Acute Hyperglycemic Syndromes: Diabetic Ketoacidosis and the Hyperosmolar State

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Abstract

The patient, often a "repeat offender" who stops taking insulin, presents with increasing urination and thirst along with nausea, vomiting, abdominal pain, dehydration, weakness, and dizziness. The patient may become confused and slip into coma. The respiratory compensation that accompanies acidemia causes deep rapid (Kussmaul) breathing. The sweet smell of the volatile ketone body acetone signals the possibility of ketoacidosis. The treating physician seeks to reestablish normal physiology and restore the patient to normal function. Thankfully, treatment is remarkably straightforward and involves intravenous fluid, insulin, potassium, and vigilance.

Keywords

Diabetic Ketoacidosis • Kussmaul • Type 1 Diabetes • Type 2 Diabetes • Ketosis • Hyperglycemia • Anion Gap Metabolic Acidosis • Free Fatty Acids • ß-hydroxybutyrate • Acetoacetate • Cerebral Edema • Hyperosmolar Hyperglycemia Syndrome

Contents

Diabetic Ketoacidosis: Clinical Presentation

A typical patient with diabetic ketoacidosis (DKA) becomes severely ill over one to several days and represents a medical emergency.

The patient presents with increasing urination and thirst along with nausea, vomiting, abdominal pain, dehydration, weakness, and dizziness. The patient may become confused and slip into coma. The respiratory compensation that accompanies acidemia

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causes deep rapid (Kussmaul) breathing. The sweet smell of the volatile ketone body acetone signals the possibility of ketoacidosis. In an analysis of three multinational type 1 diabetes registries, factors that are associated with an increased risk for DKA include female gender, country-specific ethnic minorities, and elevated HbA1C [1].

Diabetes is a heterogeneous disease [2], and patients with DKA reflect this heterogeneity [3]. While commonly considered a condition associated with type 1 diabetes, patients with type 2 diabetes can also develop DKA and, in some cases, initially present to medical attention with DKA [4–6, 99]. The majority of patients with DKA have type 1 diabetes. Consistent with this type 1 predominance, patients are likely to be young, slender, Caucasian (type 1 diabetes is 2–7 times more common in whites than blacks [7]), and lack a family history of diabetes.

In youth with type 1 diabetes, the prevalence of DKA at the diagnosis of diabetes has remained relatively stable at 31% over the last decade in the United States. However, among youth with type 2 diabetes, the prevalence of DKA at diagnosis has declined in the last decade [8]. Younger age, ethnic minority, lack of health insurance, lower body mass index, preceding infection, and delayed treatment confer an increased risk for the presence of DKA at the time of diagnosis in children and young adults. On the other hand, having a first-degree relative with type 1 diabetes at the time of diagnosis, higher parental education and higher background incidence of type 1 diabetes are protective factors [9].

Definition

Diabetic ketoacidosis (DKA) is a state of metabolic decompensation in which insulin deficiency (relative or absolute) causes both hyperglycemia and excess production of ketoacids, resulting in metabolic acidosis [10].

DKA is the first manifestation of diabetes in a minority of patients and more often occurs in patients with known diabetes taking insufficient insulin. Patients may run out of insulin or not accept the necessity for insulin. Adolescents sometimes discontinue insulin as an act of rebellion. Ill patients, who are not eating well, may reduce or omit insulin doses, not realizing that stress, which is accompanied by elevation of "counterregulatory" hormones, may have higher insulin requirements.

No absolute numbers separate uncontrolled diabetes from DKA, although there is general agreement on the definition: a glucose level >250 mg/dL (13.9 mmol/L), acidemia reflected by a pH lower than 7.30, a serum bicarbonate less than 18 mEq/L, a positive test for serum ketones, and an increase in the anion gap [11]. Reasons for exceptions to this definition are discussed below.

The Differential Diagnosis

While considering the diagnosis of DKA, it is important to recognize that many other diseases can manifest the individual components of DKA: ketosis, hyperglycemia, and an anion gap metabolic acidosis. Alcohol intake and starvation can result in ketosis. Uncontrolled diabetes mellitus (both type 1 and type 2), infection, and physiologic stress can result in hyperglycemia. And lastly, a wide number of disease states can result in a metabolic acidosis with an anion gap [12].

The most severe scenario for patients with DKA is the diabetic coma. Stupor and coma have many potential causes (Table 1). Alcoholic intoxication causing coma can be assessed by a history of alcohol intake and blood alcohol levels. Decreased level of consciousness without focal findings suggests encephalopathy (unilateral weakness could suggest a stroke). Furthermore, the patient may have taken

Table 1 Differential diagnosis of diabetic coma

A-E-I-O-U	TIPSI
Alcohol	Trauma
Encephalopathy	Infection
Infectious	Meningitis
Neurologic	Sepsis
Insulin	Psychosis
Hypoglycemia, DKA, hyperosmolar, alcoholic ketoacidosis	Seizure
Overdose, opiates	Postictal state
Uremia	

an overdose; thus, a toxicology "screen" is helpful to exclude drugs that can cause coma and acidosis. Renal failure with uremic encephalopathy can be detected with blood urea nitrogen (BUN) and creatinine measurements. Evidence of trauma should be sought. Fever and confusion may indicate central nervous system infection. A history of emotional instability may suggest psychosis or a patient who is feigning illness. Witnesses can be questioned about seizure activity, which is often followed by a decreased level of alertness. The mnemonic given in Table 1 is not comprehensive; for example, the electrocardiogram may show a cardiac arrhythmia or a myocardial infarction that can cause a drop in blood pressure and change in mental status. While reviewing the differential diagnosis, the physician simultaneously obtains the finger stick (capillary) glucose measurement to exclude hypoglycemia (low blood sugar) or hyperglycemia as a cause of coma. An elevated glucose supports a diagnosis of diabetic ketoacidosis or hyperglycemic hyperosmolar coma.

Pathophysiology

The fed state is an insulin-sufficient state. Insulin affects the internal machinery of cells in the liver, fat (adipose tissue), and muscles to promote energy production and storage.

Cellular work requires massive amounts of energy. Intermediary metabolism (named for the *intermediate* compounds that are generated prior to the final metabolic products), largely through the production of ATP (adenosine triphosphate), provides this energy and the energy for synthesizing macromolecules [13–16].

Glucose, the major cellular nutrient, is transported into cells where it is metabolized in the glycolytic pathway. Enzymes in this pathway are regulated by insulin (whose action is antagonized by glucagon). At the end of this pathway, the three-carbon glucose metabolite pyruvate is further broken down into small molecules that are used to produce complex cellular components or can be converted into chemical energy (the nucleotide ATP) when transported into the energy generator of the cell (the mitochondria).

When insulin levels are adequate, energy is stored in small quantities as glycogen for immediate use or in large quantities as triglycerides for long-term use.

Inside the hepatocyte, glucose molecules can be linked in a tightly packed branching structure to form glycogen, the polysaccharide that stores glucose. Alternatively, the two-carbon compound acetyl coenzyme A (acetyl-CoA), which is formed from glucose breakdown, can be used to manufacture larger molecules, including fatty acids for energy storage in a large fat depot (adipose tissue). Insulin acts to stimulate and maintain these storage processes.

In DKA, insulin action is inadequate to promote glucose entry into cells. The decreased flux of glucose into cells simulates fasting.

With the fall in intracellular glucose, intermediary metabolism of carbohydrates and lipids shifts away from glucose breakdown and storage to an exaggerated imitation of the fasting state. Metabolism shifts away from the utilization of glucose toward gluconeogenesis, which is the production of glucose from pyruvate (Fig. 1). Precursors for gluconeogenesis are obtained from fat, which is melted down into fatty acids and glycerol, and from proteins following breakdown into constituent amino acids. Glycerol, amino acids (particularly alanine), and lactate (derived from red cell metabolism) are converted into glucose.

The counterregulatory hormones glucagon and epinephrine, along with growth hormone and cortisol, stimulated by fasting and by stress, antagonize the effects of insulin.

