

Euglycemic Diabetic Ketoacidosis in Type 2 Diabetes: An Emerging Clinical Challenge

Keywords: SGLT2 Inhibitors; Euglycemic DKA; Diabetic Ketoacidosis; Type 2 Diabetes; Ketogenesis

Abstract

Diabetic ketoacidosis (DKA) is a life-threatening metabolic emergency characterized by insulin deficiency, ketonemia, and high-anion gap metabolic acidosis. Although traditionally associated with type 1 diabetes, DKA is increasingly recognized in Type 2 Diabetes Mellitus, particularly in the context of evolving therapies and metabolic stress.

A notable shift in recent years is the emergence of euglycemic diabetic ketoacidosis (euDKA), defined as DKA with blood glucose levels <250 mg/dL. This atypical presentation frequently delays diagnosis and contributes to under recognition.

The widespread use of SGLT2 inhibitors—including empagliflozin, dapagliflozin, and canagliflozin—has transformed diabetes management by improving glycemic control and providing cardiovascular and renal benefits. However, these agents are associated with an increased risk of DKA, often presenting in a euglycemic form. Although the absolute incidence remains low (~0.1–0.3%), studies suggest a 2-7-fold increased risk in certain populations.

The pathophysiology is multifactorial, involving reduced insulin levels, increased glucagon activity, enhanced lipolysis, and accelerated ketogenesis, combined with glycosuria-induced normoglycemia. Precipitating factors such as acute illness, surgery, fasting, dehydration, and insulin dose reduction further increase susceptibility.

Clinically, euDKA presents with nonspecific symptoms such as nausea, vomiting, abdominal pain, and dyspnea, often mimicking other acute conditions. The absence of marked hyperglycemia contributes to diagnostic delay unless ketones and acid–base status are promptly assessed.

This review synthesizes current evidence on epidemiology, pathophysiology, risk factors, diagnostic challenges, and prevention strategies of SGLT2 inhibitor–associated euDKA. Early recognition, structured prevention strategies, and appropriate patient selection are essential to optimize outcomes while preserving the therapeutic benefits of this drug class.

Introduction

Diabetic ketoacidosis is a serious acute metabolic complication characterized by the triad of hyperglycemia, ketosis, and metabolic acidosis. While historically associated with absolute insulin deficiency in type 1 diabetes, its occurrence in Type 2 Diabetes Mellitus is increasingly recognized, particularly in the presence of relative insulin deficiency, physiological stress, and modern pharmacotherapies.

Euglycemic diabetic ketoacidosis (euDKA) is defined as the presence of metabolic acidosis and ketosis with blood glucose levels below 250 mg/dL. This atypical presentation represents a clinically important diagnostic challenge. The introduction of SGLT2 inhibitors has significantly altered the landscape of diabetes care. By inhibiting renal glucose reabsorption in the proximal tubule, these agents induce glycosuria and reduce plasma glucose levels independent of insulin action. While offering substantial cardiovascular and renal benefits, they have also been associated with an increased risk of DKA, frequently presenting as euDKA.

The absence of marked hyperglycemia in euDKA often delays



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diagnosis, as clinicians may not initially consider DKA in patients with near-normal glucose levels. This creates a critical gap in recognition, particularly in emergency and inpatient settings.

Given the expanding use of SGLT2 inhibitors and increasing reports of euDKA, a comprehensive understanding of this condition is essential. This review aims to provide an updated synthesis of its epidemiology, mechanisms, risk factors, diagnostic challenges, and prevention strategies.

Epidemiology and Emerging Trends

Incidence and Clinical Significance

Euglycemic diabetic ketoacidosis (euDKA) represents a small but clinically significant subset of diabetic ketoacidosis. Although the absolute incidence is low compared to classical DKA, it carries a comparable risk of morbidity, particularly when recognition is delayed. Increasing awareness suggests that euDKA is more prevalent than previously appreciated in patients with Type 2 Diabetes Mellitus.

