



Diabetic Ketoacidosis, Pathophysiology, Diagnosis and Treatment

1. Djurayeva Zilola Aramovna
2. Jonibek Obloqulov
3. Ezoza Norova
4. Bahodirjon Xudoyberdiyev

Received 2nd Mar 2023,
Accepted 3rd Apr 2023,
Online 6th May 2023

¹ Lecturer Of The Department Of
Endocrinology, Samarkand State Medical
University
ziloladj1974@gmail.com

^{2,3,4} Students of Samarkand State Medical
University

Abstract: DKA may be the initial symptom complex that leads to a diagnosis of type 1 DM, but more frequently it occurs in individuals with established diabetes. Nausea and vomiting are often prominent, and their presence in an individual with diabetes warrants laboratory evaluation for DKA. Abdominal pain may be severe and can resemble acute pancreatitis or ruptured viscus. Hyperglycemia leads to glucosuria, volume depletion, and tachycardia. Hypotension can occur because of volume depletion in combination with peripheral vasodilatation. Kussmaul respirations and a fruity odor on the patient's breath (secondary to metabolic acidosis and increased acetone) are classic signs of the disorder. Lethargy and central nervous system depression may evolve into coma with severe DKA but should also prompt evaluation for other reasons for altered mental status (infection, hypoxia, etc.). Cerebral edema, an extremely serious complication of DKA, is seen most frequently in children. Signs of infection, which may precipitate DKA, should be sought on physical examination, even in the absence of fever. Tissue ischemia (heart, brain) can also be a precipitating factor.

Pathophysiology

DKA results from relative or absolute insulin deficiency combined with counterregulatory hormone excess (glucagon, catecholamines, cortisol, and growth hormone). Both insulin deficiency and glucagon excess, in particular are necessary for DKA to develop. The decreased ratio of insulin to glucagon promotes gluconeogenesis, glycogenolysis, and ketone body formation in the liver, as well as increases in substrate delivery from fat and muscle (free fatty acids, amino acids) to the liver.

The combination of insulin deficiency and hyperglycemia reduces the hepatic level of fructose-2,6-biphosphate, which alters the activity of phosphofructokinase and fructose-1,6-bisphosphatase. Glucagon excess decreases the activity of pyruvate kinase, whereas insulin deficiency increases the activity of phosphoenolpyruvate carboxykinase. These changes shift the handling of pyruvate toward glucose synthesis and away from glycolysis. The increased levels of glucagon and catecholamines in the face of low insulin levels promote glycogenolysis. Insulin deficiency also reduces levels of the

GLUT4 glucose transporter, which impairs glucose uptake into skeletal muscle and fat and reduces intracellular glucose metabolism.

Ketosis results from a marked increase in free fatty acid release from adipocytes, with a resulting shift toward ketone body synthesis in the liver. Reduced insulin levels, in combination with elevations in catecholamines and growth hormone, increase lipolysis and the release of free fatty acids. Normally, these free fatty acids are converted to triglycerides or VLDL in the liver. However, in DKA, hyperglucagonemia alters hepatic metabolism to favor ketone body formation, through activation of the enzyme carnitine palmitoyl-transferase I. This enzyme is crucial for regulating fatty acid transport into the mitochondria, β -oxidation and conversion to ketone bodies occur. At physiologic pH, ketone bodies exist as ketoacids, which are neutralized by bicarbonate. As bicarbonate stores are depleted, metabolic acidosis ensues. Increased lactic acid production also contributes to the acidosis. The increased free fatty acids increase triglyceride and VLDL production. VLDL clearance is also reduced because the activity of insulin-sensitive lipoprotein lipase in muscle and fat is decreased. Hypertriglyceridemia may be severe enough to cause pancreatitis.

DKA is initiated by inadequate levels of plasma insulin (Table 19-5). Most commonly, DKA is precipitated by increased insulin requirements, as might occur during a concurrent illness. Failure to augment insulin therapy often compounds the problem. Occasionally, complete omission of insulin by the patient or health care team (in a hospitalized patient with type 1 DM) precipitates DKA. Patients using insulin infusion devices with short-acting insulin are at increased risk of DKA, since even a brief interruption in insulin delivery (e.g., mechanical malfunction) quickly leads to insulin deficiency.

