DIABETIC KETOACIDOSIS: PATHOPHYSIOLOGY, RISK FACTORS, MANAGEMENT AND PREVENTION

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Article History: **Received: 26.06.2023** **Revised: 04.07.2023** **Accepted: 22.07.2023**

Abstract:
Diabetic ketoacidosis (DKA) is a form of a hyperglycemic emergency mainly characterized by the triad of hyperglycemia, ketosis, and anion gap metabolic acidosis. DKA may be the initial presentation in approximately 25-40 % of patients with type 1 diabetes. It may also occur in at least 34% of patients with type 2 diabetes. DKA has economic as well as medical implications. This review aims to explore and discuss diabetic ketoacidosis, its pathophysiology, clinical presentation, diagnosis, and management.

Keywords: Diabetic ketoacidosis, DM, insulin.

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DOI: - 10.53555/ecb/2023.12.1072

Introduction:

Diabetic ketoacidosis is a grievous complication of diabetes that occurs when there is a lack of insulin in the body, resulting in elevated blood glucose levels and the production of ketones. Diabetic ketoacidosis is a medical emergency that requires immediate treatment, as it can lead to life-threatening complications such as cerebral edema, acute respiratory distress syndrome, and sepsis. It is becoming more prevalent worldwide, particularly among type 1 diabetic children and adolescents **(1)**.

While insulin therapy and patient education have improved, diabetic ketoacidosis remains a common cause of hospitalization and is associated with notable morbidity and mortality. Among the immediate treatment options for severe diabetic ketoacidosis is a multidisciplinary approach that emphasizes correcting fluid and electrolyte imbalances, restoring insulin sensitivity, and preventing complications. Primary care aims to prevent the progression of diabetic ketoacidosis and minimize the risk of cerebral edema, a rare but potentially fatal complication **(2)**.

A publication has shed light on the pathophysiology of diabetic ketoacidosis, including the role of insulin deficiency, altered glucose metabolism, and acid-bas disturbances. Technological advances and monitoring techniques have also allowed for more precise management of fluid and electrolyte imbalances, insulin therapy, and other adjunctive therapies[5]. The management of severe diabetic ketoacidosis is not without challenges. For example, insulin therapy can rapidly drop blood glucose levels, increasing the risk of hypoglycemia **(3)**.

Similarly, fluid therapy can lead to fluid overload and other complications, particularly in patients with underlying comorbidities. To adequately address these challenges, there is a need for a comprehensive review of immediate care for severe diabetic ketoacidosis[4]. Such a review would synthesize current research findings, provide evidence-based recommendations **(4)**.

Definition and epidemiology

Diabetic ketoacidosis is a severe acute metabolic complication of diabetes mellitus characterized by hyperglycemia, hyperketonaemia, and metabolic acidosis. Patients have high insulin requirements, eventually depleting their body insulin. This insulin deficiency leads to an excessive breakdown of fat, resulting in an excessive build-up of ketone bodies. Despite improvements in diabetic patients' self-care, DKA still accounts for 14% of all hospital admissions of diabetic patients and 16% of all deaths linked to diabetes **(5)**.

DKA commonly exists in people with type 1 diabetes, and about 3% of type 1 diabetes patients initially present with DKA; the incidence is two episodes per 100 patient-years of diabetes. Patients with type 2 diabetes can also develop it, though this is less typical. Although the incidence of diabetic ketoacidosis in developing nations is unknown, it may be greater than in developed countries8. Whites have a greater prevalence of type 1 diabetes, contributing to the higher incidence of DKA in this racial group. For unknown causes, females are slightly more likely than males to develop DKA **(6)**.

Young ladies with type 1 diabetes frequently experience recurrent DKA, which is primarily brought on by failing to administer insulin therapy. DKA is much more frequent in young children and teenagers than in adults among people with type 1 diabetes; however, patients with diabetes may experience DKA at any age **(7)**.

Intervention is feasible between the onset of symptoms and the development of DKA, although numerous factors (such as ethnic minority, lack of health insurance, lower BMI, preceding infection, delayed treatment, etc.) influence the risk of DKA among children and young people **(6)**.

Pathophysiology

The abnormal physiology seen in a diabetic patient with ketoacidosis is due to absolute or relative insulin deficiency with the rise in hormones that put the body in a catabolic state and cause insulin resistance leading to hyperglycemia, hyperketonemia, hyperosmolarity, and electrolyte imbalances. These hormones include glucagon, growth hormone, and catecholamines (epinephrine and norepinephrine) **(8)**.

The event that most commonly precipitates diabetic ketoacidosis is usually a loss of insulin activity or increased demand for insulin, which can occur due to missed insulin doses, improper administration of insulin, or the presence of infections in a diabetic patient **(9)**.