Counterregulatory hormones antagonize the glucose-lowering action of insulin and act to raise the blood glucose level. Glucagon, a potent counterregulatory hormone inhibited by insulin, is secreted from pancreatic alpha cells when cells perceive low glucose. In diabetes, pancreatic insulin levels are reduced and glucagon is chronically elevated. In DKA, in addition to low insulin action, there is the cellular perception of low glucose, which further stimulates glucagon secretion. The excessive glucagon levels of DKA dominate hepatic metabolism, promoting breakdown of glycogen to glucose, stimulating gluconeogenesis, inhibiting fatty acid synthesis, and directing

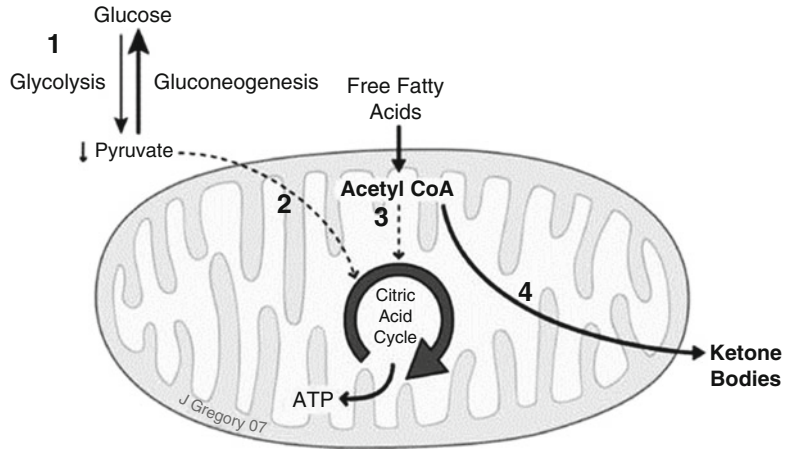

Fig. 1 The formation of ketone bodies is linked to increased gluconeogenesis. *1* When insulin levels fall, glycolysis decreases and gluconeogenesis increases, reducing pyruvate levels. *2* Pyruvate is not available for conversion into oxaloacetate. *3* Without oxaloacetate, acetyl-CoA cannot enter the TCA cycle. *4* Free fatty acids, converted into acetyl-CoA, are therefore diverted to mitochondrial ketone body formation

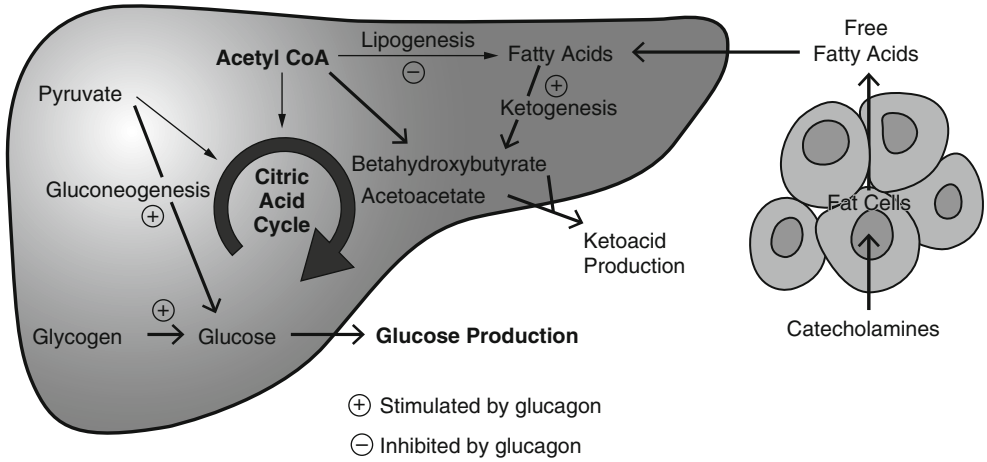

Fig. 2 Glucagon plays a central role in DKA. Glucagon stimulates glucose production through gluconeogenesis and glycogen breakdown. Lipogenesis is inhibited by glucagon. Free fatty acids derived from lipolysis in fat cells are transported into the mitochondria. Acetyl-CoA from fatty acid breakdown is diverted to ketoacid production

long-chain fatty acids into the mitochondria where they are dedicated to ketoacid formation (Fig. 2).

Catecholamines, acting on β-adrenergic receptors, are the most potent stimulators of lipolysis (breakdown of adipose tissue triglycerides with release of free fatty acids and glycerol) and also inhibits glucose uptake in adipocytes [17]. Growth hormone also stimulates lipolysis and liberates free fatty acids [18]. Cortisol contributes to elevations of blood glucose by increasing lipolysis in certain fat depots, increasing the transcription of genes that increase protein catabolism (providing precursors for gluconeogenesis), and upregulating the expression of the rate-limiting enzyme for gluconeogenesis, phosphoenolpyruvate carboxykinase (PEPCK) [19]. Glucagon and epinephrine both activate glycogen phosphorylase, which catalyzes glycogenolysis [20].

The Central Role of Free Fatty Acids (FFAs) in DKA

Free fatty acids leave the fat cell and are transported to the liver.

Without fatty acids there cannot be any ketoacids; without ketoacids there is no diabetic ketoacidosis [21]. Under the influence of insulin,

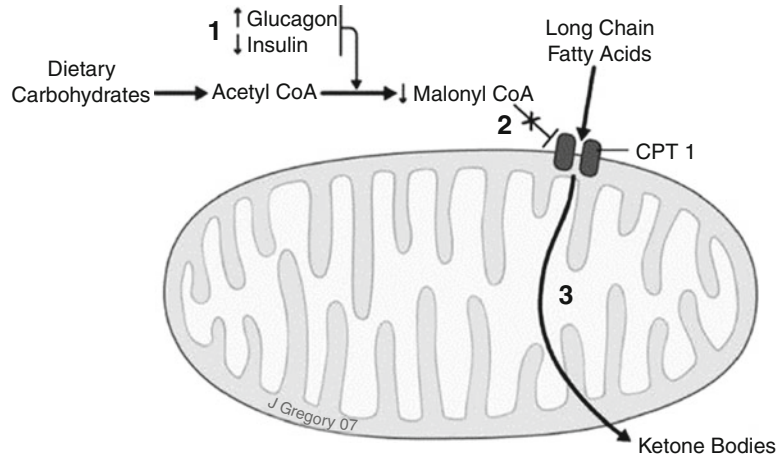

Fig. 3 Malonyl-CoA plays a pivotal role in the regulation of ketogenesis. In DKA, the *high* glucagon and the *low* insulin decrease malonyl-CoA production from acetyl-CoA. *1*. The fall in malonyl-CoA releases the inhibition of the transport protein (CPT1) that shuttles long-chain fatty acids into the mitochondria. *2*. Increased long-chain fatty acids are thus available for ketone body formation

free fatty acids are transported to and imprisoned inside a fat cell (adipocyte) bound as three chains to a glycerol molecule (triglyceride). The catecholamines are ready to "spring" FFAs out of "jail," but they are unable to do so while there is adequate insulin. During starvation, when insulin levels drop, lipids stored in adipose tissue as triglycerides are released from the fat cell as the hydrocarbon long-chain fatty acids. These fatty acids are transported to the liver bound to albumin. From the viewpoint of the FFA, the scene in the liver is chaotic. The liver does not have adequate insulin levels. Glycolysis, the most ancient metabolic pathway, is at a standstill. FFAs further inhibit insulin action and stimulate gluconeogenesis and hepatic production of lipoproteins, contributing to hyperglycemia and to the marked elevation of triglycerides seen in some patients. Under fasting conditions with adequate insulin present, this process (coupled with the release of glycerol) provides sufficient calories to serve as the glucose and energy "grocery store." In DKA, this process leads to uncontrolled glucose elevations.

Malonyl coenzyme A (CoA) levels control free fatty acid transport into the mitochondria, thereby acting as the key control of the rate of hepatic ketoacid production.

Malonyl-CoA is a precursor molecule whose levels rise during the insulin-stimulated process of triglyceride synthesis in the cytoplasm. Malonyl-CoA then inhibits the transport of fatty acids into mitochondria, by inhibiting the fatty acid transporter carnitine palmitoyltransferase 1 (CPT1). During DKA, since insulin levels fall, malonyl-CoA levels decline, permitting a rise in fatty acid transport into mitochondria (Fig. 3).

The fate of free fatty acids in the hepatic mitochondria is determined by the activity of the glycolytic pathway, because pyruvate is required for FFA derivatives to enter the TCA cycle (Fig. 1).

