https://repository.uaeh.edu.mx/revistas/index.php./MJMR/issue/archive

Mexican Journal of Medical Research ICSa

Biannual Publication, Vol. 13, No. 26 (2025) 61-68

ISSN: 2007-5235

Pathophysiology and treatment in Diabetic Ketoacidosis

Fisiopatología y tratamiento en la Cetoacidosis Diabética

Omar Azuara Antonio [a], Leonora Perea-García [b], Habacúc Enríquez Sandoval [c], Alfredo García Téllez [d], Lilian Scarlet Gerardo-Muñoz [e]

Abstract:

Diabetic ketoacidosis (DKA) is the presence of metabolic acidosis with an elevated anion gap, ketonemia or ketonuria, with or without hyperglycemia, in the context of a prior diagnosis of diabetes mellitus (DM) or a new diagnosis of DM. In this case, it is caused by a relative or absolute insulin deficiency, leading to ketogenesis, lipolysis, lipotoxicity, and metabolic acidosis. A vast amount of literature—articles, reports, books, journals, and many other sources—focuses on advances in the treatment and pathophysiology of DM and its decompensated states, primarily diabetic ketoacidosis. However, no definitive study has been established to fully explain the pathophysiology, triggers, and optimal treatment without generating controversy. Therefore, this review aims to analyze, describe, and discuss updates on the pathophysiology and treatment of DKA precisely and concisely, aiming to support healthcare personnel in managing patients with this complication. Decompensated DM can have a broad pathophysiology, so ideal treatments must be considered to avoid short- and long-term complications, including ketoacidosis, as well as certain variations in clinical presentation, such as in the case of euglycemic ketoacidosis.

Keywords:

Pathophysiology, treatment, ketoacidosis, diabetes mellitus

Resumen:

La cetoacidosis diabética (CAD) es la presencia de acidosis metabólica con desequilibrio aniónico elevado, cetonemia o cetonuria, con o sin hiperglucemia, en presencia de un diagnóstico previo de diabetes mellitus (DM) o un nuevo diagnóstico de DM. En este caso, es causada por una deficiencia relativa o absoluta de insulina, lo que resulta en cetogénesis, lipólisis, lipotoxicidad y acidosis metabólica. Existe una gran cantidad de artículos, informes, libros, revistas y muchas otras fuentes de información basadas en los avances en el tratamiento y fisiopatología de la DM y sus estados de descompensación, principalmente la cetoacidosis diabética, pero no se ha establecido ningún estudio ideal para explicar toda la fisiopatología, los desencadenantes y, por supuesto, el tratamiento óptimo sin generar controversia. Por tanto, el objetivo de la presente revisión es analizar, describir y comentar las actualizaciones sobre la fisiopatología y el tratamiento de la CAD de forma precisa y concisa, a fin de apoyar al personal de salud para el abordaje de pacientes con esta complicación. La DM descompensada puede tener una fisiopatología amplia, por lo que se deben considerar tratamientos ideales para evitar complicaciones a corto y largo plazo, incluidas la cetoacidosis, además de algunas variantes en la presentación clínica, como el caso de la cetoacidosis euglucémica.

***Palabras Clave**:*

Fisiopatología, tratamiento, cetoacidosis, diabetes mellitus

[a] Servicio de Urgencias | Hospital General de Pachuca | Pachuca de Soto-Hidalgo | México, https://orcid.org/0000-0002-8648-4573, Email: omar_5998@hotmail.com

[b] Servicio de Urgencias | Hospital General de Pachuca | Pachuca de Soto-Hidalgo | México, https://orcid.org/0009-0004-6480-3379, Email: leonoraperea@gmail.com

[c] Servicio de Urgencias | Hospital General de Pachuca | Pachuca de Soto-Hidalgo | México, https://orcid.org/0009-0005-2711-482X, Email: habacuc_955@outlook.com

[d] Servicio de Urgencias | Hospital General de Pachuca | Pachuca de Soto-Hidalgo | México, https://orcid.org/0009-0004-6964-7563, Email: dralfredgt@hotmail.com

[e] Corresponding author, Consultorio Particular, https://orcid.org/0000-0001-6396-7516, Email: scarlet.2508@gmail.com

Received: 20/03/2025, Accepted: 05/05/2025, Postprint: 06/05/2025, Published: 05/07/2025

DOI: https://doi.org/10.29057/mjmr.v13i26.14740

INTRODUCTION

There is a vast amount of articles, reports, books, journals, and many other sources of information based on advances in the treatment and pathophysiology of diabetes mellitus (DM) and its decompensated states—primarily diabetic ketoacidosis (DKA). However, no ideal study has been established to fully explain the pathophysiology, trigger factors, and optimal treatment without generating controversy.[1]

Diabetic ketoacidosis is the most common hyperglycemic crisis in decompensated diabetes. In DKA, the excessive formation of ketone bodies and acidosis occurs in the clinical context of an absolute or relative pathological insulin deficiency. Hyperglycemia has been recognized as a common finding in critically ill patients and is considered a sign of increased morbidity, even in previously non-diabetic individuals.[2]

The clinical triad of hyperglycemia, ketosis, and acidosis characterizes DKA. The symptomatic onset of DKA is rapid, beginning with polyuria, polydipsia, anorexia, vomiting, and abdominal pain. Fast and deep breathing (Kussmaul respiration) represents compensatory hyperventilation and is accompanied by the classic fruity breath odor.[2]