Laboratory Abnormalities and Diagnosis

The timely diagnosis of DKA is crucial and allows for prompt initiation of therapy. DKA is characterized by hyperglycemia, ketosis, and metabolic acidosis (increased anion gap) along with a number of secondary .

Occasionally, the serum glucose is only minimally elevated. Serum bicarbonate is frequently <10 mmol/L, and arterial pH ranges between 6.8 and 7.3, depending on the severity of the acidosis. Despite a total-body potassium deficit, the serum potassium at presentation may be mildly elevated, secondary to the acidosis. Total-body stores of sodium, chloride, phosphorous, and magnesium are also reduced in DKA but are not accurately reflected by their levels in the serum because of dehydration and hyperglycemia. Elevated blood urea nitrogen (BUN) and serum creatinine levels reflect intravascular volume depletion. Interference from acetoacetate may falsely elevate the serum creatinine measurement. Leukocytosis, hypertriglyceridemia, and hyperlipoproteinemia are commonly found as well. Hyperamylasemia may suggest a diagnosis of pancreatitis, especially when accompanied by abdominal pain. However, in DKA the amylase is usually of salivary origin and thus is not diagnostic of pancreatitis. Serum lipase should be obtained if pancreatitis is suspected.

The measured serum sodium is reduced because of the hyperglycemia [1.6-mmol/L (1.6 meq) reduction in serum sodium for each 5.6-mmol/L (100 mg/dL) rise in the serum glucose]. A normal serum sodium in the setting of DKA indicates a more profound water deficit. In “conventional” units, the calculated serum osmolality [$2 \times (\text{serum sodium} + \text{serum potassium}) + \text{plasma glucose (mg/dL)}/18 + \text{BUN}/2.8$] is mildly to moderately elevated, though to a lesser degree than that found in HHS.

In DKA, the ketone body, β -hydroxybutyrate, is synthesized at a threefold greater rate than acetoacetate; however, acetoacetate is preferentially detected by a commonly used ketosis detection reagent (nitroprusside). Serum ketones are present at significant levels (usually positive at serum dilution of $\geq 1:8$). The nitroprusside tablet, or stick, is often used to detect urine ketones; certain medications such as captopril or penicillamine may cause false-positive reactions. Serum or plasma assays for β -hydroxybutyrate more accurately reflect the true ketone body level.

The metabolic derangements of DKA exist along a spectrum, beginning with mild acidosis with moderate hyperglycemia evolving into more severe findings. The degree of acidosis and hyperglycemia do not necessarily correlate closely since a variety of factors determine the level of hyperglycemia (oral intake, urinary glucose loss). Ketonemia is a consistent finding in DKA and distinguishes it from simple hyperglycemia. The differential diagnosis of DKA includes starvation ketosis, alcoholic ketoacidosis (bicarbonate usually >15 meq/L), and other increased anion gap acidosis.

After initiating IV fluid replacement and insulin therapy, the agent or event that precipitated the episode of DKA should be sought and aggressively treated. If the patient is vomiting or has altered mental status, a nasogastric tube should be inserted to prevent aspiration of gastric contents. Central to successful treatment of DKA is careful monitoring and frequent reassessment to ensure that the patient and the metabolic derangements are improving. A comprehensive flow sheet should record chronologic changes in vital signs, fluid intake and output, and laboratory values as a function of insulin administered.

After the initial bolus of normal saline, replacement of the sodium and free-water deficit is carried out over the next 24 h (fluid deficit is often 3–5 L). When hemodynamic stability and adequate urine output are achieved, IV fluids should be switched to 0.45% saline at a rate of 200–300 mL/h, depending on the calculated volume deficit. The change to 0.45% saline helps to reduce the trend toward hyperchloremia later in the course of DKA. Alternatively, initial use of lactated Ringer's IV solution may reduce the hyperchloremia that commonly occurs with normal saline.