Impact of SGLT2 Inhibitor Use

The epidemiology of euDKA has evolved with the widespread use of SGLT2 inhibitors. Evidence from clinical trials and real-world studies indicates an increased risk of DKA associated with this drug class, with a substantial proportion presenting in euglycemic form. Although the overall risk remains low, increased utilization has contributed to a rise in reported cases globally.

High-Risk Clinical Settings

Hospitalized, perioperative, and critically ill patients are at increased risk of euDKA. Recent 2026 acute care reviews emphasize that perioperative metabolic stress, prolonged fasting, infection, and interruption of insulin therapy significantly amplify susceptibility in patients receiving SGLT2 inhibitors. Emergency and intensive care settings are particularly vulnerable environments because euDKA may initially present with only mild hyperglycemia despite severe metabolic acidosis. In unplanned surgical or emergency situations where SGLT2 inhibitors were not discontinued beforehand, clinicians

should actively evaluate for “pseudonormoglycemia,” characterized by blood glucose levels below 250 mg/dL in the presence of high-anion gap metabolic acidosis and ketosis.

Under recognition and Diagnostic Challenges

Despite growing awareness, euDKA remains underdiagnosed. The absence of significant hyperglycemia frequently delays consideration of diabetic ketoacidosis, particularly in acute care settings where glucose levels are often used as the primary diagnostic trigger. Recent acute care literature highlights that euDKA associated with SGLT2 inhibitors may follow a more prolonged clinical course than classical DKA, with metabolic resolution requiring substantially longer treatment durations in some patients. This under recognition underscores the importance of early ketone assessment and acid–base evaluation in all at-risk patients receiving SGLT2 inhibitors.

Pathophysiological Mechanisms

The development of euDKA reflects a complex interplay of hormonal imbalance, altered metabolism, and renal mechanisms. Recent mechanistic studies from 2024–2025 suggest that the pathophysiology of SGLT2 inhibitor-associated euDKA extends beyond simple insulin reduction and involves a complex multi-organ interaction among the pancreatic α -cell, renal tubule, liver, and neurohormonal pathways. SGLT2 inhibition promotes glucagon secretion from pancreatic α -cells while simultaneously enhancing renal glucose loss and altering tubular ketone handling. In addition, activation of stress-related hormonal pathways, including posterior pituitary-mediated counter-regulatory responses, may further amplify ketogenesis during acute illness, fasting, or surgery. These combined endocrine and renal effects create a metabolic environment favoring sustained ketone production despite near-normal glucose concentrations.

Altered Insulin–Glucagon Homeostasis

SGLT2 inhibitors reduce plasma glucose through insulin-independent glycosuria, leading to a decline in endogenous insulin secretion. This reduction in circulating insulin is accompanied by a paradoxical increase in glucagon secretion from pancreatic α -cells. The resulting decrease in the insulin-to-glucagon ratio is central to the pathogenesis of euDKA, as it promotes a metabolic shift from glucose utilization to fat metabolism. In this hormonal milieu, the inhibitory effect of insulin on lipolysis and ketogenesis is diminished, facilitating the accumulation of ketone bodies.

Enhanced Lipolysis and Free Fatty Acid Flux

The relative insulin deficiency and elevated counter-regulatory hormones activate hormone-sensitive lipase in adipose tissue, leading to increased breakdown of triglycerides into free fatty acids. These free fatty acids are released into the circulation and transported to the liver, where they serve as substrates for ketone body production. This enhanced lipolytic state is a key driver of the metabolic cascade that culminates in ketoacidosis.

Accelerated Hepatic Ketogenesis

Within the liver, free fatty acids undergo β -oxidation to generate acetyl-CoA, which is subsequently converted into ketone bodies, primarily β -hydroxybutyrate and acetoacetate. Under normal

physiological conditions, insulin suppresses hepatic ketogenesis; however, in the context of reduced insulin activity, this regulatory mechanism is impaired. Consequently, ketone production becomes excessive and unregulated, leading to the accumulation of organic acids and the development of high-anion gap metabolic acidosis.