It can lead to an inability to transport glucose intracellularly; when this occurs, most cells cannot utilize glucose for energy, so intracellular hunger and starvation begin. Most cells shift to free fatty acids (FFA) as an energy source. Without insulin, there becomes a plethora of FFA in the bloodstream because insulin impedes the lipolysis of adipocytes into glycerol and FFA **(9)**.

These abundantly circulating FFA are taken to the liver and transported to its mitochondria for oxidation; then, ketone bodies are formed, including beta-hydroxybutyrate, acetone, and acetoacetate**(10)**.

Insulin checks the biochemical process, but excessive ketone production results from insufficient insulin. In uncomplicated diabetes or starvation, triglycerides usually predominate ketones. The ketones produced do not overwhelm the body's ability to get rid of them, putting it in a state of ketosis **(7)**.

Glucagon, catecholamines, cortisol, and growth hormone also significantly increase blood glucose through gluconeogenesis and glycogenolysis. The release of these hormones can also be a response to stress, which can take the form of infections (i.e., urinary tract infections and respiratory tract infections, especially the lower tract); trauma; myocardial infarction; acute pancreatitis; burns; surgery; strokes; substance abuse; and so on **(11)**.

These stressors cause a release in inflammatory cytokines that increase insulin counter-regulatory hormones like glucagon, catecholamines, cortisol, and growth hormone. These hormones put the body in a catabolic state, causing more lipolysis and proteolysis to synthesize glucose, which worsens hyperglycemia **(Figure1) (11)**.