Pyruvate formed during glycolysis is the glucose-derived metabolite that enters the TCA (tricarboxylic acid, also called the Krebs or citric acid) cycle. This pathway is oxygen requiring (oxidative) and generates large amounts of ATP. In DKA, pyruvate is diverted to gluconeogenesis, less is available to enter the TCA cycle, and the rate of oxidative metabolism of glucose declines. In addition, the fall in pyruvate alters fat metabolism in the liver. Under normal conditions of energy generation, fatty acid metabolites can enter the TCA cycle in a process that requires pyruvate. Since pyruvate is necessary for fat to enter the TCA pathway, it is said that fat burns in the flame of carbohydrate. In DKA, this energy-generating "flame" is extinguished (Fig. 1).

Some pyruvate is converted to lactate in a process that restores cytoplasmic NAD^+ (nicotinamide adenine dinucleotide), necessary for minimal cellular metabolism. This can cause a lactic acidosis superimposed on top of ketoacidosis [22] (Fig. 4).

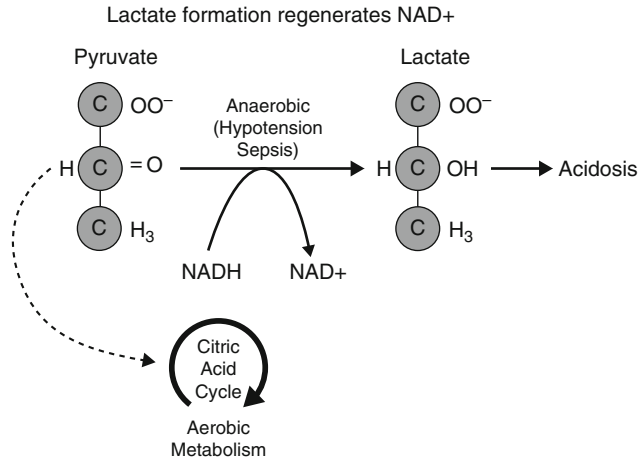

Fig. 4 Lactate formed from pyruvate can contribute to acidosis

When fatty acids cannot enter the TCA cycle in hepatic mitochondria, they are diverted to ketone body (ketoacid) formation.

Fatty acids are broken down in the mitochondrial matrix into the two-carbon compound acetyl-CoA. Unable to enter the TCA cycle during intracellular glucose privation, acetyl-CoA in hepatic mitochondria is diverted to the production of the ketoacids β-hydroxybutyrate and acetoacetate [23].

The "redox" (reduction–oxidation) status of the mitochondria, set by the NADH/NAD + ratio, determines the predominant species of ketoacid.

Coenzymes cooperate with enzymes to catalyze reactions. In these reactions, the coenzymes are reversibly altered and can be cycled back and forth between two forms, creating a "pair." The coenzyme pair NAD^+ and NADH functions to carry electrons in oxidation–reduction reactions. An increased $NADH/NAD^+$ ratio develops in DKA during β-oxidation of fatty acids and also in states of low tissue oxygenation (such as those that occur if the patient has severe fluid loss and is hypotensive from dehydration or sepsis). NADH drives the conversion of the ketoacid acetoacetate to β-hydroxybutyrate. As will be discussed later, laboratories use the nitroprusside reaction, which does not measure β-hydroxybutyrate, to test for ketones. When β-hydroxybutyrate is the major ketoacid, a misleadingly low nitroprusside test can sway the unsuspecting physician away from the correct diagnosis.

Since glucose is not available in DKA, alternative energy-releasing compounds must be utilized. The ketoacids function as an alternate fuel.

Tissues are not able to utilize glucose because of inadequate insulin action. Without insulin (or without *enough* insulin), cells are left without nutrients. The ketone bodies, or ketoacids, do not require insulin for uptake into cells. If glucose is the electric power that drives the body, ketone bodies are the batteries of the brain and the heart. When the electricity fails, hepatic mitochondria produce and export this alternate power. In the heart, skeletal muscle, brain, and kidney, ketone bodies can be converted back to acetyl-CoA, which enters the TCA cycle and provides metabolic energy through generation of ATP [24] (Fig. 5).

Assessment of a Patient with DKA

Among the long list of potential precipitating factors for DKA are serious conditions that require diagnosis and specific treatment.

Although diabetic ketoacidosis often occurs in patients who run out of insulin or stop taking insulin [25, 26], there is frequently an inciting event that must be discovered. The physician's challenge is to find what went wrong, reverse the process, return the patient to health, and prevent the next episode. In considering the possibilities, it is important to remember that common things occur commonly. The patient may have stopped

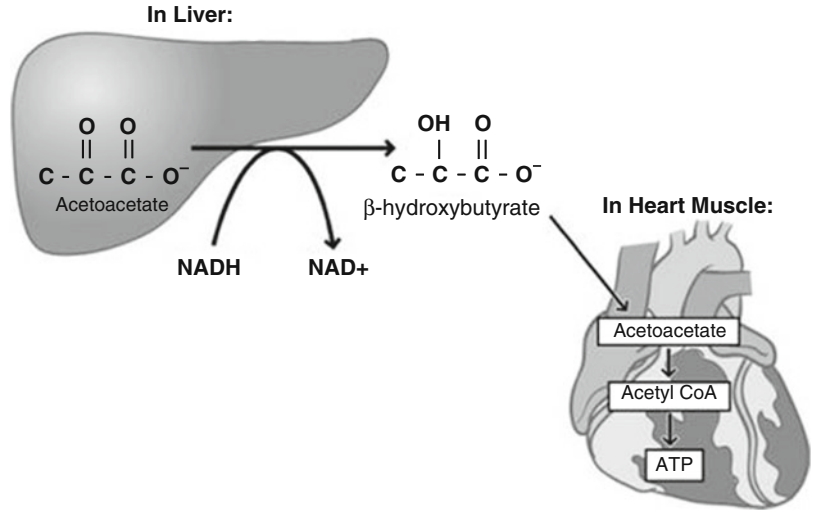

Fig. 5 Ketone bodies formed in the liver provide an alternate fuel for the heart, skeletal muscle, and brain

taking insulin or the pancreas may have gradually lost insulin secretory capacity. Counterregulatory mechanisms may be activated during any stress and may render antecedent insulin levels insufficient. Particular attention must be given to infections (with elevations of the counterregulatory hormones cortisol and catecholamines), stroke or heart attacks (extremely high epinephrine production), or pregnancy (placental lactogen or cortisol). Dehydration during gastrointestinal illness accompanied by vomiting or diarrhea may hasten the development of DKA. An alcohol binge may cause rapid decompensation in the patient with limited insulin reserve.

Very unusual causes of counterregulatory hormone elevation precipitating DKA are growth hormone elevations from acromegaly, glucocorticoid excess in Cushing's syndrome, and glucagon in the rare glucagonoma syndrome. Obscure causes of DKA, such as changing to more active pancreatic enzymes to treat chronic pancreatitis with increased absorption of nutrients or somatostatin inhibition of insulin secretion in a somatostatinoma, have been described. In teenagers, eating disorders are a consideration, especially in recurrent DKA. Antipsychotic drugs clozapine and olanzapine are also reported to cause DKA [27, 28]. An unusual fulminant nonimmune form of type 1 diabetes can present with a rapid onset [29]. Rare cases of DKA have occurred following pancreatic destruction by a virus [30, 31].

Infection is the most common precipitating cause of diabetic ketoacidosis; sites that hide infections should be examined carefully.

Patients with both type 1 and type 2 diabetes are at an increased risk for infections and hospitalizations due to infections [32, 33]. Elevated glucose levels impair the ability to fight infection, [34] potentially leading to aggressive tissue destruction. Thus, it is critical to control the blood glucose and to discover and treat infections. The physician must be particularly suspicious in patients who are more likely to harbor infections. Hidden sites of infection include the teeth, sinuses, gallbladder, abscesses in the perirectal area, and pelvis (in women) and must be examined and reexamined. The nose should be carefully inspected for eschar (black necrotic tissue), which might indicate the fungus mucormycosis, classically but rarely seen in DKA.

Measurements, tests, and calculations are used to determine the severity of acidosis, magnitude of ketonemia, and fluid and electrolyte balance.