The diagnostic criteria generally accepted for diabetic ketoacidosis are those from the American Diabetes Association (ADA), which include, blood glucose over 250 mg/dL, pH below 7.30, plasma bicarbonate below 18 mEq/L, and the presence of ketonuria or ketonemia. The severity of the condition is determined based on pH and bicarbonate levels. These criteria are often considered the standard of care. Along with the ADA guidelines, this remains one of the most frequently cited frameworks for DKA management.[2,3]

Among the mechanisms that lead to DKA is a combination of reduced insulin secretion and action, with elevated levels of counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone). The insulin deficiency in DKA may be absolute, as in type 1 diabetes, or relative, as in type 2 diabetes, in the presence of increased secretion of counter-regulatory hormones, which exacerbate insulin resistance and further impair insulin secretion.[4]

There are multiple precipitating factors, with the most common being the presence of an intercurrent infection. Other contributing factors may include irregular adherence to treatment, stroke, alcohol abuse, pancreatitis, pulmonary embolism, myocardial infarction, and the use of certain medications that affect carbohydrate metabolism, such as corticosteroids, thiazides, sympathomimetic agents, pentamidine, and atypical antipsychotics.[2]

This document reviews several publications on the pathophysiology and treatment of diabetic ketoacidosis. It aims to provide a clear and concise explanation of the condition and its management, guided by British and American guidelines. The document covers key topics such as the trigger factors, gluconeogenesis and glycogenolysis, acid-base disturbances, clinical presentation, appropriate insulin use, and crystalloid and balanced solutions administration.[1,3]

PATHOPHYSIOLOGY

In both type 1 and type 2 diabetes mellitus (DM), Diabetic Ketoacidosis (DKA) can occur when there is an absolute or relative insulin deficiency or during acute illness, associated with an increase in counter-regulatory hormones such as cortisol, growth hormone, glucagon, and catecholamines. These hormonal alterations and the subsequent inflammatory response form the basis of the pathophysiological mechanisms involved in DKA.[4]

Ketogenesis occurs physiologically during prolonged fasting, maintaining the body's energy homeostasis. When glycogen stores are depleted, the body turns to fatty acid oxidation as an energy source. However, in decompensated DM, insulin counter-regulatory hormones intensify the process, causing an imbalance between the production and clearance of ketone bodies, promoting the transition from ketosis to DKA.[5]

The resulting increase in the plasma concentration of fixed organic acids is part of the internal environment disturbances observed in diabetic patients. These disturbances trigger homeostatic mechanisms that attempt to minimize deviations in regulated variables such as blood glucose, osmolarity, and extracellular fluid pH from their set points.[5]

In both type 1 and type 2 DM, increased hepatic gluconeogenesis is due to a greater availability of gluconeogenic precursors such as lactate, glycerol, and gluconeogenic amino acids. Additionally, low insulin levels lead to muscle protein catabolism, releasing amino acids that are both gluconeogenic and ketogenic (e.g., tyrosine, isoleucine, phenylalanine) or purely ketogenic (e.g., lysine, leucine).[4,5]

The catabolism of isoleucine, lysine, and tryptophan leads to the formation of acetyl-CoA; the catabolism of phenylalanine and tyrosine leads to the formation of acetoacetate; and leucine leads to the production of β-hydroxy-β-methylglutaryl-CoA (HMG-CoA). All of these contribute to accelerated ketone body production. High concentrations of glucagon, catecholamines, and cortisol relative to insulin levels stimulate the activity of gluconeogenic enzymes (phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase, and pyruvate carboxylase), which enhance both hyperglycemia and ketogenesis.[6]

The increased levels of counter-regulatory hormones and severe insulin deficiency activate hormone-sensitive lipase in adipose tissue. The enzyme lipolyzes endogenous triglycerides, releasing significant amounts of free fatty acids (FFAs) and glycerol into the circulation. These FFAs are oxidized into ketone bodies in the hepatic mitochondria process, mediated by high glucagon levels, which reduce hepatic concentrations of malonyl-CoA, a key intermediate in the lipogenic pathway. Malonyl-CoA also acts as a potent inhibitor of fatty acid oxidation by suppressing the enzyme carnitine palmitoyltransferase 1 (CPT1), which regulates FFA uptake into mitochondria for β-oxidation, ultimately leading to an accumulation of acetyl-CoA.[6]

Acetone, β-hydroxybutyrate, and acetoacetate are the three ketone bodies produced by the liver. Exhaled acetone is responsible for the "fruity" breath odor perceived in individuals with DKA. The acidosis results from buffering protons produced by dissociating ketoacids at physiological pH. The accumulation of ketoacids leads to a decrease in serum bicarbonate levels. Together with the retention of these strong acids, this results in high anion gap metabolic acidosis. Monitoring the degree of acidity is crucial because, as the pH falls below 7.35, the intracellular biological systems begin to fail. This failure can lead to irreversible damage and, at critically low pH levels, neurological dysfunction, which may result in severe neurological impairment and, if sufficiently severe or prolonged, death.[6-8]

The severity of hyperglycemia and the high concentrations of acetoacetate and β-hydroxybutyrate cause osmotic diuresis, which leads to hypovolemia (due to extracellular volume depletion) accompanied by arterial vessel constriction. Osmotic diuresis reduces the glomerular filtration rate, decreasing the kidneys' ability to excrete glucose. Hypovolemia causes further increases in counter-regulatory hormone levels, which worsens hyperglycemia even more.[6,8,9]