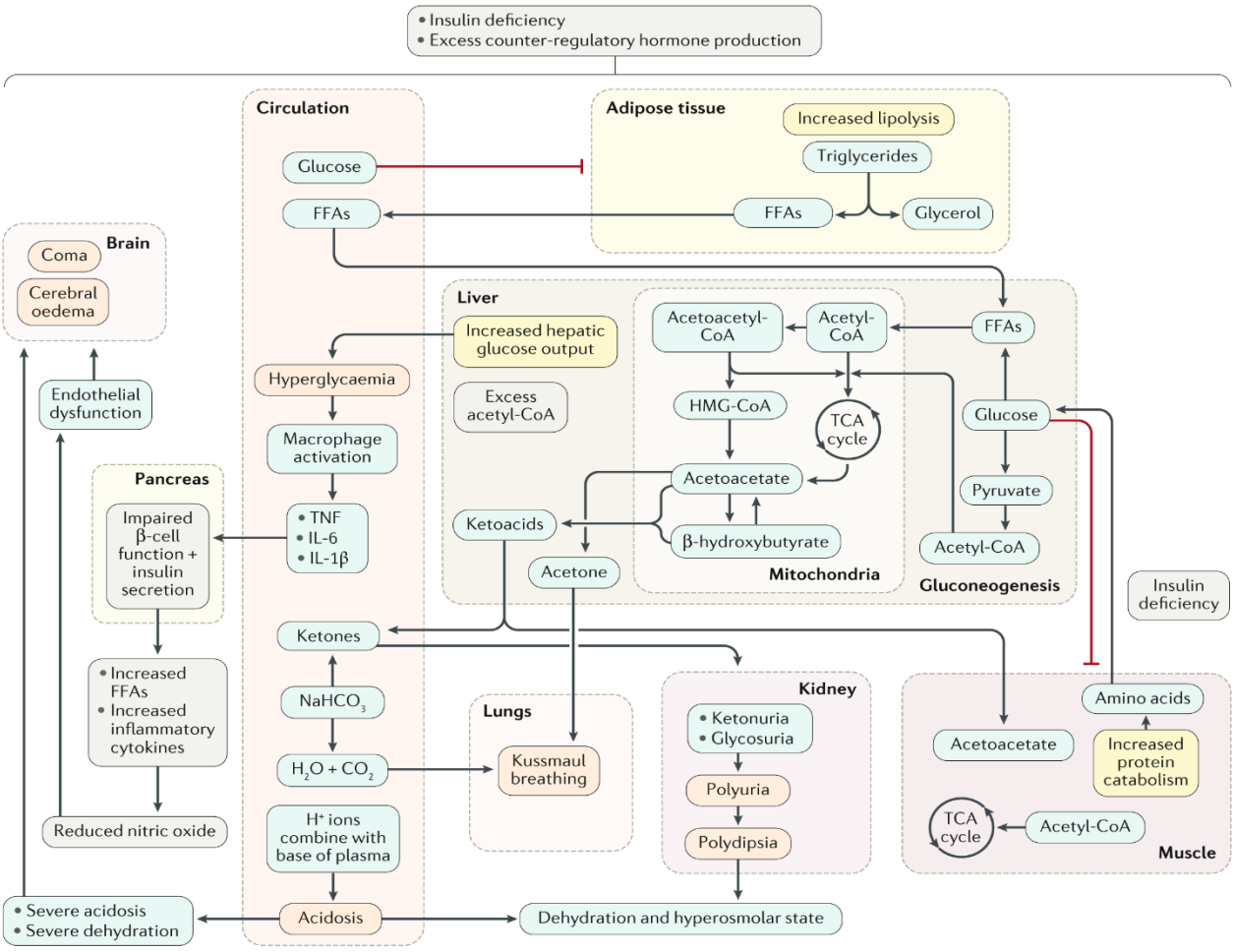

Figure 1: Pathogenesis of DKA (11)

The commonest precipitants of diabetic ketoacidosis are poor compliance with insulin therapy, infections, and a new diagnosis of diabetes. The most common precipitating factor of diabetic ketoacidosis in type 1 diabetes patients is nonadherence to treatment, while infections are the most common precipitant in type 2 diabetes patients **(12)**.

Other causes are vascular events (e.g., acute coronary syndrome, cerebrovascular accidents, critical limb ischemia, bowel ischemia, and shock); excessive alcohol intake; illicit drugs such as cocaine and methamphetamine; antipsychotic drugs, for example, clozapine, risperidone, and olanzapine **(13)**.

Hyperglycaemia develops in insulin deficiency because of three processes: increased gluconeogenesis, accelerated glycogenolysis and impaired glucose utilization by peripheral tissues. The reduction in insulin concentration together with the increase in counter-regulatory hormones leads to the activation of hormone-sensitive lipase in adipose tissue with the subsequent breakdown of triglycerides into glycerol and free fatty acids (FFAs) **(14)**.

In the liver, FFAs are oxidized to ketoacids, mainly under the influence of glucagon. FFAs undergo β-

oxidation to form acetyl coenzyme A (acetyl-CoA). Excess acetyl-CoA that does not enter the Krebs cycle (tricarboxylic acid cycle; TCA cycle) generates acetoacetyl-CoA, three molecules of which condense to form β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) **(15)**.

This, in turn, is cleaved to form acetoacetate and acetyl-CoA. Acetoacetate is further reduced by NADH to form β-hydroxybutyrate. The two major ketoacids are β-hydroxybutyrate and acetoacetate. The accumulation of ketoacids leads to a high anion gap metabolic acidosis due to the reduction in serum bicarbonate concentration and 'fixed acid' retention **(15)**.

Hyperglycaemia also activates macrophages to produce pro-inflammatory cytokines and the liver to produce C-reactive protein, which in turn impair pancreatic β-cell function, reduce endothelial nitric oxide and lead to endothelial dysfunction. Hyperglycaemia and high ketone levels cause an osmotic diuresis that leads to hypovolaemia, decreased glomerular filtration rate and worsening hyperglycaemia **(16)**.

As a result of respiratory compensation for the metabolic acidosis, deep, regular breaths (often with a 'fruity' odour), known as Kussmaul breathing, are taken by those with diabetic ketoacidosis (DKA) as a way of excreting acidic carbon dioxide. Cerebral oedema is an increased fluid content of the brain tissue that may lead to neurological signs and symptoms **(1)**.

Risk Factors

In adults with known diabetes mellitus, precipitating factors for DKA include infections, intercurrent illnesses such as acute coronary syndrome, insulin pump issues (for example, dislodgement or blockage of infusion sets), and poor adherence and non-compliance with insulin therapy. Several new studies have emphasized the effect of poor treatment adherence on the incidence of DKA. For example, in the USA, among urban Afro-Caribbean populations and in underinsured people, non-compliance was the principal cause for the development of DKA **(17)**.

As a result, poor adherence to insulin treatment accounted for >50% of DKA admissions to a large urban hospital. A study reported that persons without health insurance or with Medicaid alone (in the USA) had hospitalization rates 2–3 times higher for DKA than those with private insurance. A study examining two community hospitals in Chicago, IL, identified that most cases of DKA were caused by people with diabetes mellitus omitting their insulin (failure to administer insulin as directed), and medical illness accounted for less than one-third of admissions **(11)**.

The most frequent cause of DKA was infection, followed by non-compliance. Other conditions that are known to precipitate DKA include myocardial infarction, cerebrovascular accidents, pancreatitis, alcohol misuse, pulmonary embolism, and trauma. The risk factors for recurrent DKA include low socioeconomic status, adolescence, female sex (possibly owing to a higher incidence of deliberate insulin omission, psychological issues, eating disorders and body dysmorphia), high glycated hemoglobin (HbA_{1c}), previous episodes of DKA and a history of mental health problems **(18)**.