In order to treat DKA, the physician must measure the degree of acidosis (pH), the ability of the patient to compensate by lowering pCO_2, the elevation of the blood glucose level, and the serum potassium (K^+). Initially, an arterial sample is taken for measuring the pH, pO_2, and pCO_2 in order to know if the patient has low oxygenation (hypoxemia), a primary respiratory acidosis (indicating pulmonary disease or central hypoventilation), or

Table 2 Measurements useful in assessing a patient with DKA

Corrected serum $[Na^+]$ = measured serum $[Na^+]$ + 2 * (glucose in mg/dL – 100)/100 [35, 36]
The anion gap = $[Na^+]$ – ($[Cl^-]$ + $[HCO_3^-]$)
The normal anion gap = 8–12
In pure metabolic acidosis the last two digits of the pH = pCO_2
For example, if the pH = 7.32, the pCO_2 should be 32
In pure metabolic acidosis the blood gas pCO_2 = (serum HCO_3^- * 1.5) + 8
The calculated effective serum osmolality = 2 (Na^+ + K^+) + (glucose in mg/dL/18)
Normal total body water (TBW) = lean body mass in kg * 60%
Current TBW = (normal serum osmolality * normal TBW)/current osmolality
Water deficit = normal TBW – current TBW

a primary respiratory alkalosis (suggestive of sepsis). After the baseline arterial measurement, the calculated anion gap from chemistries (using measured – not corrected – serum sodium, chloride, and bicarbonate) and the venous pH can be used to evaluate the acid–base status (Table 2) [37]. To document or follow ketoacid production, serum ketones are typically measured. They are cleared rapidly and may be detected with greater sensitivity in urine, even when low or absent in the serum. Although it is the dominant "ketoacid" in DKA with a ratio as high as 20:1 compared to acetoacetate, β-hydroxybutyrate is not measured in the nitroprusside test for ketoacids because β-hydroxybutyrate is really an acid-alcohol. In the "redox" environment of DKA, an excess ratio of β-hydroxybutyrate to acetoacetate may result in spuriously low ketone body measurements. The astute clinician knows that DKA may occur without a markedly elevated nitroprusside reaction and is guided by the clinical presentation, pH, anion gap, and bicarbonate level [38].

Treatment of Diabetic Ketoacidosis

Introduction

The treating physician seeks to reestablish normal physiology and restore the patient to normal function. Treatment is remarkably straightforward and involves intravenous fluid, insulin, potassium, and vigilance.

The osmotic diuresis of hyperglycemia causes dehydration, which exacerbates the metabolic acidosis [15]. **The severity of dehydration determines initial rates of fluid administration.**

In the hypotensive patient, fluid resuscitation takes precedence over other concerns. A fluid "challenge" is performed with isotonic fluid given in short blocks of time (in adults, at a rate of 10–30 mL/min checking the patient every 10 min; in children, at a rate of 10–20 mL/kg over 30 min to 2 h [39, 40]). If intravascular fluid depletion is the cause of hypotension, the blood pressure responds rapidly. Failure to respond to a fluid challenge within 30 min suggests another cause for low blood pressure such as cardiac pump failure or peripheral vasodilatation in sepsis. In adults with severe dehydration, initial fluid rates of 1–2 L/h may be required. If the patient is not hypotensive, or once blood pressure is restored, a more balanced approach to fluid administration using 250–500 mL/h is desirable. These slower rates of administration avoid fluid overload with potential for pulmonary edema and hypoxemia or diuresis of potassium with resultant hypokalemia [41]. Hydration per se decreases counterregulatory hormone levels, enhances renal perfusion, and establishes a glucose diuresis, lowering the blood sugar toward the renal threshold of 180 mg/dL [42]. It is customary to choose isotonic fluid in the hypotensive, dehydrated patient; half-normal saline as the patient recovers; and dextrose-containing fluid as the blood glucose drops below 200–250 mg/dL. Fluids containing 5% or even 10% dextrose prevent the hypoglycemia that would otherwise occur with continued administration of insulin essential to restrain ketogenesis and prevent recurrence of acidosis. Dextrose containing fluids are frequently required as the duration to resolve hyperglycemia is typically shorter than the resolution of ketoacidosis. Hemodynamic monitoring, urine output, laboratory values, and clinical judgment can be used to assess the efficacy of fluid treatment in DKA.

Medical situations requiring special fluid adjustments include myocardial infarction,

congestive heart failure, and acute or chronic renal failure. These situations require individualized fluid management following initial volume resuscitation [43].

Fluid administration should be slower in pediatric patients than adults [39, 44].

In children, the physician must be concerned about cerebral edema, which occurs in 0.5–1% of DKA episodes in children [45] and associated with a high mortality rate [46, 47]. The precise mechanism of cerebral edema is unknown. The prevailing assumption that cerebral edema is a result of organic osmoles, which accumulate in the brain to balance the cellular dehydrating effect of the hyperosmolar extracellular fluid, causing excess fluid movement into cells with hydration, is unproven [45]. Alternatively, there is suggestion that cerebral edema is a result of ischemia and subsequent reperfusion injury [48]. The risk factors identified for cerebral edema are more severe acidemia (lower pCO_2), greater dehydration (higher blood urea nitrogen), and the use of bicarbonate [49]. The ketone bodies themselves may increase brain microvascular permeability [50]. Even though the role of rapid fluid administration (greater than 50 mL/kg during the first 4 h of therapy) in causing brain herniation [51] is debated, fluid overload is to be avoided.

Insulin is administered by continuous intravenous infusion using regular insulin or a rapid acting insulin analog [52, 53].

Insulin doses are adjusted against two parameters – restoring near-normal blood glucose and reversing ketoacidosis. A loading bolus of 0.1 units/kg regular insulin is commonly administered intravenously while simultaneously beginning continuous infusion at 0.1 units/kg/h. Alternatively, using a no initial bolus but a starting infusion rate of 0.14 units/kg has been found to be equally effective in treatment [54, 55]. The glucose should fall by 50–75 mg/dL each hour. If the glucose does not fall as expected, the insulin infusion rate should be increased. Since prevention of ketoacidosis requires less insulin action than prevention of hyperglycemia, it is a paradox in the therapy of DKA that it is more difficult to stop ketone body generation than to lower serum glucose. Therefore, it is essential that the physician maintains constant insulin infusion, if only at physiologic levels of 0.5–1 unit/h, to restrain lipolysis (release of FFA from adipose tissue). The continued administration of insulin without causing hypoglycemia often requires concomitant administration of glucose-containing infusions (usually 5% or, if necessary, 10%), which should be started when the serum glucose has fallen to 200 mg/dL (11 mmol/L). Conversely, should the glucose fall at a rate greater than 75 mg/dL an hour, the insulin infusion rate should be decreased to avoid hypoglycemia. The importance of hourly glucose monitoring cannot be emphasized more while a patient is receiving intravenous insulin.

The use of subcutaneous insulin protocols in the treatment of mild DKA has been studied in small randomized trials with no significant differences found in resolution of DKA, insulin required for treatment, or length of stay. It has been proposed that this may offer a reasonable treatment alternative for mild DKA; however, this has not been recommended by any professional society for general use [56].

Potassium repletion is necessary because K^+ is lost during the osmotic diuresis of DKA as the K^+ salt of ketoacids.

The serum potassium level reflects both total body stores and the distribution between the intracellular (98% of total body K^+) and extracellular spaces. The osmotic diuresis of DKA causes huge urinary K^+ losses. Yet, the serum K^+ can be low, normal, or high at the time of presentation. Redistribution of K^+ out of the intracellular compartment and into the intravascular space causes a normal or high serum K^+ in the face of total body depletion.