Glycosuria-Induced Euglycemia

A distinguishing feature of SGLT2 inhibitor therapy is the induction of glycosuria through inhibition of renal glucose reabsorption in the proximal tubule. This mechanism lowers plasma glucose levels and prevents the marked hyperglycemia typically seen in classical DKA. As a result, significant ketoacidosis may occur despite near-normal glucose levels, masking the severity of the underlying metabolic disturbance and contributing to diagnostic delays.

Renal Handling of Ketones and Volume Depletion

SGLT2 inhibitors may also influence renal ketone handling by increasing tubular reabsorption of ketone bodies, thereby contributing to systemic ketonemia. In addition, the osmotic diuresis induced by glycosuria leads to volume depletion and reduced renal perfusion, impairing the clearance of ketones. This combination of increased production and decreased excretion further exacerbates metabolic acidosis.

Role of Counter-Regulatory Hormones and Stress States

Physiological stressors such as infection, surgery, fasting, or acute illness trigger the release of counter-regulatory hormones including catecholamines, cortisol, and growth hormone. These hormones promote insulin resistance, enhance lipolysis, and stimulate hepatic gluconeogenesis and ketogenesis. In patients receiving SGLT2 inhibitors, these stress-induced metabolic changes amplify the risk of transitioning into euDKA.

Precipitating Factors and Metabolic Amplification

The onset of euDKA is often precipitated by external factors that exacerbate the underlying metabolic imbalance. Reduced oral intake or prolonged fasting decreases insulin secretion and shifts energy metabolism toward fat utilization. Similarly, inappropriate reduction or omission of insulin therapy removes a critical inhibitory control on ketogenesis. Dehydration, alcohol use, and acute medical conditions further intensify this metabolic derangement, lowering the threshold for the development of ketoacidosis.

Integrated Pathophysiological Cascade

The pathogenesis can be conceptualized as a sequence in which SGLT2 inhibition induces glycosuria, leading to reduced insulin levels and increased glucagon activity. This hormonal imbalance promotes lipolysis and hepatic ketogenesis, resulting in ketone accumulation and metabolic acidosis despite near-normal glucose levels. The central feature is a metabolic shift toward ketone production rather than hyperglycemia.

The pathogenesis can be conceptualized as a sequence:

SGLT2 inhibition \rightarrow **glycosuria** \rightarrow **lower insulin + higher glucagon** \rightarrow **increased lipolysis** \rightarrow **hepatic ketogenesis** \rightarrow **ketone accumulation + metabolic acidosis + normal glucose levels** \rightarrow **euglycemic DKA**

The central pathophysiological feature is not hyperglycemia but a **disproportionate shift toward ketone production due to hormonal imbalance (low insulin–high glucagon state)**, compounded by renal and metabolic effects of SGLT2 inhibition. (Figure 1) illustrates the pathophysiology of euDKA mechanisms and (Table 1) shows the summarised mechanisms

Risk Factors

Patient-Related Factors

Several patient-specific characteristics increase susceptibility to euglycemic diabetic ketoacidosis (euDKA) in individuals with Type 2 Diabetes Mellitus. Long-standing diabetes is associated with progressive β -cell dysfunction, resulting in reduced endogenous insulin reserve and impaired metabolic flexibility. Patients with latent autoimmune diabetes in adults (LADA) are particularly vulnerable due to underlying insulin deficiency, which predisposes them to ketosis even in the absence of overt hyperglycemia. Additionally, individuals

with low body mass index or diminished insulin reserve may have limited capacity to buffer metabolic stress, further increasing the risk. Dehydration also plays a critical role by exacerbating metabolic imbalance and impairing renal clearance of ketone bodies, thereby promoting acidosis.