In children, a lack of prompt recognition of new-onset T1DM by health-care providers increases the risk of DKA at diagnosis. Among children with known T1DM, the majority of DKA episodes are caused by insulin omission, with a minority of episodes occurring in association with infections most often gastrointestinal infections with vomiting and an inability to keep hydrated. Risk factors for DKA in children with known diabetes mellitus include poor diabetes control, previous episodes of DKA, unstable or challenging family or social circumstances, adolescent age, being a peripubertal girl and having limited access to medical services **(19)**.

Psychological factors also influence the likelihood of developing DKA. A report of ~350 adolescent girls and women (aged 13–60 years) suggested that disordered eating was a contributing factor in ~20% of recurrent episodes of DKA. Furthermore, ~30% of young women (15 ± 2 years of age) with T1DM have been suggested to have an eating disorder. When questioned, the women omitted insulin because of a fear of weight gain with good glycaemic control, diabetes-related distress, fear of hypoglycaemia and rebellion from authority **(19)**.

- **Pharmacological risk factors**

As mentioned, insulin mismanagement or omission can lead to DKA. Most often, treatment involves insulin given in a multiple dose regimen. However, data from the UK National Paediatric Diabetes Audit show that insulin pump use is also associated with an increased risk of DKA in those aged <18 years **(20)**.

DKA has also been reported in people with diabetes mellitus treated with sodium–glucose transport protein 2 (SGLT2) inhibitors. Results from randomized controlled trials (RCTs) have indicated that DKA is rare in patients with T2DM treated with SGLT2 inhibitors (incidence of 0.16–0.76 events per 1,000 patient-year). However, several RCTs have reported a higher risk of SGLT2 inhibitor-associated ketosis in adults with T1DM (5–12%) and an incidence of DKA in ~3–5% in those with T1DM treated with SGLT2 inhibitors **(19)**.

The incidence of DKA in those receiving placebo in these RCTs of people with T1DM was 0–1.9%, and DKA occurred despite the use of measures designed to minimize the risk of ketosis. These risk mitigation strategies have been described elsewhere. With the regulatory approval of SGLT2 inhibitors for use in patients with overweight and T1DM in Europe, the actual rates of DKA outside of a clinical trial setting remain to be determined. The only other drug licensed in the USA for use in people with T1DM is pramlintide **(19)**.

The use of this drug is not associated with the development of DKA, but pramlintide is seldom used because it needs to be injected at each meal as a separate injection to insulin, it causes nausea and hypoglycaemia might occur if the insulin to carbohydrate ratio is incorrect **(21)**.

Thus, there is a need to develop better adjunctive treatments alongside insulin for people with T1DM. Data from the T1DM exchange registry in the USA have shown that cannabis use is associated with an increased risk of developing DKA. In addition, drugs that affect carbohydrate metabolism, such as corticosteroids, sympathomimetic agents (used in nasal decongestants) and pentamidine (an antimicrobial agent most frequently used to treat protozoal infection or pneumonia), can precipitate the development of DKA **(22)**.

Atypical antipsychotic agents have been associated with weight gain and T2DM but are also associated with DKA, which occurs acutely even in the absence of weight gain. Cancer treatment using immune checkpoint inhibitors, such as those that block cytotoxic T lymphocyte antigen 4 (CTLA4) and PD1 or its ligand PDL1, have been linked to new-onset autoimmune T1DM **(23)**.

The WHO database of individual case safety reports described a total of 283 cases of new-onset diabetes mellitus, with >50% of patients with immune checkpoint inhibitor-induced diabetes mellitus presenting with DKA. Additionally, a case series involving large academic medical centers estimated an incidence of 1% of new-onset T1DM with a median time of 49 days to onset, and 76% of the cases presented with DKA **(21)**.

Laboratory abnormalities and diagnosis

The diagnosis of DKA consists of a triad of hyperglycemia, ketonemia, and metabolic acidosis.

All patients with positive ketones, constitutional symptoms, or suspicion of DKA and significantly elevated blood glucose levels [>13.9 mmol/l (>250 mg/dl)] should have electrolytes and blood gases checked to look for an anion gap metabolic acidosis. Significantly in type 1 diabetes, DKA can develop within hours if patients stop insulin injections or an insulin pump malfunction **(4)**.

The new American Diabetes Association definition of DKA includes a blood glucose level of 13.9 mmol/l (250 mg/dl)2. Many studies show that DKA is infrequent at lower levels except in situations with poor oral intake or pregnancy. It is also essential to consider DKA in differential diagnoses for patients with anion gap metabolic acidosis. Check serum glucose even when the patient has no history of diabetes (**24).**

Consider DKA if the serum glucose is more significant than 13.9 mmol/l (250 mg/dl), but an elevated glucose level alone is insufficient to diagnose DKA. Suspect DKA in patients with diabetes with a concurrent infection, stroke, myocardial infarction, or other serious illness. These intercurrent illnesses should be sought and treated aggressively. Similarly, it is vital to consider DKA when patients with diabetes experience nausea and vomiting, even if the blood sugar level is less than 13.9 mmol/l (250 mg/dl) **(25)**.