Acidemia may worsen due to lactate production as peripheral tissues become hypoxic and shift to anaerobic respiration. Additionally, impaired renal perfusion can lead to prerenal failure and an inability to adequately excrete acids such as sulfate, phosphate, or urate. Osmotic diuresis, vomiting, incapacity to consume oral fluids, or reduced consciousness may all contribute to worsening dehydration.[10]

Severe hyperglycemia and the onset of ketoacidosis result in a pro-inflammatory state, evidenced by elevated oxidative stress markers and increased concentrations of pro-inflammatory cytokines. Altered insulin signalling that leads to severe hyperglycemia can stimulate the liver to produce C-reactive protein (a pro-inflammatory marker) under the influence of activated macrophages, which secrete pro-inflammatory cytokines such as IL-6, IL-1β, and tumor necrosis factor (TNF).[10,11]

Cerebral edema in DKA is vasogenic (due to blood-brain barrier disruption), although the exact mechanism remains incompletely understood. Observations show that some patients are alert and oriented at a pH of 6.9, while others are quite disoriented at a pH of 7.2, suggesting a possible role of "physiological reserve." The extent of circulatory volume depletion, high glucose concentrations, and rapid electrolyte shifts between intra- and extracellular spaces also act as destabilizing factors.[1,5,12]

As for electrolytes, potassium in particular is known to be predominantly intracellular, a distribution maintained by factors including insulin. Hypoinsulinemia turns into potassium efflux within the extracellular fluid, causing hyperkalemia and hypokalocytosis due to cellular dehydration and extracellular fluid hypertonicity. Administering glucose to these patients exacerbates the situation, as their inability to produce or secrete sufficient insulin limits their capacity to metabolize glucose.[2,4]

In the DKA context, hyperkalemia occurs primarily due to hypertonicity and hypoinsulinemia does not happen directly due to metabolic acidosis. However, as acidosis progresses and bicarbonate (HCO_3^-) attempts to buffer the excess hydrogen ions (H^+), bicarbonate levels deplete, and extracellular H^+ is exchanged for intracellular K^+; consequently, for every 0.1 unit decrease in pH, serum potassium increases by approximately 0.6 mmol/L.[2,4,13]

The internal pH is maintained between 7.32 and 7.42 thanks to body plasma, intracellular buffers, and the tight regulation of acid balance. For organic (fixed) acids, daily acid production must equal the bicarbonate (HCO_3^-) generated by the kidneys and its breakdown in metabolizing tissues. It follows that if the rate of ketone body formation is equal to their rate of peripheral oxidation, there would be no change in blood pH because the complete ketoacid oxidation through the tricarboxylic acid cycle and oxidative phosphorylation consumes hydrogen ions (H^+), counterbalancing those produced during hepatic synthesis.[13,14]

As previously explained, this balance does not occur in decompensated diabetic patients. The imbalance between production and peripheral oxidation leads to a state known as metabolic acidosis. Although high-anion-gap metabolic acidosis is likely the most frequently described acid-base disorder in the literature, it should be noted that up to 50% of cases also present with a significant component of hyperchloremic metabolic acidosis or mixed acid-base disturbances.[13,15,16]

Data from a 2014 national survey in the UK showed that 76% of institutions measured ketone concentrations using point-of-care testing. The 2019 National Diabetes Inpatient Audit (NaDIA) report, published in 2020, showed that 71.3% of hospitals used networked glucose meters. The British Diabetes Society also recommended using remote glucose and ketone monitors in its 2018 report titled *"Making Hospitals Safe for People with Diabetes.[17-19]

These data reflect the development of high-anion-gap metabolic acidosis, ketonemia (>3.0 mmol/L), or significant ketonuria (≥2+ on standard urine dipsticks) in people known to have diabetes, but whose glucose levels are normal or not particularly elevated. Improved patient education and increased home monitoring of capillary glucose and ketones have led to partial treatment of diabetic ketoacidosis (DKA) before hospital admission, resulting in lower blood glucose levels upon presentation. This condition is treated the same way as hyperglycemic DKA.[13,16,20,21]

With the widespread use of the sodium-glucose co-transporter 2 (SGLT2) inhibitor drug class (e.g., dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, sotagliflozin) in individuals with type 2 diabetes mellitus and increasingly in those with type 1 emphasis has shifted to using pH and ketone levels (rather than solely focusing on glucose) to guide diagnosis and treatment, due to the risk of developing euglycemic diabetic ketoacidosis (euDKA) with these agents. Historical data before widespread SGLT2 inhibitor use shows that euDKA was not uncommon.[19,22,23]

However, the real-world rates of SGLT-associated ketoacidosis outside of clinical trial populations are still unknown and may be higher than trial data suggest. It may be due to the careful selection, education, monitoring of trial participants, and varying definitions of DKA used in different studies. If ketoacidosis occurs while on SGLT2 inhibitors, the drugs must be discontinued, and regulatory authorities notified of the adverse drug reaction. In the UK, it is done through the "Yellow Card" system. It is necessary to discuss with the diabetes care team whether to restart the medication once the individual has recovered.[8,9]

When a patient arrives at the emergency room with the criteria for DKA (as shown in Table 1), timely and appropriate treatment decisions are crucial to improving prognosis and preventing complications. These decisions are typically divided into the following sections.[24]

