

Review Article

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Atypical Feature of Diabetic Ketoacidosis with Low or Normal Plasma Glucose: a Narrative Review

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Abstract

Context: Diabetic ketoacidosis (DKA) is a well-known emergency in diabetic patients. In a subgroup of patients ketoacidosis is present but is not accompanied by the marked hyperglycemia considered part of the diagnostic criteria for DKA. This is known as Euglycemic DKA (EuDKA).

Evidence acquisition: We searched the PubMed for the existing literature on the topic of normoglycemic ketoacidosis, including its prevalence, pathogenesis, and treatment.

Results: The study showed that there are many reports of the cases in which diabetic patients developed ketoacidosis without experiencing hyperglycemia. Several predisposing factors have been proposed but the precise pathophysiologic mechanisms are still under investigation. Some pathways have been suggested. Timely diagnosis is of paramount importance. Treatment is similar to DKA.

Conclusion: EuDKA is a medical emergency that should be considered when evaluating a diabetic patient with ketoacidosis. It should be diagnosed and treated promptly.

Key words: Diabetic Ketoacidosis; Euglycemic DKA; Normoglycemic DKA; Review

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CONTEXT

Hyperglycemia crisis, either in the form of hyperglycemic, hyperosmolar state or diabetic ketoacidosis (DKA), is an acute complication of diabetes mellitus frequently seen in the emergency departments.

DKA, one of the gravest complications of diabetes mellitus, is characterized by the triad of hyperglycemia (plasma glucose >250 mg/dl), metabolic acidosis (arterial pH <7.3 and serum bicarbonate less than 18 mEq/L) typically with a wide anion gap, and ketosis (1-3). At present, mortality attributable to DKA is fairly low, but in some groups, such as patients of higher age and those with several episodes of DKA, the mortality may still be high (1, 3). Moreover, in children with type 1 diabetes mellitus, DKA is still one of the main causes of mortality (3). It is often precipitated by factors such as infections, insufficient insulin therapy (inadequate dose or discontinuation of treatment), pancreatitis, myocardial infarction, cerebrovascular accident, or illicit drug use (1, 2, 4).

Although hyperglycemia is a fundamental criterion for diagnosis of DKA, in practice, plasma glucose levels on admission can vary across a wide range (5). DKA patients may be encountered with blood

glucose levels below 200 mg/dl. Although this condition may be considered as a less severe variant of DKA, the reported in-hospital mortality rate of patients with EuDKA is similar to that of cases with typical DKA (2, 3).

Euglycemic diabetic ketoacidosis (EuDKA), defined as DKA without marked hyperglycaemia (<200 mg/dL), was first described by Munro in 1973 (2, 4, 6). This condition is considered to be relatively uncommon, but may in fact be underreported (4). More formally, EuDKA is defined as a triad of wide anion gap metabolic acidosis, ketonemia and ketonuria, and a plasma glucose level lower than 200 mg/dL (1, 7).

EVIDENCE ACQUISITION

We searched the literature for reports on EuDKA, using the keywords ketoacidosis, normoglycemic, euglycemic, hyperglycemic crisis, and diabetic emergencies, using PubMed. We also we extracted the references the retrieved articles and reviewed them for relevant information.

RESULTS

Pathogenesis

EuDKA is particularly encountered in patients suffering from type 1 diabetes in the context of

starvation in conjunction with an inter-current illness (4). However, it may also be encountered in patients with type 2 diabetes (8). The incidence of EuDKA in the latter type is on increase with the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors (9). Predisposing factors associated with the occurrence of EuDKA in patients taking SGLT2 inhibitors include surgery, low carbohydrate regimen, insulin cessation or dose reduction, acute medical illness, and latent autoimmune diabetes of adulthood (10-12)

The main anabolic hormone, insulin, causes glycogenesis, lipogenesis, and proteogenesis. It also increases peripheral glucose consumption. Counter-regulatory hormones (CRHs) including glucagon, growth hormone, glucocorticoids, and catecholamines oppose the action of insulin and also decrease peripheral insulin sensitivity (10, 13). Insulin deficiency, either absolute or relative, in tandem with elevated levels of CRHs, gives rise to DKA. Shortage of insulin results in glycogenolysis, lipolysis, and proteolysis. Increased glucagon leads to oxidation of free fatty acids and production of ketone bodies. Ketone bodies are strong acids and in large quantities create metabolic acidosis. Glycogenolysis resulting from insulin deficiency and abundance of CRHs causes hyperglycemia (10). In the presence of prolonged fasting or starvation, hepatic glycogen stores are depleted. Therefore, lipolysis and ketoacidosis occur as a result of inadequate insulin levels and increased CRH levels, but lack of glycogen stores prevents from pronounced hyperglycemia. EuDKA then ensues. The magnitude of insulin deficiency and insulin resistance is generally smaller, thus there is a less pronounced increase in glucose production and reduction in glucose consumption. Furthermore, glucose clearance in EuDKA is twice as much as in DKA, an effect mediated through CRHs (9).