Euglycemic DKA occurs more often in patients who have not eaten but continue taking insulin. A blood sugar level of less than 13.9 mmol/l (250 mg/dl) occurs in 1–7% of reported DKA cases and seems more common in patients with hepatic dysfunction or in those who are in patients **(6)**.

Several drugs, such as glucocorticoids or thiazides, are well-known causes of hyperglycemia that may lead to DKA. Clinicians should also consider DKA in patients taking atypical antipsychotic drugs who present with hyperglycemia **(6)**.

Atypical antipsychotic drugs have increased the frequency of diabetes, glucose intolerance, and DKA. The healthcare provider should measure such patients' anion gap and ketone levels. Another type of antipsychotic drug must be chosen to help resolve this complication **(26)**.

The presentation of a patient with DKA varies substantially depending on the severity of the episode. Mild or moderately ill patients may describe vague symptoms of fatigue, lethargy, poor appetite, or headache. In type 1 diabetes, the history of polyuria and polydipsia may be relatively recent, but in type 2 diabetes, these symptoms may have been building for weeks to months **(27)**.

Nausea, vomiting, and abdominal pain are commonly seen in DKA and may be related to the combined effects of dehydration, hypokalemia, ketonemia, and delayed gastric emptying. Signs of dehydration, including poor skin turgor, decreased axillary sweat, or postural hypotension, may be present on physical examination **(28)**.

Kussmaul respirations (a pattern of deep breathing and hyperventilation in response to metabolic

acidosis) may be present5. Patients' breath may smell fruity due to increased acetone from ketonemia, but the absence of this finding does not rule out DKA **(28)**.

One examination aspect that can be confusing is abdominal tenderness, which may resolve with the treatment of DKA or reflect a more acute abdominal process that precipitates DKA. Abdominal pain correlates with the level of acidosis **(29)**.

The physical examination should identify potential precipitating factors, such as infections or cardiovascular events. Patients may have mental status changes ranging from mild lethargy to delirium or coma. The most severe cases have features like hypotension, tachycardia, and coma **(30)**.

Capillary blood ketone measurement is a relatively new quantitative and enzymatic test that determines levels of 3-β-hydroxybutyrate, one of the three ketone bodies. The equipment is like that patients use for home blood glucose determination, but it requires specific strips. However, checking capillary blood ketones is much more expensive than checking urine ketones, and further clinical studies are needed to define the most appropriate role for β-hydroxybutyrate monitoring **(31)**.

If clinical suspicion of DKA is high, a negative urine dipstick for ketones does not exclude DKA. Clinicians should know that urine test sticks do not measure β-hydroxybutyrate, the predominant ketone. Acetoacetate measured on the dipstick may not be high until later during the illness. Arterial blood gas assessment is generally considered the most reliable method to evaluate the degree of acidosis in DKA, but a venous pH may be a more practical alternative **(32)**.

The average anion gap is 7–9 mmol/l but is ~25 mmol/l in DKA2. Rarely do patients with DKA have mixed acidosis and alkalosis with a pH close to normal **(33)**.

However, this unexpected laboratory result should not affect the treatment of DKA. Determination of the arterial blood gas may be optional **(32)**.

Most DKA guidelines indicate that hyperglycemia of more than 13.9 mmol/l is necessary for diagnosing DKA; however, this is not an absolute requirement, as there are reports about DKA without hyperglycemia. DKA without hyperglycemia is reported chiefly during pregnancy and in patients with prolonged vomiting or starvation **(34)**.

It can also occur in patients with liver failure or alcohol abusers9. Ketone bodies are produced in the liver from acetyl-CoA liberated during lipolysis from fatty acids. For DKA to develop, an absolute or relative insulin deficiency must be present. Three ketone bodies are produced: acetone (resulting in the fruity odor of DKA patients), acetoacetate, and β-hydroxybutyrate (β-OHB). β-OHB is the most prominent contributor to metabolic acidosis in patients with DKA **(35)**.

Acetone does not contribute to acidosis and is not usually measured as such. Acetoacetate can be measured in the urine with a urine dipstick utilizing the nitroprusside reaction. As DKA resolves, β-OHB is oxidized to acetoacetate. Therefore, if only a urine ketone dipstick procedure is done, it might give the impression that the condition is not improving. Blood ketones can be measured with a point of care (bedside) meter utilizing capillary finger prick blood10. This measures β-OHB directly and accurately **(35)**.