Table 1. *Characteristics and Criteria for Diabetic Ketoacidosis.*[10]

Criteria	Mild	Moderate	Severe
Glucose	>250 mg/dl	>250 mg/dl	>250 mg/dl
pH	7.30-7.25	7.24-7.00	<7.00
Bicarbo-nate	18-16 mmol/l	15-10 mmol/l	<10 mmol/l
Ketones	**Serum/Urine***	**Serum/Urine***	**Serum/Urine***
BHB	>17.43 mg/dl	>17.43 mg/dl	>17.43 mg/dl
Anion-Gap	>10	>12	>12
Mental Status	Alert	Alert/ **Drowsy**	**Stupor/Coma**

* Presence of ketones in either serum or urine. BHB = β-hydroxybutyrate

Patients with mild to moderate DKA should receive treatment in an emergency department or inpatient care such as intermediate care units. Patients with severe DKA should be treated in the ICU, if available. Treatment will depend on the availability of infrastructure, supplies, and trained personnel for monitoring and treatment.[24,25]

TREATMENT OF DIABETIC KETOACIDOSIS

Fluid therapy

Fluid administration is the first line of treatment. Proper fluid resuscitation not only restores intravascular volume but also lowers blood glucose levels, increases blood pressure, ensures peripheral tissue perfusion, and facilitates the resolution of metabolic acidosis. It aims to replenish volume within 24–36 hours, with 50% of the volume administered within the first 8–12 hours after presentation.[1,25,26]

The free water deficit in these patients is approximately 100 ml/kg of body weight or more than 10% of total body weight. Fluid replacement should aim to achieve three main goals: circulating volume restoration, ketone clearance, and correction of electrolyte imbalance. The gradual resolution of the problem requires a prior calculation of the water deficit, which is estimated using the following formula:

$$\text{Water deficit} = 0.6 \times \text{weight (kg)} \times ([Na^+] - 140 / 140)$$

(Use 0.5 in women instead of 0.6)[26-28]

It is important to note that this formula is only an estimate; it does not account for osmotic losses that may have occurred and must be assessed within the clinical context. Therefore, frequent plasma and urinary sodium concentration monitoring is essential to adjust fluid replacement.[26,29,30]

The ADA recommends administering 1000–1500 ml of 0.9% sodium chloride solution during the first hour. However, volume correction should be aggressive but done cautiously, as overly rapid correction may pose a risk of cerebral edema. Therefore, the infusion rate of 0.9% sodium chloride solution should be 250 ml/h, or use, 0.45% sodium chloride solution at an infusion rate of 250–500 ml/h after the first hour of fluid replacement.[1,31,32]

The infusion of 0.9% sodium chloride solution must be guided by the patient's serum sodium concentration and hydration status. When serum glucose reaches 200 mg/dl (11.1 mOsm/L), the ADA recommends adding 5% dextrose to the IV solution to allow for the continuous infusion of insulin at a sufficient rate to resolve ketonemia and prevent hypoglycemia, i.e., maintaining serum glucose between 150–200 mg/dl. In the absence of cardiac compromise, also it is recommended to administer a 0.9% sodium chloride solution at a rate of 15–20 mL/kg of body weight, or 1–1.5 L during the first hour.[1,33,34]

Patients with mild diabetic ketoacidosis who are alert and able to tolerate oral intake may be treated in the emergency room, potentially with oral fluids and subcutaneous insulin, without the need for hospitalization. Patients with more severe forms of this metabolic disorder should be admitted to inpatient units for intensive monitoring as well as administration of intravenous fluids, potassium, and insulin.[34-36]

The rate of intravenous fluid administration should be adjusted based on the patient's hemodynamic and electrolyte status. Typically, this rate should be maintained between 250 and 500 mL per h for adult patients who do not have cardiac, renal, or hepatic compromise, nor are experiencing any form of fluid overload. There are no established indicators available to guide the optimal IV fluid rate. The ADA recommends that patients with normal or elevated corrected sodium levels may switch to a 0.45% sodium chloride solution after the first hour of fluid replacement.[1,32,36]

A recently developed fluid replacement strategy is the two-bag method, which involves using two 0.45% sodium chloride solution bags, one containing 10% dextrose and the other without dextrose. These are adjusted based on hourly blood glucose monitoring to maintain an IV fluid rate of 250 mL/h.[1,35,36]

Retrospective studies indicate that this method is linked to earlier correction of acidosis and a shorter duration of IV insulin use compared to the traditional administration of IV fluids. In the emergency room, this method may decrease hospitalization needs and may lead to fewer hypoglycemia compared to conventional treatment.[2,37]

There is significant interest in balanced solutions that have an electrolyte composition similar to that of plasma, with reduced amounts of chloride ions. These can help prevent hyperchloremia and hyperchloremic metabolic acidosis. Hyperchloremia can adversely affect critically ill patients, particularly by causing acute kidney injury due to renal vasoconstriction. In 2018, Selmer and colleagues conducted a randomized clinical trial in which they administered balanced solutions to critically ill adult patients.[2,37,38]

The primary outcome was a composite of death from any cause, new renal replacement therapy, or persistent renal dysfunction. Final data analysis showed that balanced solutions significantly reduced this outcome. However, the benefit was modest: one out of every 94 patients gained this benefit, which was mainly observed in patients with sepsis and those requiring large volumes of crystalloids.[2,39]