Physiologic insulin levels drive K^+ into cells [57]. With the decreased insulin action of DKA, potassium moves out of cells into the serum. This redistribution may raise serum K^+. Further elevation of serum K^+ may occur because of redistribution related to acidosis (K^+ moving out of cells in exchange for H^+ moving in). Insulin administration during treatment moves potassium back into the cells, halts the generation of ketoacids, and reverses acidosis. Dangerous degrees of hypokalemia may then occur and are postulated to be the cause of the 30–50% DKA mortality in the 1950s [58]. The

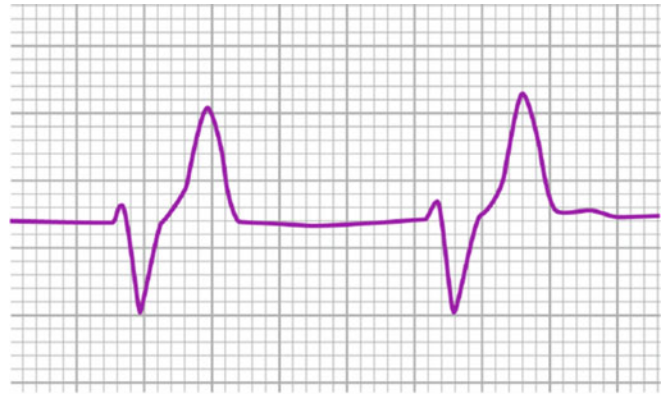

Fig. 6 The electrocardiogram in hyperkalemia progressively shows tall-peaked T waves followed by low-amplitude "P" wave (not even discernible in this example) and widening of the QRS

treating physician must anticipate and prevent this hypokalemia. Typically, 20–40 mEq K^+ is administered with each liter of fluid. If the fluid is administered more rapidly, the patient will (appropriately) receive more K^+ per unit time. In the event of severe hypokalemia at the initial presentation of DKA, potassium repletion with fluid resuscitation should be initiated prior to insulin therapy. Conversely, two caveats against K^+ administration are renal impairment, which prevents normal excretion of excess K^+, and dangerous hyperkalemia at the time of presentation. The physician may administer potassium as soon as urine flow is established. In addition, the physician must order an electrocardiogram (EKG) on presentation. If signs of hyperkalemia are present (tall-peaked T waves, followed by low-amplitude P wave and widening QRS complex) (Fig. 6), no potassium is given until the "stat" K^+ levels are back from the laboratory. In the absence of signs of hypokalemia on the EKG (low-amplitude T waves with rising amplitude U waves), some physicians do not administer K^+ until the laboratory measurement is available.

More and more evidence shows that bicarbonate administration plays no role in the therapy of DKA.

When insulin therapy reverses ketoacid formation, bicarbonate is rapidly regenerated from retained ketone body anions. To the extent that these anions were lost in the urine, the kidney takes several days to fully reclaim bicarbonate. In the past, bicarbonate was administered out of concern that severe acidosis would impair cardiac function and precipitate congestive heart failure or vascular collapse. On the other hand, administration of bicarbonate may cause fluid retention, brain edema, and unfavorable pH shifts. Current data suggest that bicarbonate administration does not favorably influence patient outcome down to a pH of 6.90 [59, 60, 61]. Below this level, there is a consensus to administer bicarbonate even if its value is unproven.

Complications of DKA include death, cerebral edema, pancreatitis, rhabdomyolysis, pulmonary edema, hypertriglyceridemia, and hypophosphatemia.

Mortality in DKA is 0.25–10%, striking mostly the very young and the elderly [62–65]. Multiple organ failure (cardiac, renal, hepatic, and pulmonary) portends a high mortality in adult patients.

Cerebral edema is an uncommon but significant cause of morbidity and mortality in diabetic ketoacidosis. It occurs more frequently in the pediatric population and rarely occurs in adult patients [47]. The pathogenesis of cerebral edema in DKA is not clear. It was originally thought to be a consequence of aggressive fluid resuscitation; however, more recently, there is evidence that vasogenic and cytotoxic edema is a consequence of cerebral hypoperfusion [66]. It is the major cause of death and disability for children with diabetic ketoacidosis.

Rhabdomyolysis, the necrosis of skeletal muscle leading to the release of intracellular contents to the circulation, is a potential complication of DKA [67]. Rhabdomyolysis in the setting of DKA can have a variable clinical presentation with elevations in muscle enzymes, electrolyte disturbances, and acute kidney injury. The pathogenesis of rhabdomyolysis from DKA is unclear but is likely a result of the electrolyte and glucose disturbances in DKA.

Pulmonary symptoms may indicate pneumonia but may also occur with a "capillary leak" or interstitial edema associated with DKA [68]. Pulmonary edema, observed in association with DKA, is thought to be caused by a decrease in capillary osmotic pressure during fluid resuscitation but does not always have clinical significance [66]. However, it can lead to hypoxia and can confound treatment of DKA where volume resuscitation is a pillar of treatment.

Elevated pancreatic enzymes, such as amylase and lipase, are correlated with the degree of hyperglycemia, acidemia, and dehydration. Although not usually clinically important [69]. Dehydration with hypoperfusion of the pancreas and elevations in triglycerides may preceipitate acute pancreatitis [70, 71]. Elevated triglycerides occur because insulin stimulation of endothelial lipoprotein lipase is necessary to remove lipids from the circulation, and insulin inhibition of adipose tissue lipase prevents mobilization of lipids out of the fat cell. Hypertriglyceridemia resolves following DKA unless there is an underlying defect but may contribute to pancreatitis [72]. Mild hypophosphatemia commonly occurs in DKA; there is evidence that treatment is not required unless clearly symptomatic [73–75].

DKA costs lives and dollars; the epidemiology of DKA targets educational and preventive solutions.

In developing countries, mortality rates for type 1 diabetic patients are high, with DKA as the leading cause of death [76]. In US children and young adults with type 1 diabetes mellitus, DKA is also the most common cause of mortality and appears to affect nonwhites with greatly increased frequency compared to whites [77]. DKA, with an estimated annual incidence of 179,387 in the United States, is estimated to incur costs of nearly $90 million per year [1]. In youth, the presence of DKA is estimated to increase the predicted annual cost of medical expenditures by nearly 70% in the United States [78] and up to 3.6 fold higher diabetes-related costs in Germany [79].

Educational programs may decrease the incidence of DKA [80], although the emotional and psychological factors that stimulate knowledgeable patients to discontinue insulin are not easily addressed. Studies have shown that patients can be safely discharged following care in the emergency room if DKA is mild (pH $>$ 7.20, HCO_3 $>$ 10) [81]. Admission to a general hospital bed rather than a more expensive intensive care unit bed is also possible for less severely ill patients [82]. Specialty care may provide significant cost savings: endocrinologists treat and discharge their patients with DKA more rapidly, with fewer tests and fewer readmissions than do general internists [83].

Patients may present with DKA with exceptions to the definition including lower glucose, higher pH, and negative nitroprusside test for ketones.

The glucose at presentation in DKA varies widely from less than 180 to 1000 mg/dL. If a patient is not eating well prior to the onset of DKA and able to maintain adequate hydration, the glucose may be lower [84]. Young people with good kidney function or pregnant patients [85] with increased glomerular filtration rate (GFR) and lowered glucose threshold can develop DKA with normal blood sugars since they have a greater capacity to excrete glucose [86]. Patients who treat their finger stick glucose elevations with small doses of insulin may develop diabetic ketoacidosis with normal glucose levels if the stress hormones during illness stimulate sufficient lipolysis. DKA may develop unusually rapidly during fasting [87] or dehydration because these conditions increase the counterregulatory hormone glucagon and increase the pace at which acidosis occurs when insulin is withdrawn.

Patients who have excessive vomiting and develop DKA may have pH levels above the definition for DKA (pH < 7.35) because H^+ lost in emesis fluid superimposes metabolic alkalosis on the metabolic acidosis of DKA. Other states that cause metabolic alkalosis can have the same effect, such as DKA with Cushing's syndrome.

Patients with low tissue oxygenation, sepsis, and hypotension can present with a large predominance of β-hydroxybutyrate over acetoacetate. The test for ketoacids in these patients may be negative at presentation and become positive as the patient improves and converts β-hydroxybutyrate to acetoacetate.

The patient with atypical diabetes mellitus is exceptional in the ability to recover normal pancreatic function [88–90].

In the United States, perhaps 10% of black Americans who present with DKA will have a subsequent course characterized by long-term remission of diabetes mellitus. This course has been labeled "atypical diabetes mellitus," "type 1.5" diabetes, and "Flatbush" diabetes for the area of Brooklyn, New York, where it has been best characterized. Relapses occurred over a time period of months to longer than 5 years; 20% of patients were in remission beyond 6 years. Patients may have a family history of similar remissions of diabetes mellitus. This pattern is seen in younger, less obese, and more insulin-sensitive patients than the typical patient with type 2 diabetes, and in Japanese and Chinese patients with atypical diabetes mellitus who often do not require insulin after the episode. Unlike in type 1 diabetes, antibodies against glutamic acid decarboxylase (GAD) and islet cell antibodies are negative.

Hyperosmolar Hyperglycemic Syndrome (HHS)

Hyperosmolar hyperglycemic syndrome differs from DKA in the more dramatic degree of dehydration, higher serum glucose, lack of acidosis, advanced patient age, and much higher mortality (Fig. 7) [91].