The blood ketone measurement of β-OHB is preferable to urine measurement for diagnosing and monitoring DKA. An arterial pH of less than 7.3 should be present in diagnosing DKA. The measurement of pH or serum bicarbonate is essential for the diagnosis and estimation of the severity of DKA. The pH is also an important measure to assess improvement and treatment adjustment. A venous pH determination would probably be sufficient unless respiratory function must also be evaluated. The venous pH is, on average, 0.03 lower than the arterial Ph **(36)**.

Biochemical Criteria for DKA

DKA occurs in individuals with diabetes mellitus who omitted insulin or had improper intercurrent illness management or subjects having new-onset diabetes. The ketoacidosis biochemical criteria include:

a) PH less than 7.3
b) Serum bicarbonate less than 18 mmol/L
c) Plasma glucose level more than 13.88 mmol/L
d) A raised ketone level in serum and the presence of ketone in urine.

The diagnostic criteria of DKA was modified by introducing severity categories of mild, moderate, and severe, as displayed in Table. Abnormal changes in laboratory values give a significant clue of what exactly happens in patients with suspected diabetic ketoacidosis

Table 1) (37).

Table 1: Diagnostic criteria and severity of diabetic ketoacidosis (37)

	Mild	Moderate	Severe
Plasma glucose (mmol/l)	>13.9	>13.9	>13.9
Arterial pH	7.25–7.30	7.00–7.24	<7.00
Serum bicarbonate (mmol/l)	15–18	10–14.9	<10
Urine ketones	++	++	+++
Serum ketones	+++	+++	+++
Anion gap	>10	>12	>12
Sensorium	Alert	Alert/drowsy	Stupor/coma
Serum sodium	Normal	Low	Low
Serum potassium	Normal	High	High
Serum phosphate	Normal	High	High

DKA Mimicking Bacterial Infection

Since DKA symptoms often have similarities to infection, it is difficult to differentiate between an inflammatory response due to sepsis and non-sepsis. The formation and secretion of cytokines are stimulated via hyperglycemia. There is an elevation of plasma CRP, interleukin-1 β, interleukin-6, and TNF-α in diabetic individuals without infection.

A study by **Hoffman et al. (38)** noted a significant rise in all cytokines in patients with DKA compared to those without DKA. However, the study reported that neutrophil percentage, leukocyte count, and CRP were more in the case of DKA with infection when compared to patients without infection **(Figure 2)** {Hoffman, 2003 #1909}.

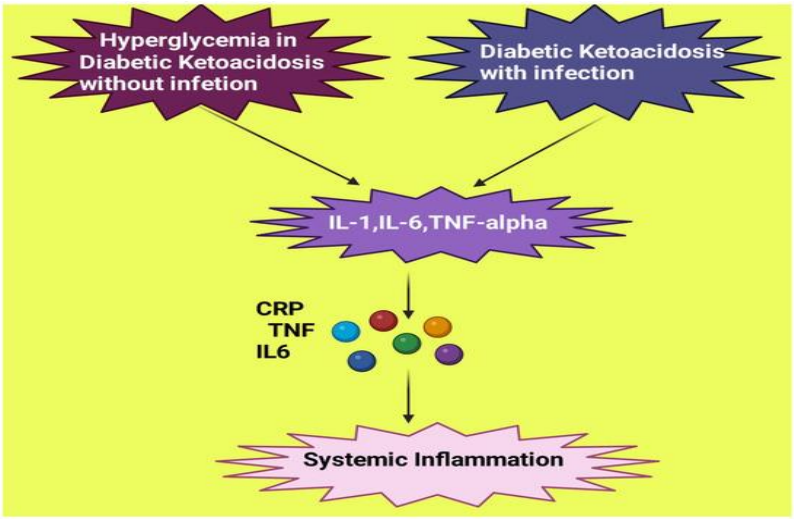

Figure 2: Similar inflammatory response exhibited by diabetic ketoacidosis with and without infection. IL: Interleukin; TNF: tumor necrosis factor; CRP: C reactive protein (38) {Hoffman, 2003 #1909}

Diagnostic Tools for DKA

- **The Link between Serum Lactate and Severity of DKA**

Diabetic ketoacidosis is a type of metabolic acidosis with a high anion gap associated with hyperglycemia, high levels of ketone, and acidosis that may, in severe cases, lead to the individual's demise. Anaerobic metabolism in the body produces lactate primarily in muscle tissue by pyruvate reduction with the help of lactate dehydrogenase enzyme **(39)**.