Treatment-Related Factors

Therapeutic interventions, particularly the use of SGLT2 inhibitors, significantly influence the risk of euDKA. These agents induce glycosuria, leading to reduced plasma glucose levels and subsequent decline in insulin secretion, thereby facilitating ketogenesis. In addition, inappropriate reduction or omission of insulin therapy removes a key inhibitory mechanism against lipolysis and ketone production. Dietary practices such as low-carbohydrate or ketogenic diets further shift metabolism toward fat utilization, increasing ketone body formation. Alcohol consumption compounds this risk by promoting ketogenesis and impairing hepatic gluconeogenesis, thereby contributing to metabolic instability.

Precipitating Factors

Acute physiological stressors frequently act as triggers for euDKA in susceptible individuals. Infections increase the release of counter-regulatory hormones, such as catecholamines and cortisol, which promote insulin resistance and enhance ketogenesis. Surgical procedures and prolonged fasting reduce caloric intake and insulin secretion while increasing metabolic stress, thereby shifting energy

Table 1: Shows the summarised mechanisms underlying in euglycemic diabetic ketoacidosis.

Mechanism	Effect
Glycosuria	Lower plasma glucose
Insulin reduction	Enhanced lipolysis
Glucagon increase	Ketogenesis
Volume depletion	Reduced ketone clearance

Figure 1. PATHOPHYSIOLOGY OF EUGLYCEMIC DIABETIC KETOACIDOSIS (euDKA) IN TYPE 2 DIABETES

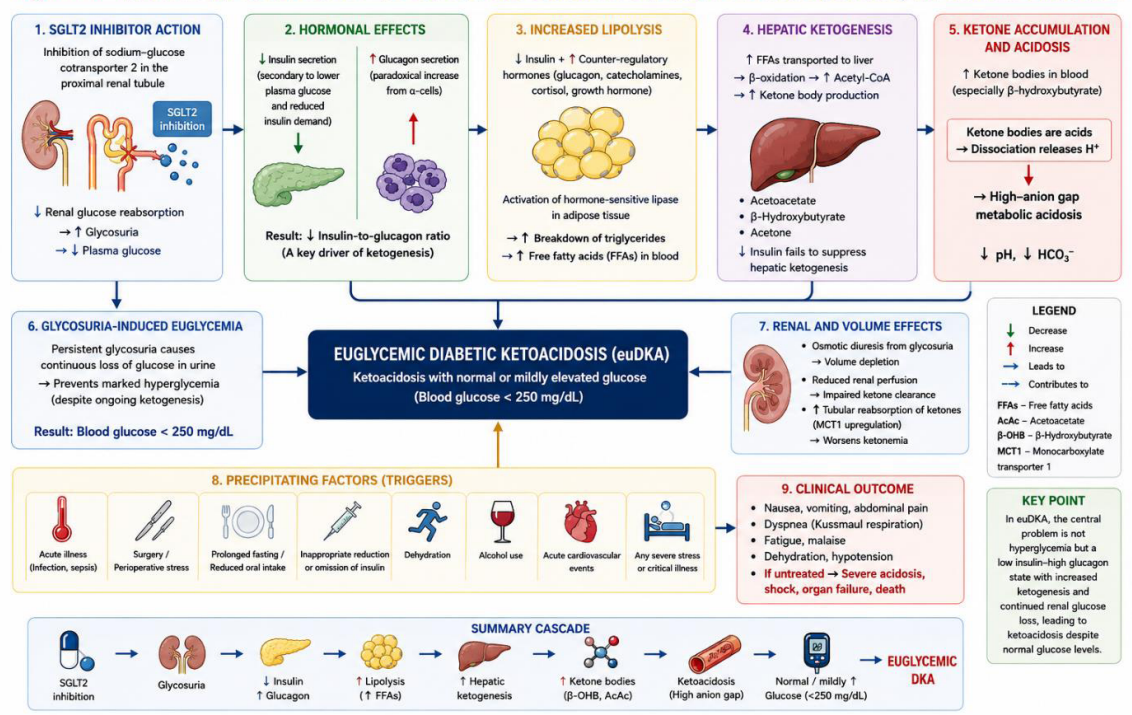


Figure 1: Pathophysiological mechanisms underlying euglycemic diabetic ketoacidosis (euDKA) in patients with type 2 diabetes mellitus (T2DM), highlighting the interplay between insulin deficiency, increased glucagon secretion, enhanced lipolysis and ketogenesis, reduced carbohydrate availability, and renal glucose loss leading to metabolic acidosis despite near-normal blood glucose levels.