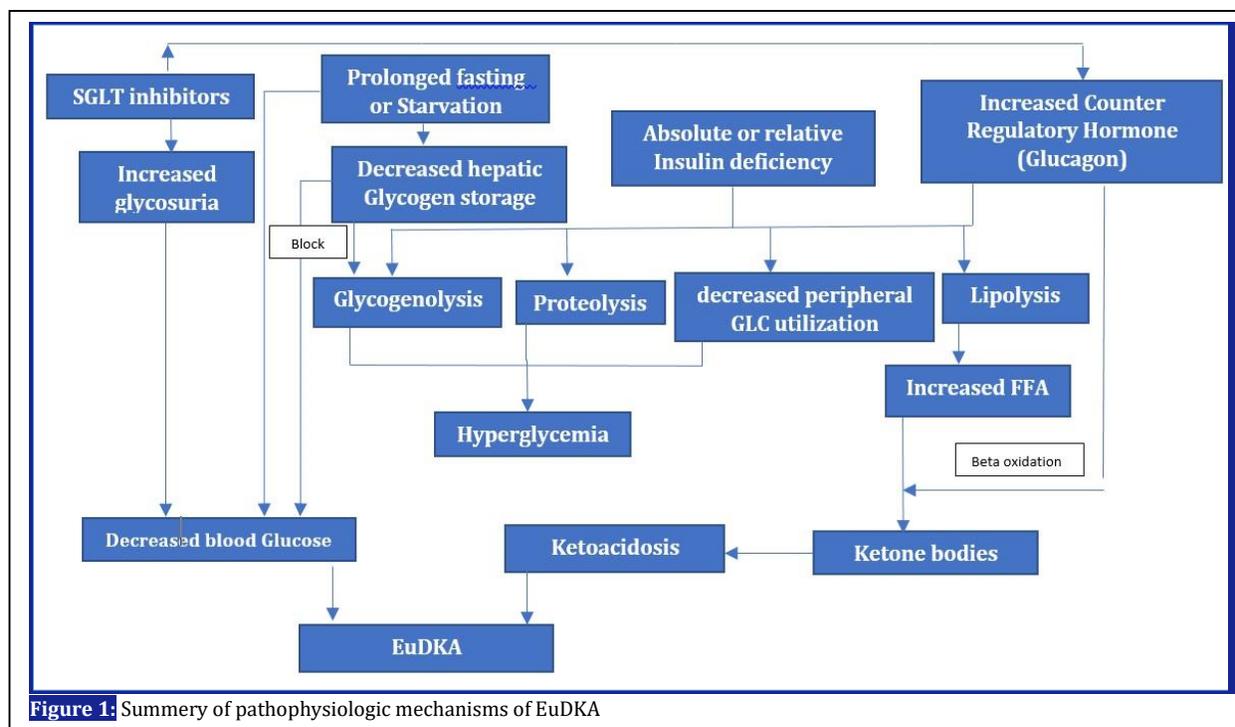
Nausea or vomiting, either due to ketoacidosis itself or resulting from a precipitating illness, usually leads to a decline in caloric intake and inadequate hydration. Under these circumstances, if the patient continues to use sufficient quantities of insulin, insulin suppresses hepatic production of glucose and results in low serum glucose levels, while not capable of stopping the formation of ketone bodies (1, 2, 4). This, in turn, causes DKA with mildly elevated levels of serum glucose or even relatively normal serum glucose. In situations where the patient experiences a prolonged fasting, depletion of glycogen stores of the liver (resulting from increased secretion of CRHs especially glucagon) contributes to the state of normal serum

glucose levels while metabolic acidosis builds up (8-10). On the other hand, dehydration triggers secretion of glucagon with subsequent lipolysis and production of free fatty acid (10). During fasting, insulin is less capable of lipolysis and ketogenesis suppression, which then exacerbates acidosis and excessive ketone body production (10, 11, 14, 15).

Secretion of CRHs are increased in the presence of dehydration, further worsening the EuDKA. The following situations have so far been reported in the literature as the causes of EuDKA: low caloric intake, fasting or starvation, bariatric surgery, dehydration, pregnancy, pancreatitis, glycogen storage diseases, cocaine intoxication, consumption of large amounts of alcohol, chronic liver disease, prolonged vomiting or diarrhea, and insulin pump use (7, 16).