Insulin Therapy

Insulin administration is a fundamental component in handling DKA, as it aims to reduce hepatic glucose production, improve peripheral glucose utilization, and inhibit lipolysis, ketogenesis, and glucagon secretion, leading to reduced plasma glucose levels and a decrease in ketone bodies. Insulin therapy should be initiated when potassium levels are >3.3 mmol/L.[37,40]

It is recommended to administer regular insulin at a rate of 0.14 U/kg/h without an initial bolus dose, or to start with an IV bolus of 0.1 U/kg followed by a continuous infusion at a rate of 0.1 U/kg/h. Capillary glucose levels are expected to fall by 50 to 75 mg/dL per hour. If glucose does not decrease at this rate, the infusion dose should be increased, or an additional bolus of 0.14 U/kg administered. When blood glucose levels drop below 250 mg/dL, the insulin dose should be reduced to 0.05–0.2 U/kg/h. To prevent hypoglycemia, dextrose should be added to the IV fluids for maintenance.[40,41]

Rapid-acting subcutaneous insulin, such as lispro or aspart, is an efficient substitute for regular insulin and is recommended for mild to moderate DKA. Therapy should begin with an initial bolus of 0.2–0.3 U/kg, followed by 0.1–0.2 U/kg every 1–2 hours. When glucose levels are <200 mg/dL, at least two of the following three additional criteria must be met: a serum bicarbonate level ≥15 mEq/L, a venous pH >7.3, and a calculated anion gap ≤12 mEq/L.[40,42,43]

Reviewing the patient's medical history to identify and modify any precipitating factors is crucial to prevent future events. Many DKA cases can be prevented with proper patient education and medication for chronic diabetes management.[42,44]

Using long-acting insulin analogs in the early hours following a DKA diagnosis is appealing for several reasons. Among the observed benefits are a reduced time to solve the condition and a lower incidence of rebound hyperglycemia.[36,40,45]

Rebound hyperglycemia, is when blood glucose >180 mg/dl within the first 24 hours after stopping IV insulin infusion, and is commonly observed when switching to a subcutaneous insulin regimen after diabetic ketoacidosis has resolved.[28,36]

In a meta-analysis of clinical trials involving 135 DKA cases treated with insulin glargine, significant reductions were observed in time to resolution (mean difference: -4.19 h [95% ci: -7.81 to -0.57]; p = 0.02; 110 participants; 3 trials) and in the incidence of rebound hyperglycemia, without showing significant differences in hypoglycemia episodes (rr: 1.02 [95% ci: 0.41–2.50]; p = 0.97; 135 participants; 4 trials).[28,36]

Potassium therapy

Potassium is the electrolyte most commonly lost during DKA, with a total deficit ranging from 300 to 1,000 mmol/l, and continues to worsen during treatment until osmotic diuresis is under control. Despite this depletion, it is not uncommon for patients to initially present with mild to moderate hyperkalemia; however, serum concentrations decrease due to insulin therapy, correction of acidosis, and volume expansion.[14,15]

For this reason, the development of severe hypokalemia is the most serious electrolyte disturbance that can occur during treatment. It is relevant to replenish potassium and maintain a serum concentration between 4 and 5 mmol/l. The potassium amount administered depends on the serum levels, it should be added when serum levels are below 5.5 meq/l and an adequate urine output is documented. The recommended amount is 20 to 30 meq of potassium per liter of infused solution.[14,46]

Insulin therapy should only begin after confirming the serum potassium levels. And should be postponed until levels exceed 3.3 meq/l to avoid arrhythmias, cardiac arrest, and respiratory muscle weakness (Patients presenting with normal or low potassium at admission are estimated to have a significantly greater total potassium deficit).[14,46]

Potassium should not be added to the first liter of saline used for volume resuscitation, as administering potassium without insulin in a hyperkalemic patient may dangerously increase extracellular potassium levels and trigger fatal arrhythmias. Initially, electrolyte panels should be performed every 1 to 2 hours, since the most significant changes in potassium concentrations occur during the early hours of treatment. Continue monitoring every 4 to 6 hours, depending on the clinical situation. ECG monitoring is recommended for patients with hypokalemia upon admission and for those with arrhythmias other than sinus tachycardia.[14,46]

Bicarbonate therapy

Bicarbonate use in DKA treatment is controversial. It should not be administered in patients with a pH above 7.0, as insulin alone is adequate to reverse DKA. Nevertheless, its use should be considered in severe ketoacidosis cases, as failure to administer it may result in further pH decline.[47-49]

When the pH is below 6.9, it is recommended to administer 100 mmol of sodium bicarbonate diluted in 400 ml of isotonic solution with 20 mmol of potassium chloride. Studies in pediatric patients have shown an increased risk of cerebral edema when using bicarbonate in children with high blood urea nitrogen levels and low co_2 pressure.[47-48]

Acidosis is typically corrected through intravenous fluids, improving tissue and renal perfusion and enhancing the

excretion of organic acids. Insulin therapy is also crucial, as it promotes the metabolism of ketoacids. The use of bicarbonate as adjunctive therapy may increase the risk of hypokalemia; therefore, potassium levels need to be carefully managed with intravenous fluids.[47,50]

There is a discrepancy between U.S. and U.K. guidelines regarding the use of bicarbonate in DKA. The former supports its use when the pH is below 6.9. While the latter completely contraindicates it due to potential adverse effects (hypokalemia, paradoxical intracellular acidosis, reduced tissue oxygenation, etc.), emphasizing that using it may delay the lactate clearance and ketone bodies. On the other hand, in severe diabetic ketoacidosis, it is believed that bicarbonate may improve myocardial contractility and cardiovascular response to catecholamines; however, this has not been demonstrated in clinical studies.[24,47,48]