metabolism toward fat oxidation. Acute cardiovascular events, including myocardial infarction, further exacerbate hormonal imbalance and metabolic demand. More broadly, any severe illness or systemic stress can precipitate DKA by amplifying the underlying metabolic derangements.

Clinical Spectrum and Presentation

Spectrum of Diabetic Ketoacidosis

Diabetic ketoacidosis in Type 2 Diabetes Mellitus exists along a continuum of clinical presentations. Classical DKA is characterized by marked hyperglycemia, ketosis, and metabolic acidosis, typically resulting from significant insulin deficiency. In contrast, mixed DKA–hyperosmolar states exhibit overlapping features of DKA and hyperosmolar hyperglycemic syndrome, often seen in older patients with T2DM. Euglycemic DKA represents a distinct variant in which significant ketosis and acidosis occur despite normal or mildly elevated glucose levels, making diagnosis particularly challenging.

Clinical Presentation

The clinical manifestations of euDKA are often nonspecific and may mimic other acute conditions. Patients commonly present with nausea and vomiting due to metabolic acidosis and gastrointestinal irritation. Abdominal pain is frequent and may resemble an acute surgical abdomen, leading to potential misdiagnosis. Dyspnea, often manifesting as Kussmaul respiration, reflects compensatory hyperventilation in response to metabolic acidosis. Generalized fatigue and malaise are also common, representing the systemic impact of metabolic derangement. The absence of significant hyperglycemia often obscures the diagnosis, delaying appropriate intervention.

Diagnostic Challenges and Pitfalls

Normoglycemia and Diagnostic Delay

A defining challenge in euDKA is the presence of normal or only mildly elevated blood glucose levels, which may falsely reassure clinicians and delay consideration of Diabetic Ketoacidosis. This atypical biochemical profile contributes significantly to underrecognition.

Misdiagnosis and Clinical Overlap

The nonspecific symptomatology of euDKA frequently leads to misdiagnosis. Conditions such as sepsis, gastroenteritis, or other acute abdominal pathologies are often considered first, particularly in emergency settings, resulting in delayed identification of the underlying metabolic disorder.

Inadequate Ketone Assessment

Failure to assess serum or urine ketones in patients with unexplained metabolic acidosis is a major contributor to missed or delayed diagnosis. Reliance solely on glucose measurements without evaluating ketone status can overlook euDKA.

Glucose-Centric Diagnostic Bias

Traditional diagnostic frameworks for DKA emphasize hyperglycemia, which may not be present in euDKA. This glucose-

centric bias underscores the need for a broader diagnostic approach that incorporates assessment of anion gap and ketone levels.

Diagnostic Approach

Current evidence suggests that the diagnosis of euDKA should be based on the following biochemical criteria:

- Blood β -hydroxybutyrate (BHB) ≥ 3.0 mmol/L
- Arterial or venous pH < 7.3 or serum bicarbonate < 18 mmol/L
- Blood glucose typically < 200 – 250 mg/dL, often ranging between 100 – 150 mg/dL
- Presence of high–anion gap metabolic acidosis

Measurement of serum β -hydroxybutyrate is preferred over urine ketone testing because urine assays primarily detect acetoacetate and may underestimate the severity of ketosis during active treatment.

Laboratory Findings

The diagnosis of euDKA is established through a combination of biochemical abnormalities. Patients typically exhibit high–anion gap metabolic acidosis, reflected by low pH and reduced bicarbonate levels, indicating systemic acid accumulation. Elevated anion gap signifies the presence of unmeasured acids, primarily ketone bodies. Positive serum or urine ketones confirm ketosis, while blood glucose levels are usually below 250 mg/dL, distinguishing euDKA from classical DKA.