During pregnancy, lipolysis and ketone body production is increased during pregnancy while insulin sensitivity is decreased (17). Moreover, in the second and third trimesters of pregnancy, maternal glucose is consumed in large quantities as the main source of energy by both the fetus and the placenta, creating a state of accelerated starvation. This, in turn, leads to decreased fasting plasma glucose in the mother. Increased production of free fatty acids resulting from relative insulin deficiency occurs. These fatty acids then transported to the liver and are converted to ketones (10, 18). The pregnancy-induced respiratory alkalosis leads to an increased excretion of bicarbonate through urine. Therefore, the body loses its ability to buffer changes in pH which is caused by increased production of body ketones (15, 19). This leads to EuDKA in pregnancy.

As mentioned earlier, the recent use of SGLT2 inhibitors has also been mentioned as the precipitating cause of EuDKA. This finding has helped us understand another possible mechanism of EuDKA. SGLT2 inhibitors (such as Canagliflozin, Dapagliflozin, Empagliflozin, Tofogliflozin, Luseogliflozin) prevent the reabsorption of glucose in the kidney at the proximal renal tubules, promoting its excretion in the urine. A possible mechanism for SGLT2 inhibitors-related EuDKA is through increasing urinary glucose excretion, and the resultant reduction of insulin secretion from pancreatic beta cells. Decreased circulating insulin level enhances the production of free fatty acids, which are then transformed into ketone bodies by the liver (20). Moreover, SGLT2 inhibitors stimulate glucagon secretion. This action is exerted either directly by effect of SGLT2 inhibitors on pancreatic α -cells, or indirectly through a decrease



in insulin secretion. Recent evidence has demonstrated that SGLT2 are present in pancreatic α -cells (11). Increased secretion of glucagon also leads to the overproduction of ketone bodies. Therefore, treatment with SGLT2 inhibitors reduce the insulin-to-glucagon ratio, exacerbating ketogenesis, gluconeogenesis, and glycogenolysis (12, 14). Figure 1 illustrate a summary of the pathophysiologic mechanisms of EuDKA.

Diagnosis

EuDKA is a medical emergency which needs to be diagnosed and treated quickly and appropriately (7). Diagnosis of EuDKA is difficult and poses a challenge to physicians. This diagnosis can easily be delayed or even missed due to low plasma glucose levels (1, 4), which may lead to disastrous consequences. Successful diagnosis of EuDKA requires a high index of suspicion. Potential triggers of EDKA should be born in mind when visiting susceptible patients and other differential diagnosis should be actively ruled out (4, 7). In patients with unexplained acidosis, serum ketone levels should be obtained and differential diagnoses should be born in mind.

EuDKA is primarily a diagnosis of exclusion (2, 3, 5). It should be distinguished from other causes of ketoacidosis in which plasma glucose is normal. These include starvation ketoacidosis and alcoholic ketoacidosis (AKA). The differentiation can be made through clinical assessment and serum bicarbonate levels.

Starvation ketoacidosis (SKA) is a rare cause of acid-base disturbance presenting as severe metabolic acidosis following prolonged fasting. In an otherwise-healthy individual, a 12- to 14-hour fast usually increases ketone body production resulting in mild ketosis without significant change in serum pH. The pH almost invariably remains above 7.30 (21, 22). Under conditions of physiologic stress or when body's glucose requirement is increased (e.g. during pregnancy, severe depression, in the elderly, and in young infants), prolonged fasting may lead to a severe acid-base disturbances (21, 23).

During starvation, plasma glucose concentration decreases, accompanied by reduced levels of serum insulin and elevated levels of serum glucagon. A depletion of hepatic glycogen stores then follows. Decreased insulin enhances lipase activity, which converts triglyceride into free fatty acid chains. Free fatty acids are then metabolized in the liver to form keton bodies. This amount of ketones exceeds the quantities that the body can use as a source of energy, leading to a state of pathological ketosis. SKA is diagnosed based on the following criteria: history of diminished caloric intake, low glucose concentration in plasma, the presence of ketonaemia or ketonuria, and a high serum beta-hydroxybutyrate level (21, 22).

AKA is an acute metabolic disorder. Typical patient is a chronic alcohol abuser who went on a recent binge and abruptly terminated eating owing to

Table 1: Laboratory values in various causes of ketoacidosis

Variable	Diabetic ketoacidosis	Euglycemic DKA	Alcoholic ketoacidosis	Starvation ketoacidosis
Anion gap	High	High	High \pm Lactic acidosis	High
Serum bicarbonate	Very low (even <10)	Low (<18)	Very low (even <10)	> 18
Plasma glucose	High	Normal to high (<200mg/dl)	Normal to low	Low
Urine ketone	Present	Present	Absent or present	Present
Ketonemia	Present	Present	present	Mildly Present
Serum osmolality	Variable	Normal	Normal	Normal
Free fatty acid level	High	High	Very High	High