Hyperosmolar hyperglycemic syndrome (HHS) connotes severe hyperglycemia without (or with mild) acidemia or ketoacidosis. Diagnostic criteria include a plasma glucose level >600 mg/dl, an effective plasma osmolarity >320 mOsm/L, and an absence of significant ketoacidosis [92]. The pathogenesis of HHS bears similarities to that of DKA. In HHS, there is a relative insulin deficiency combined with increased levels of counterregulatory hormones. An increase in gluconeogenesis and glycogenolysis lead to hyperglycemia. Elevated glucose levels create an osmotic gradient leading to osmotic diuresis. HHS differs from DKA in its absence of ketoacidosis. The presence of insulin and lower levels of glucagon avoid ketoacid formation [93]. The severe dehydration and hyperglycemia often results in effective serum osmolality (Table 2)

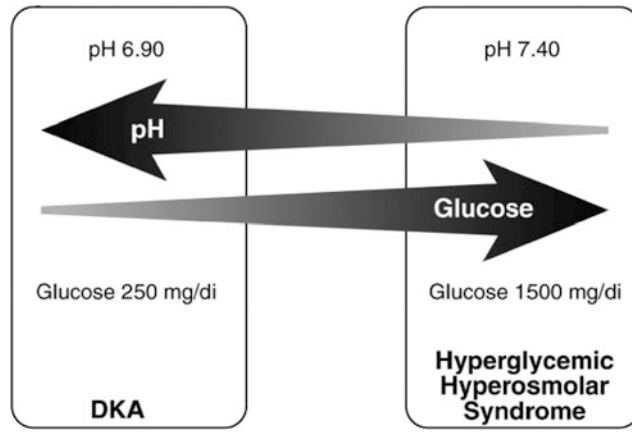

Fig. 7 Hyperglycemic Hyperosmolar Syndrome (HHS) is characterized by elevated glucose levels and increased plasma osmolality in the absence of ketoacidosis. In between, there is overlap and the clinician tailors therapy accordingly

greater than 320 mOsm/L, a level at which depression of consciousness or coma can be attributed to the hyperosmolar state [94, 95]. Patients commonly have type 2 diabetes mellitus, with poor antecedent glucose control, and are older; however, HHS has been reported in those with type 1 diabetes as well as in children [96, 97].

Thrombotic complications, which may occur in DKA [98], are a feared complication of HHS. Coronary arteries may clot, and arterial clots may propagate from the periphery to include the large central vessels. Presumably, the severe dehydration results in hemoconcentration and a hypercoagulable state. Because of the typically advanced patient age, the hypercoagulability, and decreased perfusion accompanying severe dehydration, myocardial infarction must be specifically excluded as a precipitating or a complicating event. Investigations for precipitating events, similar to that in cases of DKA, should be pursued during evaluation of a patient with HHS.

Patients should be treated in an intensive care setting. Fluid management with aggressive rehydration is the critical aspect of treatment of hyperosmolar syndrome. An immediate fluid challenge should be given to guarantee continued renal perfusion and urine output. One or two liters of fluid in the first hour of therapy followed by 1 L/h for the next 4 h is commonly recommended. The water deficit can be calculated from the serum osmolality (the serum sodium can be substituted for osmolality in the equation). Half the water deficit should be replaced in the first 8–12 h. Exceptions include patients with renal or congestive heart failure, who require highly individualized fluid management.

The "corrected" serum sodium (Table 2) indicates the degree of free water loss – the higher the corrected sodium, the greater the water loss. In spite of marked free water loss, initial fluid replacement is with isotonic solutions, usually normal saline (NS), to establish blood pressure and perfusion. The subsequent fluid chosen depends on hemodynamics, serum sodium, and urine output.

Insulin plays only a minor role in the treatment of HHS, since these patients are not "ketosis prone," are not acidotic, and do not require restraint of free fatty acid release. The glucose osmotic diuresis that occurs with fluid administration is the most important factor in lowering the blood glucose toward the renal threshold of 180 mg/dL.

Insulin treatment is currently recommended in the treatment of HHS if glucose levels are not declining with fluid therapy alone. The rapid blood lowering of the serum glucose with insulin is not recommended because the osmotic pull of glucose helps to maintain intravascular volume and rapid changes in osmolality could result in cerebral edema. Maintenance of glucose levels of 200–300 mg/dL is currently recommended [92].

When it is over, the physician must educate the patient not to omit insulin at times of stress.

Patients with type 1 diabetes must always take insulin; patients with type 2 diabetes must understand when insulin doses need to be increased. Common misconceptions have to be corrected. The patient must take insulin even when not able to eat. Ordinarily, the diabetic patient will have a basal insulin that remains active between meals or when not eating. This basal insulin can be in the form of long or intermediate acting insulin or a rapid acting insulin, continuously infused subcutaneously by an insulin pump. Patients get confused, however, when they are not eating because of illness, such as gastrointestinal "upset." At these times, counterregulatory hormones may rise resulting in increased insulin requirements. Patients must know that they need to be more vigilant with self-monitored blood glucose testing and if necessary, ketone testing.

Conclusions

The next patient will likely be different, but the culprits – glucose, free fatty acids, and ketoacids – will be the same. The absolute or relative insulin deficiency permitting substrates (free fatty acids, amino acids and glycerol) to reach the liver and counterregulatory excesses driving hepatic gluconeogenesis and ketogenesis are important to consider when interpreting lab results and enacting a treatment plan. The reversal of controlled storage and synthetic processes resulting in hyperglycemia, systemic acidosis, osmotic diuresis, and

dehydration will be pillars of the treatment plan. Therapy is straightforward, requiring insulin, fluid, and electrolyte administration. Key to a successful clinical outcome is careful monitoring of the patient, anticipation of responses, and investigation of potential precipitating factors.

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References

1. Maahs DM, Hermann JM, Holman N, Foster NC, Kapellen TM, Allgrove J, Schatz DA, Hofer SE, Campbell F, Steigleder-Schweiger C, Beck RW, Warner JT, Holl RW, National Paediatric Diabetes Audit and the Royal College of Paediatrics and the Child Health, the DPV Initiative, and the T1D Exchange Clinic Network. Rates of diabetic ketoacidosis: international comparison with 49,859 pediatric patients with type 1 diabetes from England, Wales, the U.S., Austria, and Germany. Diabetes Care. 2015;38:1876–82.
2. Pietropaolo M, Barinas-Mitchell E, Kuller LH. The heterogeneity of diabetes: unraveling a dispute: is systemic inflammation related to islet autoimmunity? Diabetes. 2007;56:1189–97.
3. Balasubramanyam A, Garza G, Rodriguez L, et al. Accuracy and predictive value of classification schemes for ketosis-prone diabetes. Diabetes Care. 2006;29:2575–9.
4. Klingensmith GJ, Connor CG, Ruedy KJ, Beck RW, Kollman C, Haro H, Wood JR, Lee JM, Willi SM, Cengiz E, Tamborlane WV. Presentation of youth with type 2 diabetes in the pediatric diabetes consortium. Pediatr Diabetes. 2015. doi: 10.1111/pedi.12281. [Epub ahead of print] PMID: 25951940
5. Rodríguez-Gutiérrez R, Camara-Lemarroy CR, Quintanilla-Flores DL, González-Moreno EI, González-Chavez JM, Lavalle-González FJ, González-Gonzalez JG, Caballero AE. Severe ketoacidosis (pH $\leq$ 6.9) in type 2 diabetes: more frequent and less ominous than previously thought. Biomed Res Int. 2015;2015:134780. Epub 2015 Jun 21. PMID: 26180779
6. Valabhji J, Watson M, Cox J, Poulter C, Elwig C, Elkeles RS. Type 2 diabetes presenting as diabetic ketoacidosis in adolescence. Diabet Med. 2003;20:416–7.
7. Umpierrez GE, Woo W, Hagopian WA, et al. Immunogenetic analysis suggests different pathogenesis for obese and lean African-Americans with diabetic ketoacidosis. Diabetes Care. 1999;22:1517–23.
8. Dabelea D, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, Imperatore G, D'Agostino Jr RB, Mayer-Davis EJ, Pihoker C, Group SfDiYS. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. Pediatrics. 2014;133:e938–45.
9. Usher-Smith JA, Thompson MJ, Sharp SJ, Walter FM. Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review. BMJ. 2011;343:d4092.
10. Fleckman AM. Diabetic ketoacidosis. Endocrinol Metab Clin N Am. 1993;22:181–207.
11. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. Diabetes Care. 2006;29(12):2739–48.
12. Mehta AN, Emmett JB, Emmett M. GOLD MARK: an anion gap mnemonic for the 21st century. Lancet. 2008;372:892.
13. Davis SN, Umpierrez GE. Diabetic ketoacidosis in type 2 diabetes mellitus – pathophysiology and clinical presentation. Nat Clin Pract Endocrinol Metab. 2007;3(11):730–1.
14. Cooper GM, Hausman RE. The cell: a molecular approach. 4th ed. Washington, DC: ASM Press; 2007. p. 73–102, 433–71.
15. Nelson DL, Cox MM. Lehninger principles of biochemistry. 4th ed. New York: Freeman; 2005, Chapter 14-1, Glycolysis; Chapter 17, Fatty acid catabolism; Chapter 23.2 Tissue-specific metabolism.
16. DeFronzo RA, Matsuda M, Barrett EJ. Diabetic ketoacidosis. Diabetes Rev. 1994;2:209–38.
17. Mullins GR, Wang L, Raje V, Sherwood SG, Grande RC, Boroda S, Eaton JM, Blancquaert S, Roger PP, Leitinger N, Harris TE. Catecholamine-induced lipolysis causes mTOR complex dissociation and inhibits glucose uptake in adipocytes. Proc Natl Acad Sci U S A. 2014;111:17450–5.
18. Ottosson M, Lönnroth P, Björntorp P, et al. Effects of cortisol and growth hormone on lipolysis in human adipose tissue. J Clin Endocrinol Metab. 2000;85:799–803.
19. Seckl JR, Walker BR. Minireview: 11beta-hydroxysteroid dehydrogenase type 1 – a tissue-specific amplifier of glucocorticoid action. Endocrinol. 2001;142:1371–6.
20. Gaboriaud-Kolar N, Skaltsounis AL. Glycogen phosphorylase inhibitors: a patent review (2008–2012). Expert Opin Ther Pat. 2013;23:1017–32.
21. Zammit VA. Regulation of ketone body metabolism. Diabetes Rev. 1994;2:132–55.
22. Kreisberg RA. Lactate homeostasis and lactic acidosis. Ann Intern Med. 1980;92(2 Pt 1):227–37.
23. Laffel L. Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. Diabetes/Metab Res Rev. 1999;15:412–26.