Recommended Diagnostic Evaluation

A comprehensive evaluation includes measurement of serum β -hydroxybutyrate, which is the most sensitive and specific marker of ketosis. Blood gas analysis, either arterial or venous, is essential to assess the severity of metabolic acidosis. In addition, evaluation of electrolytes and renal function provides critical information for guiding management and identifying complications associated with volume depletion and metabolic imbalance. Table 2 shows the differentiation features between DKA and euDKA.

Differential Diagnosis

The diagnosis of euglycemic diabetic ketoacidosis (euDKA) can be challenging because its clinical presentation frequently overlaps with several other causes of high–anion gap metabolic acidosis. Accurate differentiation is essential because management strategies differ substantially among these conditions. In patients receiving SGLT2 inhibitors, clinicians should maintain a high index of suspicion for euDKA even when blood glucose levels are normal or only mildly elevated.

Starvation Ketosis

Starvation ketosis develops during prolonged fasting or severe caloric restriction when hepatic glycogen stores become depleted and fatty acid oxidation increases. Although mild ketonemia may occur, metabolic acidosis is usually less severe than in euDKA, and serum bicarbonate levels generally remain above 18 mmol/L. Patients are often non-diabetic or have a history of prolonged fasting without significant systemic illness. In contrast, euDKA is characterized by marked ketonemia, high–anion gap metabolic acidosis, and relative insulin deficiency despite near-normal glucose levels.

Table 2: Key Differences Between Classical Diabetic Ketoacidosis (DKA) and Euglycemic Diabetic Ketoacidosis (euDKA)

Feature	Classical DKA	Euglycemic DKA (euDKA)
Blood glucose level	Usually markedly elevated, typically >250 mg/dL and often much higher	Normal or mildly elevated blood glucose, typically <250 mg/dL
Ketosis	Present; significant ketone body production in blood and urine	Present; ketone production occurs despite near-normal glucose levels
Metabolic acidosis	Present with high anion gap metabolic acidosis	Present with high anion gap metabolic acidosis
Serum bicarbonate / pH	Low bicarbonate and reduced arterial pH	Low bicarbonate and reduced arterial pH similar to classical DKA
Clinical presentation	Polyuria, polydipsia, dehydration, vomiting, abdominal pain, altered sensorium	Similar symptoms, but dehydration and hyperglycemic symptoms may be less obvious
Diagnosis	Usually recognized early because of marked hyperglycemia	Frequently missed or delayed due to absence of severe hyperglycemia
Common precipitating factors	Insulin omission, infection, myocardial infarction, stroke, trauma	SGLT2 inhibitor therapy, prolonged fasting, low-carbohydrate diet, pregnancy, surgery, acute illness
Association with SGLT2 inhibitors	Uncommon	Strongly associated
Degree of dehydration	Often severe due to osmotic diuresis	May be mild to moderate
Urinary glucose excretion	Elevated due to marked hyperglycemia	Elevated because SGLT2 inhibitors promote glucosuria
Risk of delayed treatment	Lower because diagnosis is more apparent	Higher because normal glucose levels may mislead clinicians
Management principles	Intravenous fluids, insulin therapy, electrolyte correction, treatment of precipitating cause	Similar management, with special attention to discontinuation of SGLT2 inhibitors and early ketone monitoring
Mortality and complications	Potentially life-threatening if untreated	Equally serious and potentially life-threatening despite normal glucose levels

Alcoholic Ketoacidosis

Alcoholic ketoacidosis typically occurs in individuals with chronic alcohol use, especially after episodes of binge drinking followed by vomiting and poor oral intake. Patients often present with dehydration, abdominal pain, and metabolic acidosis with elevated ketone levels. Unlike euDKA, glucose levels are usually low or normal, and a history of significant alcohol intake is prominent. Additionally, alcoholic ketoacidosis is frequently associated with elevated lactate levels and electrolyte abnormalities such as hypomagnesemia and hypophosphatemia.