Phosphate therapy

Osmotic diuresis and insulin therapy cause intracellular phosphate depletion, which may persist for several days. However, phosphate supplementation has not shown clear benefits and may lead to hypocalcemia. Despite this, severe hypophosphatemia accompanied by unexplained weakness should be corrected. Although severe hypophosphatemia can occur at any point during DKA treatment, continuing intravenous therapy without food intake for more than 24 hours is a risk factor for its development. Phosphate replacement is indicated in patients with serum phosphate concentrations of <1.0 to 1.5 mg/dl (0.3 to 0.5 mmol/l).[48,50]

Severe hypophosphatemia (<1 mg/dl [0.32 mmol/l]), whether symptomatic or not, requires immediate treatment. It may be necessary to reduce or temporarily stop the insulin infusion until phosphate levels improve. Potassium phosphate can be combined with potassium chloride or potassium acetate to provide phosphate supplementation without a significant risk of hypocalcemia. During phosphate infusion, serum calcium and magnesium levels should be closely monitored to prevent hypocalcemia.[49]

Phosphate levels should be monitored every 4 to 6 hours during treatment, though more frequent monitoring (every 2 to 3 hours) is recommended for patients not receiving supplementation. If administering phosphate, calcium levels must be carefully monitored. Potassium phosphate may be used as an alternative or combined with potassium chloride or acetate in fluid therapy. The total body phosphate deficit in DKA can average 1 mmol/kg.[49,50]

Insulin therapy during DKA further reduces serum phosphate concentration; studies have shown that 90% of patients developed hypophosphatemia during insulin and fluid infusion. ADA consensus suggests phosphate replacement with 20–30 mmol of potassium phosphate added to the replacement solution may be appropriate for patients with cardiac dysfunction, respiratory depression, anemia, or phosphate levels <3.2 mmol/l. However, there is no conclusive evidence that phosphate therapy improves clinical outcomes.[48,50]

CONCLUSION

Decompensated diabetes mellitus has a complex pathophysiology and a wide range of medical treatments supported by clinical evidence. Although many protocols have been established and suggested worldwide, these treatments require more in-depth research to achieve a clearer and more comprehensive understanding. It is also essential to consider the ideal treatment based on the healthcare setting and patient population, including the comorbidities present in that population, to tailor appropriate medical management. Numerous sources agree on the pathophysiology of DKA, providing detailed explanations from the molecular basis to the clinical manifestations, which aids in recognition and medical intervention. This review was carried out to streamline and combine the available information for both inpatient medical treatment and academic use.

REFERENCES

[1] Self WH, Evans CS, Jenkins CA, Brown RM, Casey JD, Collins SP, et al. Clinical Effects of Balanced Crystalloids vs Saline in Adults with Diabetic Ketoacidosis: A Subgroup Analysis of Cluster Randomized Clinical Trials. JAMA Netw. Open. 2020; 3(11):e2024596.

[2] Andrade-Castellanos CA Cetoacidosis diabética: puesta al día. Med. Int. Méx. 2022; 38(3): 634-41.

[3] Correa Guerrero J, Bello Simanca JD, Betancurt Mendoza RG, Rodríguez Arrieta L, Castellanos Pinedo AA, Dueñas Castel C. Cetoacidosis diabética. ACCI. 2024; 24(3): 243-54.

[4] Hassan EM, Mushtaq H, Mahmoud EE, Chhibber S, Saleem S, Issa A, et al. Overlap of diabetic ketoacidosis and hyperosmolar hyperglycemic state. World J. Clin. Cases. 2022; 10(32): 11702-11.

[5] Ramírez Rojas F, Charpentier Arias A, Rodríguez Umaña D, Rodríguez Loría A, Suárez Urhan A. Cetoacidosis diabética: Fisiopatología y alteraciones del medio interno. Rev. Méd. Univ. Costa Rica. 2018; 12(1): 50-66.

[6] Hatting M, Tavares CDJ, Sharabi K, Rines AK, Puigserver P. Insulin regulation of gluconeogenesis. Ann. N. Y. Acad. Sci. 2018; 1411(1): 21-35.

[7] Foti Ransazzese S, La Rocca M, Bombaci B, Di Pisa A, Giliberto E, Inturri T, et al. Severe Diabetic Ketoacidosis in Children with Type 1 Diabetes: Ongoing Challenges in Care. Children. 2025; 12(1): 110.

[8] Rahmati M, Keshvari M, Mirnasuri S, Yon DK, Lee SW, Shin JI, et al. The global impact of COVID-19 pandemic on the incidence of pediatric new-onset type 1 diabetes and ketoacidosis: A systematic review and meta-analysis. J. Med. Virol. 2022; 94(11): 5112-27.

[9] Rodríguez Escobedo R, Lambert C, Huidobro Fernandez B, Mayoral Gonzalez B, Menéndez Torre E, Riaño-Galán I, et al. Cetoacidosis diabética al diagnóstico de diabetes mellitus tipo 1 en Asturias entre 2011 y 2020: influencia de la duración de los síntomas en la prevalencia de cetoacidosis y en la pérdida de peso. Rev. Esp. Salud Pública. 2023; 97: e1-e13.