A bolus of IV (0.1 units/kg) or IM (0.3 units/kg) short-acting insulin should be administered immediately (Table 19-6), and subsequent treatment should provide continuous and adequate levels of circulating insulin. IV administration is preferred (0.1 units/kg per h), because it ensures rapid distribution and allows adjustment of the infusion rate as the patient responds to therapy. In mild episodes of DKA, short-acting insulin analogues can be used subcutaneously. IV regular insulin should be continued until the acidosis resolves and the patient is metabolically stable. As the acidosis and insulin resistance associated with DKA resolve, the insulin infusion rate can be decreased (to 0.05–0.1 units/kg per h). Intermediate or long-acting insulin, in combination with SC short-acting insulin, should be administered as soon as the patient resumes eating, as this facilitates transition to an outpatient insulin regimen and reduces length of hospital stay. It is crucial to continue the insulin infusion until adequate insulin levels are achieved by the SC route. Even relatively brief periods of inadequate insulin administration in this transition phase may result in DKA relapse.

Hyperglycemia usually improves at a rate of 4.2–5.6 mmol/L (75–100 mg/dL) per h as a result of insulin-mediated glucose disposal, reduced hepatic glucose release, and rehydration. The latter reduces catecholamines, increases urinary glucose loss, and expands the intravascular volume. The decline in the plasma glucose within the first 1–2 h may be more rapid and is mostly related to volume expansion. When the plasma glucose reaches 13.9 mmol/L (250 mg/dL), glucose should be added to the 0.45% saline infusion to maintain the plasma glucose in the 11.1–13.9 mmol/L (200–250 mg/dL) range, and the insulin infusion should be continued. Ketoacidosis begins to resolve as insulin reduces lipolysis, increases peripheral ketone body use, suppresses hepatic ketone body formation, and promotes bicarbonate regeneration. However, the acidosis and ketosis resolve more slowly than hyperglycemia. As ketoacidosis improves, β -hydroxybutyrate is converted to acetoacetate. Ketone body levels may appear to increase if measured by laboratory assays that use the nitroprusside reaction, which only detects acetoacetate and acetone. The improvement in acidosis and anion gap, a result of bicarbonate regeneration and decline in ketone bodies, is reflected by a rise in the serum bicarbonate level and the arterial pH depending on the rise of serum chloride, the anion gap (but not bicarbonate) will normalize. A hyperchloremic acidosis [serum bicarbonate of 15–18 mmol/L (15–18

meq/L)] often follows successful treatment and gradually resolves as the kidneys regenerate bicarbonate and excrete chloride.

Potassium stores are depleted in DKA [estimated deficit 3–5 mmol/kg (3–5 meq/kg)]. During treatment with insulin and fluids, various factors contribute to the development of hypokalemia. These include insulin-mediated potassium transport into cells, resolution of the acidosis (which also promotes potassium entry into cells), and urinary loss of potassium salts of organic acids. Thus, potassium repletion should commence as soon as adequate urine output and a normal serum potassium are documented. If the initial serum potassium level is elevated, then potassium repletion should be delayed until the potassium falls into the normal range. Inclusion of 20–40 meq of potassium in each liter of IV fluid is reasonable, but additional potassium supplements may also be required. To reduce the amount of chloride administered, potassium phosphate or acetate can be substituted for the chloride salt. The goal is to maintain the serum potassium >3.5 mmol/L (3.5 meq/L). If the initial serum potassium is <3.3 mmol/L (3.3 meq/L), do not administer insulin until the potassium is supplemented to >3.3 mmol/L (3.3 meq/L).

Despite a bicarbonate deficit, bicarbonate replacement is not usually necessary. In fact, theoretical arguments suggest that bicarbonate administration and rapid reversal of acidosis may impair cardiac function, reduce tissue oxygenation, and promote hypokalemia. The results of most clinical trials do not support the routine use of bicarbonate replacement, and one study in children found that bicarbonate use was associated with an increased risk of cerebral edema. However, in the presence of severe acidosis (arterial pH <7.0 after initial hydration), the ADA advises bicarbonate [50 mmol/L (meq/L) of sodium bicarbonate in 200 mL of sterile water with 10 meq/L KCl over 1 h if pH = 6.9–7.0; or 100 mmol/L (meq/L) of sodium bicarbonate in 400 mL of sterile water with 20 meq/L KCl over 2 h if pH <6.9]. Repeat the dose of bicarbonate every 2 h until the arterial pH is >7.0 . Hypophosphatemia may result from increased glucose usage, but randomized clinical trials have not demonstrated that phosphate replacement is beneficial in DKA. If the serum phosphate is <0.32 mmol/L (1.0 mg/dL), then phosphate supplement should be considered and the serum calcium monitored. Hypomagnesemia may develop during DKA therapy and may also require supplementation.