The lactate levels remain within a narrow range, and its rise may result from a raised formation, a reduced clearance, or multiple other factors. Lactate levels have been found to help in the prediction or monitoring of the severity of pathologies that are critical in nature, like sepsis, cardiovascular emergencies, trauma, and burns. The concentration of lactate ≥2.5 mmol/L is the definition of lactic acidosis **(40)**.

Severe lactic acidosis occurs when the lactate level in the blood is >5 mmol/L, and the anion gap is ≥10. In DKA, hyperlactatemia is when lactate levels are >2 mmol/L. Serum lactate levels are high in patients with DKA and may also be used in the emergency room to determine the severity of the patient's condition **(41)**.

A study conducted by **Cetin et al.** observed a positive correlation between serum lactate levels and the severity of DKA. The study suggested that serum lactate levels can be used as a marker for the severity of this life-threatening emergency since there is very little time to intervene in critical cases of DKA. The study found the median lactate levels for mild, moderate, and severe DKA to be 1.9 mmol/L, 2.8 mmol/L, and 3.3 mmol/L, respectively **(42)**.

Serum lactate levels reflect a hypoperfusion of tissue and hypoxia and thus indicate the disease's severity. In the case of sepsis, there is also a rise in serum lactate levels, and a study conducted using the data from the Surviving Sepsis Campaign reported that the cut-off point for a serum lactate level of 4 mmol/L was linked to poor outcome in patients with sepsis **(43)**.

Howell et al. noted a mortality rate of 28% in septic subjects with a serum lactate cut-off point of 4 mmol/L **(44)**. Another study by **Shapiro et al.** suggested that serum lactate levels may predict mortality in sepsis patients **(45)**.

Another study conducted by **Cox et al.** found that 68% of patients with DKA had raised lactate levels, and 40% of the subjects had a cut-off value of more than 4 mmol/L **(46)**.

High lactate levels did not result in an increased mortality in the study, and the mortality rate for subjects with serum lactate levels more than 4 mmol/L was 3.7% was due to the death of a subject suffering DKA with sepsis **(47)**.

They suggested that patients with DKA alone have a lower mortality rate than subjects with sepsis with similar serum lactate levels. Several other studies have found different values for the percentage of subjects with DKA having raised serum lactate levels, like 90% **(47)**, 57% **(48)**, and 67.9% **(40)**.

Therefore, using serum lactate cut-off points can help recognize and monitor the severity of DKA and the possible presence of sepsis in the emergency room. However, serum lactate alone may not be a specific diagnostic tool for DKA with infection since the raised lactate levels may have occurred due to fluid loss, microcirculation disorder, and stress intensity in DKA, even in the absence of infection. Therefore, other diagnostic tools must also be included to determine if infection further complicates DKA **(49)**.

Differential diagnosis

Diabetic ketoacidosis may have a diverse and complex presentation, which makes it share many similarities in the way and manner it presents compared to other common pathologies; hence, other common pathologies may mimic diabetic ketoacidosis. It is, therefore, essential to rule out other pathologies with similar presentations whenever a case of diabetic ketoacidosis is suspected. Differentials include starvation ketoacidosis, pancreatitis, alcoholic ketoacidosis, lactic acidosis, uremia, overdose on diabetic medication, hyperosmolar hyperglycemic nonketotic syndrome, and myocardial infarction **(Figure4) (50)**.

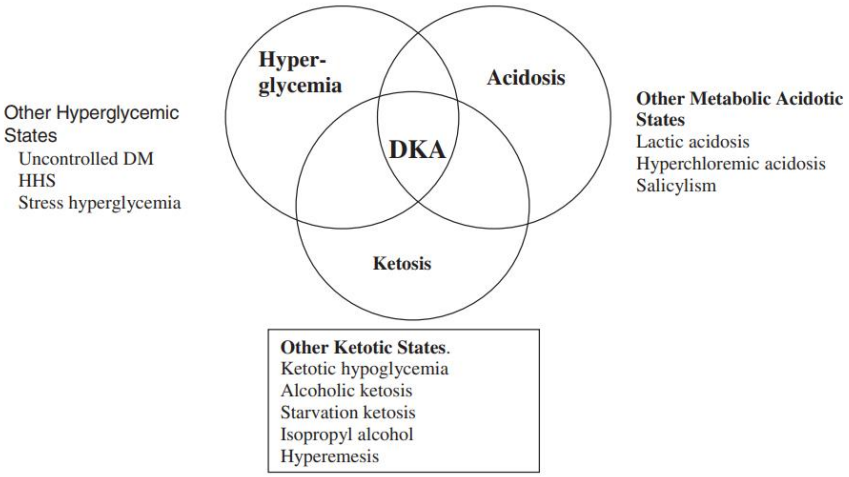

Figure 4: Differential diagnosis of DKA (50)

Complications

The most frequent complications of DKA are hypoglycemia and hypokalemia, which result from overzealous treatment with insulin. Hypokalemia may also complicate bicarbonate therapy. A transient hyperchloremic non-anion gap acidosis could occur in the recovery phase of DKA; due to the loss of large quantities of ketoanions **(51)**.