Lactic Acidosis

Lactic acidosis results from excessive lactate accumulation due to tissue hypoperfusion, hypoxia, severe infection, shock, seizures, or certain medications such as metformin. Patients present with high-anion gap metabolic acidosis; however, ketosis is typically absent or minimal. Measurement of serum lactate is critical for differentiation. In euDKA, elevated serum β -hydroxybutyrate and significant ketonemia are dominant biochemical findings, whereas lactate elevation is secondary or mild.

Sepsis-Associated Metabolic Acidosis

Sepsis may produce metabolic acidosis through tissue hypoperfusion, mitochondrial dysfunction, and increased lactate production. Clinical manifestations such as fever, hypotension, leukocytosis, and organ dysfunction may overlap with euDKA. Importantly, sepsis itself may also precipitate euDKA in patients receiving SGLT2 inhibitors, creating a diagnostic challenge. Concurrent evaluation of serum ketones, lactate, infection markers, and acid-base status is therefore essential in critically ill patients.

Toxic Ingestions

Toxic alcohol ingestion, including methanol or ethylene glycol poisoning, can present with severe high-anion gap metabolic acidosis and altered mental status. Unlike euDKA, these conditions are often associated with an elevated osmolar gap, visual disturbances, acute kidney injury, or neurologic manifestations. Ketosis is generally absent or mild. A careful exposure history and toxicology evaluation are important for differentiation.

Hyperosmolar Hyperglycemic State (HHS)

Hyperosmolar hyperglycemic state is characterized by profound hyperglycemia, hyperosmolality, and severe dehydration with minimal or absent ketosis. Neurological symptoms such as confusion, lethargy, or coma are more prominent in HHS. In contrast, euDKA presents with significant ketosis and metabolic acidosis despite glucose levels typically below 250 mg/dL. Mixed presentations involving features of both DKA and HHS may occasionally occur in patients with Type 2 Diabetes Mellitus.

Clinical Importance of Differential Diagnosis

Because euDKA lacks marked hyperglycemia, clinicians may initially attribute high-anion gap metabolic acidosis to alternative etiologies such as sepsis, starvation, or lactic acidosis. Therefore, routine assessment of serum β -hydroxybutyrate, anion gap, bicarbonate level, and acid-base status is essential in any at-risk patient presenting with unexplained metabolic acidosis, particularly those receiving SGLT2 inhibitor therapy. Table 3 shows summary of differential diagnosis of euDKA from other similar clinical conditions.

Acute Management Principles

Management of euDKA follows the core principles of classical diabetic ketoacidosis treatment but requires special consideration because of near-normal glucose levels and prolonged ketogenesis.

Immediate Discontinuation of SGLT2 Inhibitors

SGLT2 inhibitors should be stopped immediately once euDKA is suspected or confirmed to eliminate the precipitating pharmacological trigger.

Fluid Resuscitation

Early and aggressive intravenous fluid therapy is essential to correct hypovolemia, improve renal perfusion, and facilitate ketone clearance. Isotonic crystalloids are generally recommended during initial resuscitation.

Table 3: Differential Diagnosis of Euglycemic Diabetic Ketoacidosis (euDKA)