With appropriate therapy, the mortality of DKA is low ($<5\%$) and is related more to the underlying or precipitating event, such as infection or myocardial infarction. The major nonmetabolic complication of DKA therapy is cerebral edema, which most often develops in children as DKA is resolving. The etiology of and optimal therapy for cerebral edema are not well established, but overreplacement of free water should be avoided. Venous thrombosis, upper gastrointestinal bleeding, and acute respiratory distress syndrome occasionally complicate DKA.

Following treatment, the physician and patient should review the sequence of events that led to DKA to prevent future recurrences. Foremost is patient education about the symptoms of DKA, its precipitating factors, and the management of diabetes during a concurrent illness. During illness or when oral intake is compromised, patients should (1) frequently measure the capillary blood glucose; (2) measure urinary ketones when the serum glucose is >16.5 mmol/L (300 mg/dL); (3) drink fluids to maintain hydration; (4) continue or increase insulin; and (5) seek medical attention if dehydration, persistent vomiting, or uncontrolled hyperglycemia develop. Using these strategies, early DKA can be prevented or detected and treated appropriately on an outpatient basis.

Conclusion

Thus, the data obtained suggest, as a prevention of DR, the normalization of the following factors: compensation of carbohydrate and lipid metabolism, normalization of blood pressure and, most

importantly, the detection of DR at earlier stages for timely and adequate laser coagulation of the retina and surgical treatment.

Reference

1. Aramovna D. Z., Azamatovna H. D. Features of the Pathology of the Reproductive System in Pubertal Patients with Hypothalamic-Pituitary Dysfunction //EUROPEAN JOURNAL OF BUSINESS STARTUPS AND OPEN SOCIETY. – 2023. – Т. 3. – №. 2. – С. 74-77.
2. Dedov I.I., Shestakova M.V. // Soharny diobet - Moscow - 2003 - P. 231-243. 2. Dear T.M. // Diabetic Retinopathy - Moscow – 2000.-P.3.
3. Djurayeva, Z. A., and D. A. Davranovna. "Of Combined Sugar-Reducing Therapy in Treatment of Patients with Type 2 Diabetes." Eurasian Medical Research Periodical 18 (2023): 103-106.
4. Djurayeva Z.A., Togayeva G.S., Davranova A.D., "Knowledge and Attitude towards Psychiatry among Nursing Staffs in Tertiary Health Care Hospital" Advances in Clinical Medical Research. Volume 3. Issue 2 April-June 2022.
5. Mustafakulov, I. B., and Z. A. Djuraeva. "Severe associated trauma to the abdomen diagnosis and treatment." European journal of pharmaceutical and medical research 7.6 (2020): 113-116.
6. Mustafakulov, I. B., Elmuradov, A., Djuraeva, Z. A., & Umedov, H. A. (2021). DIAGNOSTIC TOOLS AND THERAPEUTIC POSSIBILITIES OF ENDOVIDEOLAPAROSCOPY FOR COMBINED ABDOMINAL TRAUMA. Journal of Natural Remedies, 22(1 (2)), 181-186.
7. UK Prospective Diabetes Study (UKPDS) Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38) // BMJ - 1998 - No 317 - P. 703-713.
8. Wilczynski M., Dziegielewski K. // Klin Oczna - 2005 - No 10-12)-P.672-674.
9. Джураева З.А., Гарифулина Л.М. "Динамическая оценка развития осложнений сахарного диабета 1 типа у подростков". Инфекция, иммунитет и фармакология. №1 2015. Тошкент стр 47-50
10. Джураева З.А., Насруллаева У.Ф. Эффективность и безопасность комбинированной сахароснижающей терапии в лечении больных сахарным диабетом 2 типа. Достижения науки и образования. №9 (63)-2020. стр 74-76.