusion [38-42].

Potassium

Children with diabetic ketoacidosis suffer total-body potassium deficits of the order of 3– 6mmol/kg [35,36]. Loss of potassium largely occurs from the intracellular pool. Intracellular potassium is reduced because of transcellular shifts of this ion caused by hypertonicity. Increased plasma osmolality results in osmotic water transport from cells to the ECF, thereby concentrating cellular potassium. Potassium is drawn out of cells as a result of increased potassium gradient. Glycogenolysis and proteolysis which are secondary to insulin deficiency may also cause potassium efflux from cells. But acidosis may play a minor role in the distribution of potassium to the ECF. As a result of vomiting, urinary ketoanion excretion which requires excretion of cations, particularly sodium and potassium, and osmotic diuresis potassium gets gradually depleted from the body. Volume depletion may also lead to secondary hyperaldosteronism, which promotes urinary potassium excretion.

Thus, total-body depletion of potassium occurs, but at presentation serum potassium levels may be normal, increased, or decreased [43]. Administration of insulin and the correction of acidosis drives potassium back into the cells, decreasing serum levels [44]. The serum potassium concentration may be reduced suddenly, predisposing the patient to cardiac arrhythmias. Start potassium replacement immediately after initial volume expansion and before starting insulin therapy if the patient is hypokalemic. The initial potassium concentration in the infusion should be 40 mmol/l; subsequent replacement therapy of potassium should be based on serum potassium level measurements. Potassium administration should be continued throughout the period of intravenous fluid therapy is continued. Potassium phosphate may be also used in combination with potassium chloride or acetate [e.g., 20 mmol/l potassium chloride and 20 mmol/l potassium phosphate or 20 mmol/l potassium phosphate and 20 mmol/l potassium acetate] develops, administration of phosphate should be stopped. An alternative like Potassium phosphate salts may also be safely used or it is used in combination potassium chloride or acetate provided that careful monitoring is performed to avoid hypocalcemia [45,46].

Acidosis

Fluid and insulin replacement can reverse the severe acidosis. Insulin can stop further ketoacid production and allows ketoacids to be metabolized, which generates bicarbonate. Treating hypovolemia improves tissue perfusion and renal function, thereby increasing the excretion of organic acids. Controlled trials have shown no clinical benefit from bicarbonate administration [47-50], and there are well recognized adverse effects of bicarbonate therapy, including paradoxical CNS acidosis [51,52] and hypokalemia from rapid correction of acidosis [51,53,54].

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Reducing the NaCl concentration of the fluids can result in increased osmolality [51]. In few patients, there might be benefit from cautious alkali therapy like in patients with severe acidemia whose arterial pH is 6.9, in whom decreased cardiac contractility and peripheral vasodilatation can further impair tissue perfusion and patients with life-threatening hyperkalemia [55]. Bicarbonate administration is not recommended for resuscitation unless the acidosis is profound and likely to during resuscitation. If bicarbonate is considered necessary, cautiously administer 1–2 mmol/kg over 60 min. diversely affect the action of epinephrine during resuscitation. If bicarbonate is considered necessary, cautiously administer 1–2 mmol/kg over 60 min [24].

Conclusion

Diabetic ketoacidosis is a medical emergency that is handled effectively with an organized approach. It is a severe complication of diabetes and should be immediately diagnosed by a proper approach to reduce further complications.

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