[10] Dhatariya KK, Glaser NS, Codner E, Umpierrez GE. Diabetic ketoacidosis. Nat. Rev. Dis. Primers. 2020; 6(1): 40.

[11] Munsakul N, Manosroi W, Buranapin S. Predictors and Predictive Score of In-Hospital Mortality in Diabetic Ketoacidosis: A Retrospective Cohort Study. Medicina (Kaunas). 2024; 60(11): 1833.

[12] Blanco Espinola CF, Rolón MA, Anzoátegui Espínola RE, Neves de Souza Espínola CP. Cetoacidosis diabética en niños y adolescentes. Actualización en diagnóstico y tratamiento. Pediatr. (Asunción).2024; 15(2): 133-45.

[13] Kamel KS, Halperin ML. Acid–Base Problems in Diabetic Ketoacidosis. N. Engl. J. Med. 2015; 372(6): 546-54.

[14] Lizzo JM, Goyal A, Gupta V. Adult Diabetic Ketoacidosis. In: StatPearls [Internet]. Treasure Island (FL). 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560723/

[15] Eledrisi MS, Elzouki AN. Management of Diabetic Ketoacidosis in Adults: A Narrative Review. Saudi J. Med. Med. Sci. 2020; 8(3): 165-73.

[16] Long B, Lentz S, Gottlieb M. Alcoholic Ketoacidosis: Etiologies, Evaluation, and Management. J. Emerg. Med. 2021; 61(6): 658-65.

[17] Eskandarani RM, Sawan S. Diabetic Ketoacidosis on Hospitalization with COVID-19 in a Previously Nondiabetic Patient: A Review of Pathophysiology. Clin. Med. Insights Endocrinol. Diabetes. 2020; 13: 1179551420984125.

[18] Goldmand S, Pinhas-Hamiel O, Weinberg A, Auerbach A, German A, Haim A, et al. Alarming increase in ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the first wave of the COVID-19 pandemic in Israel. Pediatr. Diabetes 2022; 23(1): 10-8.

[19] Ho J, Rosolowsky E, Pacaud D, Huang C, Lemay JA, Brockman N, et al. Diabetic ketoacidosis at type 1 diabetes diagnosis in children during the COVID-19 pandemic. Pediatr. Diabetes. 2021; 22(4): 552-7.

[20] Chicote-Álvarez E, Camino-Ferró H, Mainar-Gil I, Vilella-Llop LA, Ruiz de la Cuesta-López M, Lizama-Gómez NG. Cetoacidosis diabética euglucémica en paciente gestante con infección por SARS-CoV-2: reporte de caso. Acta Colombiana de Cuidado Intensivo. 2023; 23(1): 78-81.

[21] Leiva-Gea I, Antúnez Fernández C, Cardona-Hernandez R, Ferrer Lozano M, Bahíllo-Curieses P, Arroyo-Díez J, et al. Increased Presentation of Diabetic Ketoacidosis and Changes in Age and Month of Type 1 Diabetes at Onset during the COVID-19 Pandemic in Spain. J. Clin. Med. 2022; 11(15): 4338.

[22] Muhammad A, Hakim M, Afaq S, Khattak FA, Shakireen N, Jawad R, et al. Diabetic ketoacidosis amongst patients with COVID- 19: A retrospective chart review of 220 patients in Pakistan. Endocrinol. Diabetes Metab. 2022; 5(3):e00331.

[23] Somagutta MR, Agadi K, Hange N, Jain MS, Batti E, Emuze BO, et al. Euglycemic Diabetic Ketoacidosis and Sodium-Glucose Cotransporter-2 Inhibitors: A Focused Review of Pathophysiology, Risk Factors, and Triggers. Cureus. 2021; 13(3): e13665.

[24] Dhatariya KK. The management of diabetic ketoacidosis in adults—An updated guideline from the Joint British Diabetes Societyfor Inpatient Care. Diabet. Med. 2022; 39(6): e14788.

[25] Padilla Elizondo DS, Chaves Morales KP, Vargas Fernández R. Manejo de la cetoacidosis diabética. Rev. Méd. Sinerg. 2022; 7(7): e864.

[26] Oseguera Birzuela MA. Cetoacidosis diabética: un cuadro de importancia en pediatría. Acta Med. GA. 2023; 21 (2): 158-61.

[27] Izquierdo Coronel D; Álvarez Ochoa RI, Marrero Escalona E. Capítulo 8. Cetoacidosis Diabética. En: Torres Criollo LM, Álvarez Ochoa RI, Pérez Ramírez JE, coordinadores. Medicina de Urgencias, Tomo I. Primera Edición. Argentina: Puerto Madero Editorial Académica; 2022. P.131-44.

[28] Martín Guerra JM, Martín Asenjo M, Tellería Gómez P, Iglesias Pérez C. Cetoacidosis diabética como guía diagnóstica: Caso clínico. Rev. Med. Clin. Condes. 2019; 30(4): 323-5.

[29] Fonseca Filho AC, Veronez de Lima B. Cetoacidose diabética: uma revisão bibliográfica sobre o tratamento desta complicação aguda do Diabetes Mellitus. Revista Sociedade Científica. 2024; 7(1): 4080-8.

[30] De Aquino Morais da Silva B, Moura Vasconcelos JL, Alves de Oliveira Júnior C, Alvares Vasconcelos D, De Queiroz Neves da Rocha EP, Machado Gonçalves M, et al. Abordagens efetivas no manejo da cetoacidose diabética: Uma revisão atualizada. BJIHS. 2023; 5(5): 4470-8.