abdominal pain, nausea, and vomiting. Depletion of hepatic glycogen stores, increased lipolysis in peripheral tissues, and increased production of ketones (24). On the other hand, dehydration from vomiting leads to decreased renal perfusion, which in turn decreases ketone body clearance. Dehydration also increases the concentration of CRHs, which further enhance lipolysis and ketogenesis. Physical examination reveals a conscious patient with tachycardia, hypotension, increased respiratory rate, and generalized abdominal tenderness (without peritoneal signs). Features of dehydration or even early stages of acute alcohol withdrawal may be present concomitantly. In AKA patients, serum glucose levels are normal, and may even be low. A wide anion gap metabolic acidosis is almost invariably present. Since patients usually stop drinking because of their symptoms, ethanol levels are typically low. Blood urea and creatinine levels are normal or moderately elevated. Urine and serum analysis usually reveals ketones. Lactic acidosis may accompany anion gap metabolic acidosis. However, the lactate level is insufficiently high to explain extent of acidosis. While tests for ketonemia and ketonuria are positive, a negative test does not exclude AKA (24, 25). In the presence of high levels of NADH, acetoacetate is converted to hydroxybutyrate. Nitroprusside test is able to detect acetoacetate but not hydroxybutyrate. Hydroxybutyrate to acetoacetate ratio is usually 8:1 compared to DKA where the ratio is 3:1 (24-26).

Differentiation between EuDKA, SKA, and AKA should be based on a history, physical examination, as well as laboratory data (Table 1). Unlike DKA, AKA patients often have almost normal level of conscious in spite of a marked acidosis. Free fatty acids level is higher in AKA as compared to SKA. The level of ketonaemia in SKA appears to be relatively mild as compared to ketonemia observed in DKA or AKA. In cases of SKA serum bicarbonate concentration is usually higher than 18 mEq/L (5,

7, 16, 22, 27).

In addition to the above-mentioned conditions, other causes of wide anion gap metabolic acidosis such as lactic acidosis, tricyclic antidepressant overdose, salicylate overdose, and renal tubular acidosis should also be distinguished from EuDKA (5, 13, 28).

Treatment

If diagnosed early and management started aggressively, EuDKA may be easily reversed and the risk of morbidity and mortality minimized (7). In general, EuDKA is managed more or less the same way as DKA except that it requires lesser dose and duration of insulin treatment. The cornerstone of management of EuDKA is rapid correction of dehydration with intravenous fluids (13). The next step in the treatment of EuDKA is the administration of insulin drip together with a dextrose-containing fluid until the normalization of anion gap and bicarbonate levels. Since relatively high doses of insulin are required to reverse the severe acidosis in EuDKA patients, higher concentrations of dextrose (10 or 20%) are needed to allow concomitant administration of large amounts of insulin (13, 29, 30). Adequate glucose must also be administered to restore normal cellular utilization and correct ketoacidosis (13, 30). Adequate hydration could prevent hyperglycemia in the presence of ketoacidosis by enhancing renal excretion of glucose and decreasing counter-regulatory hormone release (7). There is often no need for intravenous bicarbonate administration because acidosis usually improves with restoration of serum bicarbonate (13, 29, 30). In a subset of patients who are apparently not in a state of insulin deficiency and the ketoacidosis is primarily from starvation resulting in ketoacids production, an approach with IV fluids treatment with close monitoring can be attempted with less risk of hypoglycemic episodes (4, 30).

DISCUSSION

There are several reports on patients with diabetic ketoacidosis in whom the serum glucose level is not elevated. The pathophysiologic basis of this condition has been extensively discussed in the literature, but the exact mechanism is yet to be determined. Many newer findings, including the observation that EuDKA may be seen in diabetic patients taking SGLT2 inhibitors, have helped us understand the possible mechanisms behind this disease. In summary, depletion of glycogen stores in the liver following starvation or urinary loss of glucose, slows the hyperglycemic phase of diabetic ketoacidosis, while lipolysis and production of the ketone bodies continues. This results in a state of ketoacidosis without marked hyperglycemia. Diagnosis of EuDKA requires a high index of suspicion on the clinician's side and measurement of the presence of ketones in the plasma and urine. EuDKA is principally a diagnosis of exclusion and several conditions should also be considered. These include AKA and SKA. SKA may overlap with EuDKA. History, physical examination, and laboratory values may help differentiate these disease states. While diagnosed, treatment should be instituted promptly and meticulously.

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Hydration with intravenous fluids together with insulin is the mainstay of treatment.

CONCLUSIONS

EuDKA is an endocrine emergency with mortalities as high as DKA. Clinicians should keep a high index of suspicion for this diagnosis when evaluating a diabetic patient with ketoacidosis, especially those taking SGLT2 inhibitors.

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AUTHORS' CONTRIBUTION

MJ conceived the idea. MN conducted literature review, organized the outline, and drafted the manuscript. MJ edited the draft.

CONFLICT OF INTEREST

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