24. Berg JM, Tymoczko JL, Stryer L. Biochemistry. 6th ed. New York: Freeman; 2007. p. 632–3, Chapter 22, Fatty acid metabolism: ketone bodies are a major fuel in some tissues.
25. Randall L, Begovic J, Hudson M, Smiley D, Peng L, Pitre N, Umpierrez D, Umpierrez G. Recurrent diabetic ketoacidosis in inner-city minority patients: behavioral, socioeconomic, and psychosocial factors. Diabetes Care. 2011;34:1891–6.
26. Maldonado MR, Chong ER, Oehl MA, Balasubramanyam A. Economic impact of diabetic ketoacidosis in a multiethnic indigent population: analysis of costs based on the precipitating cause. Diabetes Care. 2003;26:1265–9.
27. Jin H, Meyer JM, Jeste DV. Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: an analysis of 45 published cases. Ann Clin Psychiatry. 2002;14(1):59–64.
28. Ramaswamy K, Masand PS, Nasrallah HA. Do certain atypical antipsychotics increase the risk of diabetes? A critical review of 17 pharmacoepidemiologic studies. Ann Clin Psychiatry. 2006;18(3):183–94.
29. Imagawa A, Hanafusa T, Miyagawa JI, et al. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. N Engl J Med. 2000;342:301–7.
30. Yoon JW, Austin M, Onodera T, et al. Isolation of a virus from the pancreas of a child with diabetic ketoacidosis. N Engl J Med. 1979;300(21): 1173–9.
31. Chen LK, Chou YC, Tsai ST, et al. Hepatitis C virus infection-related type 1 diabetes mellitus. Diabetic Med. 2005;22(3):340–3.
32. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care. 2003;26:510–3.
33. Muller LM, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AI, Rutten GE. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis. 2005;41:281–8.
34. Koh GC, Peacock SJ, van der Poll T, Wiersinga WJ. The impact of diabetes on the pathogenesis of sepsis. Eur J Clin Microbiol Infect Dis. 2012;31:379–88.
35. Katz MA. Hyperglycemia-induced hyponatremia – calculation of expected serum sodium depression. N Engl J Med. 1973;289(16):843–4.
36. Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med. 1999;106:399–403.
37. Brandenburg MA, Dire DJ. Comparison of arterial and venous blood gas values in the initial emergency department evaluation of patients with diabetic ketoacidosis. Ann Emerg Med. 1998;31:459–65.
38. Fulop M, Murthy V, Michili A, et al. Serum beta-hydroxybutyrate measurement in patients with uncontrolled diabetes mellitus. Arch Intern Med. 1999;159:381–4.
39. White NH. Diabetic ketoacidosis in children. Endocrinol Metab Clin. 2000;29:657–82.
40. Wolfsdorf J, Glaser N, Sperling MA. Diabetic ketoacidosis in infants, children, and adolescents. Diabetes Care. 2006;29:1150–9.
41. Adrogué HJ, Barrero J, Eknoyan G. Salutary effects of modest fluid replacement in the treatment of adults with diabetic ketoacidosis. JAMA. 1989;262:2108–13.
42. Rave K, Nosek L, Posner J, et al. Renal glucose excretion as a function of blood glucose concentration in subjects with type 2 diabetes – results of a hyperglycaemic glucose clamp study. Nephrol Dial Transplant. 2006;21:2166–71.
43. Kawata H, Inui D, Ohto J, et al. The use of continuous hemodiafiltration in a patient with diabetic ketoacidosis. J Anesth. 2006;20(2):129–31.
44. Kaufman FR. Diabetes in children and adolescents: areas of controversy. Med Clin N Am. 1998;82:721–38.
45. Muir A. Cerebral edema in diabetic ketoacidosis: a look beyond rehydration. J Clin Endocrinol Metab. 2000;85:509–13.
46. Edge JA, Ford-Adams ME, Dunger DB. Causes of death in children with insulin dependent diabetes 1990–96. Arch Dis Child. 1999;81:318–23.
47. Lawrence SE, Cummings EA, Gaboury I, Daneman D. Population-based study of incidence and risk factors for cerebral edema in pediatric diabetic ketoacidosis. J Pediatr. 2005;146:688–92.
48. Glaser N. Cerebral injury and cerebral edema in children with diabetic ketoacidosis: could cerebral ischemia and reperfusion injury be involved? Pediatr Diabetes. 2009;10:534–41.
49. Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. N Engl J Med. 2001;344:264–9.
50. Isales CM, Min L, Hoffman WH. Acetoacetate and beta-hydroxybutyrate differentially regulate endothelin-1 and vascular endothelial growth factor in mouse brain microvascular endothelial cells. J Diabet Complications. 1999;13:91–7.
51. Mahoney CP, Vlcek BW, DelAguila M. Risk factors for developing brain herniation during diabetic ketoacidosis. Pediatr Neurol. 1999;21:721–7.
52. Wagner A, Risse A, Brill HL, et al. Therapy of severe diabetic ketoacidosis: zero-mortality under very-low-dose insulin application. Diabetes Care. 1999;22:674–7.
53. Umpierrez GE, Jones S, Smiley D, Mulligan P, Keyler T, Temponi A, Semakula C, Umpierrez D, Peng L, Ceron M, Robalino G. Insulin analogs versus human insulin in the treatment of patients with diabetic ketoacidosis: a randomized controlled trial. Diabetes Care. 2009;32:1164–9.
54. Kitabchi AE, Murphy MB, Spencer J, Matteri R, Karas J. Is a priming dose of insulin necessary in a low-dose insulin protocol for the treatment of diabetic ketoacidosis? Diabetes Care. 2008;31:2081–5.