[31] Albalate Ramón M, Alcáraz Arroyo R, de Sequera Ortíz P. Trastornos del Agua. Disnatremias. En: Lorenzo V, López Gómez JM (Editores). Nefrología al día; 2022.

[32] Long B, Lentz S, Koyfman A, Gottlieb M. Euglycemic diabetic ketoacidosis: Etiologies, evaluation, and management. AJEM. 2021; 44: 157-60.

[33] Agra Montava I, Seres Roig M, Jodar Manzaneda V. Cetoacidosis diabética euglucémica, ¿más iatrogenia? SEMERGEN. 2021; 47(2): 135-6.

[34] Reyes Melo CA, Jiménez Correa DE, Bonilla Sánchez PK, Córdova Reibán AS. Cetoacidosis diabética euglucémica. RECIAMUC.2024; 8(1): 108-14

[35] Palma Jiménez I, Fernández Martínez SC, Domínguez Pech RJ, Tino Parra IA, Bustos Muñoz AK. Cetoacidosis Diabética Hiperglucémica y Euglucémica. Innovación y Desarrollo Tecnológico Revista Digital. 2021; 13(4): 972-80

[36] Algarni A. Treatment Considerations and Pharmacist Collaborative Care in Diabetic Ketoacidosis Management. J. Pharmacol. Pharmacother. 2022; 13(3): 215-21.

[37] Lucero Álvarez E, Simón Gutiérrez G, Bastantes Jácome G, Vicuña Yumbla AM, Tarira Cerezo KL, Vargas Vargas W, et al. Cetoacidosis diabética asociada a inhibidores SGLT2: situación actual. Diab. Inter. Endocrinol. 2021; 13(1): 30-4.

[38] Evans K. Diabetic ketoacidosis: update on management. Clin. Med. (Lond). 2019; 19(5): 396-8.

[39] Venegas Godinez A, Quintana López LA, Padrón Moreira T, Reina Rodríguez CE, Lorenzo Reyes A. Insulinoterapia en pacientes con diabetes mellitus tipo 2 Arch. Hosp. Univ. Gen. Calixto García. 2019; 7(3): 411-24.

[40] Aldhaeefi M, Aldardeer NF, Alkhani N, Alqarni SM, Alhammad AM, Alshaya AI. Updates in the Management of Hyperglycemic Crisis. Front. Clin. Diabetes Healthc. 2022; 2: 820728.

[41] Glaser N, Fritsch M, Priyambada L, Rewers A, Cherubini V, Estrada S, et al. ISPAD clinical practice consensus guidelines 2022: Diabetic ketoacidosis and hyperglycemic hyperosmolar state. 2022; 23(7):835-56.

[42] Pérez-Nieto OR, Soto-Páramo DG, Rojas-Cruz G, Vidal-Mayo JJ, Zamarrón-López EI, Sánchez-Díaz JS, et al. Hyperglycemic Crises:

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome. Narrative Review. CC&EM. 2023; 1(1): 1-18.

[43] Almeida Alvarado JC, Tamayo Calle AV, Barriga Guevara NA. Enfoque diagnóstico y manejo inicial de cetoacidosis y estado hiperosmolar hiperglucémico en adultos: revisión narrativa. CIEM. 2024; 15(Edición especial): 119-30.

[44] Karslioglu French E, Donihi AC, Korytkowski MT. Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome: review of acute decompensated diabetes in adult patients. BMJ. 2019; 365: |1114.

[45] Guía de Práctica Clínica: Evidencias y Recomendaciones. Diagnóstico y tratamiento de la Cetoacidosis diabética y el Estado Hiperglucémico Hiperosmolar en población mayor de 18 años de edad. México: Centro Nacional de Excelencia Tecnológica en Salud (CENETEC); 2022 Available from: http://www.cenetec-difusion.com/CMGPC/GPC-SS160-22/ER.pdf

[46] Almutari T, Dargham S, Jayyousi A, Al Suwaidi J, Abi Khalil C. Diabetic ketoacidosis and hyperglycemic hyperosmolar state are associated with higher in-hospital mortality and morbidity in diabetes patients hospitalized with ST-elevation myocardial infarction, but not within 30 days of readmission. PLoS One. 2025; 20(2):e0318774.

[47] Rosero Moncayo Y, De la Cruz Córdoba DN, Zurita Espinoza CG, Figueroa Zambrano MD. Cetoacidosis diabética: Revisión de la literatura: Artículo de Revisión. Ciencia Ecuador. 2024; 6(25): 37-54.

[48] Duran Casseb AL, Ortiz Rocha N, Ito Marques R, Gabas Stuchi-Perez E. Manejo de cetoacidose diabética: revisão sistemática. Cuid. Enferm. 2022; 16(2): 266-73.

[49] Wysham C, Bindal A, Levrat-Guillen F, Kostadinova D, Poon Y. A systematic literature review on the burden of diabetic ketoacidosis in type 2 diabetes mellitus. Diabetes Obes. Metab. 2025; 27(5): 2750-67.

[50] Villalobos Zúñiga, G, Solano Guillén, MJ, Vargas Cruz, AV. Cetoacidosis diabética: revisión de literatura. Revista Ciencia Y Salud Integrando Conocimientos. 2023; 7(2): 21-8.