Ketoanions are metabolized with regeneration of bicarbonate, their loss in the urine hinders regeneration of bicarbonate during treatment thus predisposing to acidosis. Administration of

intravenous fluids containing chloride that exceeds the plasma chloride concentration and the intracellular shifts of NaHCO3 during correction of DKA also contribute to hyperchloremic acidosis **(52)**.

This complication is usually of little clinical consequence. Cerebral edema is a rare but serious complication of DKA, occurring in 0.7–1.0% of children with DKA; especially in those with newly diagnosed diabetes. Cerebral edema can also occur in patients with previously diagnosed diabetes and in very young adults under 20 years of age **(33)**.

Headache, the earliest symptom of cerebral edema is followed by lethargy and altered sensorium. Neurological deterioration may occur rapidly with seizures, incontinence, pupillary changes, bradycardia, and respiratory arrest setting in as brain stem herniation occurs. Papilledema may be absent if onset is rapid. Mortality rate may be >70% if neurological symptoms are established, with only 7–14% of patients recovering without sequalae. Postulated mechanisms for cerebral edema include osmotically driven movement of water into the central nervous system when plasma osmolality declines too rapidly during the treatment **(27)**.

A study, which assessed cerebral water diffusion and cerebral vascular perfusion during the treatment of children with DKA using magnetic resonance imaging, reported that cerebral edema was due to increased cerebral perfusion **(53)**.

Another putative mechanism for cerebral edema involves the cell membrane Na+/H+ exchanger, which is activated in DKA. The high H+ level allows more Na + into the cell, which attracts water into the cell leading to edema. The ketone bodies acetoacetate and β-hydoxybutyrate may also play a role in the pathogenesis of cerebral edema **(54)**.

Ketone bodies have been shown to affect vascular integrity and permeability and contribute to edema formation. Measures that may reduce the risk of cerebral edema in high-risk patients include gradual replacement of sodium and water deficits in patients who have hypertonicity and the addition of dextrose to the correction fluid once blood glucose reaches 250mg/dl**(55)**.

Hypoxemia and, rarely, noncardiogenic pulmonary edema may complicate the treatment of DKA. Hypoxemia is due to a reduction in colloid osmotic pressure that results in increased lung water content and decreased lung compliance **(15)**.

Patients with DKA who have a widened alveolo-arteriolar oxygen gradient noted on initial blood gas measurement or with pulmonary rales on physical examination appear to be at higher risk for the development of pulmonary edema. Thrombosis including disseminated intravascular coagulation has been reported in DKA and high levels of pro-inflammatory cytokines and plasminogen activator inhibitor-1 (PAI-1) have been demonstrated in DKA, which resolve with insulin therapy and correction of hyperglycemia, therefore, prophylactic use of heparin may be indicated**(56)**.

Prevention

Although mortality from DKA is all course mortality in subjects surviving DKA may be high; a retrospective analysis of over 600 episodes of DKA in nearly 300 patients seen in a hospital in the UK from 2007 to 2012 recorded no inpatient mortality. However, 14% of the patients died within 5 years of follow up and mortality was higher in subjects who had recurrent DKA **(17)**.

Predictors of mortality during follow up included psychological issues, peripheral neuropathy, ischemic heart disease, alcoholism, and prior admission to intensive care. Therefore, measures to prevent recurrent DKA should be pursued vigorously **(14)**.

Subjects with diabetes have increased cardiovascular morbidity and mortality; although SGLT-2 inhibitors have been associated with DKA, empagliflozin, an SGLT-2 inhibitor was reported to reduce all-cause and cardiovascular mortality in patients with type 2 diabetes at high risk for cardiovascular events **(57)**.

Prospective clinical studies have identified poor adherence to insulin therapy as the major precipitant of DKA in some populations. Education of the patient and care giver about diabetes care especially sick day management would be beneficial in preventing DKA. An interventional study in teen age patients with type 1 diabetes, which incorporated frequent outpatient clinics, reported better diabetes control and less diabetes related hospitalization in the intervention group **(58)**.

Again, a home-based psychotherapy program reduced hospital admission for DKA over 24 months in a prospective randomized study of 127 youths. Illicit drug use is associated with recurrent DKA; therefore, rehabilitation should be helpful in drug addicts. A significant proportion of DKA occur in subjects with type 2 diabetes; adoption of healthy lifestyle and maintenance of ideal body weight would contribute in reducing the surging incidence of DKA **(58)**.

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