55. Goyal N, Miller JB, Sankey SS, Mossallam U. Utility of initial bolus insulin in the treatment of diabetic ketoacidosis. J Emerg Med. 2010;38:422–7.
56. Vincent M, Nobecourt E. Treatment of diabetic ketoacidosis with subcutaneous insulin lispro: a review of the current evidence from clinical studies. Diabetes Metab. 2013;39:299–305.
57. Weiner ID, Wingo CS. Hypokalemia – consequences, causes, and correction. J Am Soc Nephrol. 1997;8:1179–88.
58. Tattersall RB. A paper which changed clinical practice (slowly). Jacob Holler on potassium deficiency in diabetic acidosis (1946). Diabet Med. 1999;16:978–84.
59. Viallon A, Zeni F, Lafond P, et al. Does bicarbonate therapy improve the management of severe diabetic ketoacidosis? Crit Care Med. 1999;27:2690–3.
60. Morris LR, Murphy MB, Kitabchi AE. Bicarbonate therapy in severe diabetic ketoacidosis. Ann Intern Med. 1986;105:836–40.
61. Lever E, Jaspan JB. Sodium bicarbonate therapy in severe diabetic ketoacidosis. Am J Med. 1983;75:263–8.
62. Malone ML, Gennis V, Goodwin JS. Characteristics of diabetic ketoacidosis in older versus younger adults. J Am Geriatr Soc. 1992;40:1100–4.
63. Ezeani I, Eregie A, Ogedengbe O. Treatment outcome and prognostic indices in patients with hyperglycemic emergencies. Diabetes Metab Syndr Obes. 2013;6:303–7.
64. Decourcey DD, Steil GM, Wypij D, Agus MS. Increasing use of hypertonic saline over mannitol in the treatment of symptomatic cerebral edema in pediatric diabetic ketoacidosis: an 11-year retrospective analysis of mortality*. Pediatr Crit Care Med. 2013;14:694–700.
65. Azevedo LC, Choi H, Simmonds K, Davidow J, Bagshaw SM. Incidence and long-term outcomes of critically ill adult patients with moderate-to-severe diabetic ketoacidosis: retrospective matched cohort study. J Crit Care. 2014;29:971–7.
66. Bialo SR, Agrawal S, Boney CM, Quintos JB. Rare complications of pediatric diabetic ketoacidosis. World J Diabetes. 2015;6:167–74.
67. Wang LM, Tsai ST, Ho LT, Hu SC, Lee CH. Rhabdomyolysis in diabetic emergencies. Diabetes Res Clin Pract. 1994;26:209–14.
68. Hoffman WH, Locksmith JP, Burton EM, et al. Interstitial pulmonary edema in children and adolescents with diabetic ketoacidosis. J Diabet Complications. 1998;12:314–20.
69. Vantyghem MC, Haye S, Balduyck M, et al. Changes in serum amylase, lipase and leukocyte elastase during diabetic ketoacidosis and poorly controlled diabetes. Acta Diabetol. 1999;36:39–44.
70. Nair S, Pitchumoni CS. Diabetic ketoacidosis, hyperlipidemia, and acute pancreatitis: the enigmatic triangle. Am J Gastroenterol. 1997;92:1560–1.
71. Nair S, Yadav D, Pitchumoni CS. Association of diabetic ketoacidosis and acute pancreatitis: observations in 100 consecutive episodes of DKA. Am J Gastroenterol. 2000;95:2795–800.
72. Fulop M, Eder H. Severe hypertriglyceridemia in diabetic ketosis. Am J Med Sci. 1990;300:361–5.
73. Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. J Clin Endocrinol Metab. 1983;57:177–80.
74. Gaasbeek A, Meinders AE. Hypophosphatemia: an update on its etiology and treatment. Am J Med. 2005;118:1094–101.
75. Mégarbane B, Guerrier G, Blancher A, et al. A possible hypophosphatemia-induced, life-threatening encephalopathy in diabetic ketoacidosis: a case report. Am J Med Sci. 2007;333(6):384–6.
76. Podar T, Solntsev A, Reunanen A, et al. Mortality in patients with childhood-onset type 1 diabetes in Finland, Estonia, and Lithuania: follow-up of nationwide cohorts. Diabetes Care. 2000;23:290–4.
77. Lipton R, Good G, Mikhailov T, et al. Ethnic differences in mortality from insulin-dependent diabetes mellitus among people less than 25 years of age. Pediatrics. 1999;103:952–6.
78. Shrestha SS, Zhang P, Barker L, Imperatore G. Medical expenditures associated with diabetes acute complications in privately insured U.S. youth. Diabetes Care. 2010;33:2617–22.
79. Icks A, Strassburger K, Baechle C, Rosenbauer J, Giani G, Beyer P, Holl RW. Frequency and cost of diabetic ketoacidosis in Germany – study in 12,001 paediatric patients. Exp Clin Endocrinol Diabetes. 2013;121:58–9.
80. Vanelli M, Chiari G, Ghizzoni L, et al. Effectiveness of a prevention program for diabetic ketoacidosis in children: an 8-year study in schools and private practices. Diabetes Care. 1999;22:7–9.
81. Bonadio WA, Gutzeit MF, Losek JD, et al. Outpatient management of diabetic ketoacidosis. Am J Dis Child. 1988;142:448–50.
82. Marinac JS, Jesa L. Using a severity of illness scoring system to assess intensive care unit admissions for diabetic ketoacidosis. Crit Care Med. 2000;28:2238–41.
83. Levetan CS, Passaro MD, Jablonski KA, et al. Effect of physician specialty on outcomes in diabetic ketoacidosis. Diabetes Care. 1999;22:1790–5.
84. Thawabi M, Studyvin S. Euglycemic diabetic ketoacidosis, a misleading presentation of diabetic ketoacidosis. N Am J Med Sci. 2015;7:291–4.
85. Chico M, Levine SN, Lewis DF. Normoglycemic diabetic ketoacidosis in pregnancy. J Perinatol. 2008;28:310–2.
86. Cullen MT, Reece EA, Homko CJ, et al. The changing presentations of diabetic ketoacidosis during pregnancy. Am J Perinatol. 1996;13(7):449–51.
87. Bas VN, Uytun S, Torun YA. Diabetic euglycemic ketoacidosis in newly diagnosed type 1 diabetes

mellitus during Ramadan fasting. J Pediatr Endocrinol Metab. 2015;28:333–5.
88. Winter WE, Maclaren NK, Riley WJ, et al. Maturity-onset diabetes of youth in black Americans. N Engl J Med. 1987;316:285–91.
89. Banerji MA, Chaiken RL, Huey H, et al. GAD antibody negative NIDDM in adult black subjects with diabetic ketoacidosis and increased frequency of human leukocyte antigen DR3 and DR4. Flatbush diabetes. Diabetes. 1994;43:741–5.
90. Banerji MA, Chaiken RL, Lebovitz HE. Long-term normoglycemic remission in black newly diagnosed NIDDM subjects. Diabetes. 1996;45:337–41.
91. Matz R. Management of the hyperosmolar hyperglycemic syndrome. Am Fam Physician. 1999;60:1468–76.
92. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32:1335–43.
93. Chupin M, Charbonnel B, Chupin F. C-peptide blood levels in keto-acidosis and in hyperosmolar non-ketotic diabetic coma. Acta Diabetol Lat. 1981;18:123–8.
94. Fulop M, Tannenbaum H, Dreyer N. Ketotic hyperosmolar coma. Lancet. 1973;2:635–9.
95. Daugirdas JT, Kronfol NO, Tzamaloukas AH, et al. Hyperosmolar coma: cellular dehydration and the serum sodium concentration. Ann Intern Med. 1989;110:855–7.
96. Cochran JB, Walters S, Losek JD. Pediatric hyperglycemic hyperosmolar syndrome: diagnostic difficulties and high mortality rate. Am J Emerg Med. 2006;24:297–301.
97. Bagdure D, Rewers A, Campagna E, Sills MR. Epidemiology of hyperglycemic hyperosmolar syndrome in children hospitalized in USA. Pediatr Diabetes. 2013;14:18–24.
98. Ileri NS, Buyukasik Y, Karaahmetoglu S, et al. Evaluation of the haemostatic system during ketoacidotic deterioration of diabetes mellitus. Haemostasis. 1999;29:318–25.
99. Balasubramanyam A, Zern JW, Hyman DJ, et al. New profiles of diabetic ketoacidosis: type 1 vs type 2 diabetes and the effect of ethnicity. Arch Intern Med. 1999;159:2317–22.

Recommended Websites

Medline Plus. Diabetic ketoacidosis. 2014. https://www.nlm.nih.gov/medlineplus/ency/article/000320.htm. Accessed 30 Sept 2015.
eMedicine from WebMD. Diabetic ketoacidosis. 2015. http://emedicine.medscape.com/article/118361-overview. Accessed 30 Sept 2015.