Condition	Ketosis	Blood Glucose	Lactate Level	Osmolar Gap	Key Clinical Features	Distinguishing Features
Euglycemic Diabetic Ketoacidosis (euDKA)	Markedly elevated	Normal or mildly elevated (<250 mg/dL)	Normal or mildly elevated	Usually normal	Nausea, vomiting, abdominal pain, dyspnea, dehydration	High-anion gap metabolic acidosis with significant ketonemia despite near-normal glucose; commonly associated with SGLT2 inhibitor use
Classical Diabetic Ketoacidosis (DKA)	Markedly elevated	Markedly elevated (>250 mg/dL)	Normal or mildly elevated	Usually normal	Polyuria, polydipsia, dehydration, Kussmaul breathing	Severe hyperglycemia with ketosis and metabolic acidosis
Starvation Ketosis	Mild to moderate	Normal or low	Normal	Normal	Prolonged fasting, malnutrition, weight loss	Acidosis usually mild; serum bicarbonate often >18 mmol/L
Alcoholic Ketoacidosis	Elevated	Low, normal, or mildly elevated	Often elevated	Usually normal	Chronic alcohol use, vomiting, dehydration	History of binge alcohol intake with poor nutrition; associated electrolyte abnormalities
Lactic Acidosis	Absent or mild	Variable	Markedly elevated	Normal	Shock, sepsis, hypoxia, metformin use	Predominant hyperlactatemia with minimal ketosis
Sepsis-Associated Metabolic Acidosis	Usually absent	Variable	Elevated	Normal	Fever, hypotension, infection, organ dysfunction	Elevated inflammatory markers and lactate; ketosis not dominant
Hyperosmolar Hyperglycemic State (HHS)	Minimal or absent	Very high (>600 mg/dL)	Usually normal	Elevated serum osmolality	Severe dehydration, altered sensorium	Extreme hyperglycemia and hyperosmolality with minimal ketosis
Methanol Poisoning	Absent	Normal	Variable	Elevated	Visual disturbances, CNS depression	Increased osmolar gap with severe metabolic acidosis
Ethylene Glycol Poisoning	Absent	Normal	Variable	Elevated	Acute kidney injury, neurologic symptoms	Calcium oxalate crystals in urine; elevated osmolar gap
Salicylate Toxicity	Mild or absent	Variable	Variable	Normal	Tinnitus, hyperventilation, mixed acid-base disorder	Respiratory alkalosis with metabolic acidosis
Uremic Acidosis (Advanced Renal Failure)	Absent or mild	Variable	Mild elevation possible	Normal	Chronic kidney disease, fluid overload	Elevated urea and creatinine with reduced renal acid excretion

Abbreviations: euDKA = Euglycemic Diabetic Ketoacidosis; DKA = Diabetic Ketoacidosis; HHS = Hyperosmolar Hyperglycemic State; CNS = Central Nervous System.

Intravenous Insulin Therapy

Continuous intravenous insulin infusion (typically 0.1 U/kg/hour) should be initiated promptly to suppress ketogenesis and reverse metabolic acidosis. Because glucose levels are frequently normal or only mildly elevated, insulin therapy must not be withheld despite the absence of severe hyperglycemia.

Early Dextrose Administration

Dextrose-containing intravenous fluids (5–10%) are often required early during treatment to prevent hypoglycemia while allowing continued insulin administration necessary for suppression of ketone production and correction of acidosis.

Electrolyte and Ketone Monitoring

Frequent monitoring of serum electrolytes, particularly potassium, is critical during treatment. Serial assessment of serum β-hydroxybutyrate is preferred over urine ketone testing because urine ketones may remain falsely elevated or misleading during recovery.

Prolonged Resolution Time

Recent studies suggest that SGLT2 inhibitor-associated euDKA may require substantially longer treatment duration than classical DKA, with some reports demonstrating resolution times approaching 90 hours compared with approximately 35 hours in traditional DKA. Accordingly, prolonged metabolic monitoring may be necessary even after glucose normalization.

Sick-Day Management

Patients receiving SGLT2 inhibitors should receive detailed “sick-day rules” education. These agents should be temporarily withheld during acute illness or situations associated with increased ketogenesis risk, including:

- Fasting or markedly reduced oral intake
- Vomiting or diarrhea
- Infection or sepsis
- Prolonged or intense physical exercise
- Low-carbohydrate or ketogenic diets

Patients should be advised to maintain hydration, monitor ketone levels when symptomatic, and seek early medical attention if nausea, vomiting, abdominal pain, or dyspnea develop.

Perioperative Management

Updated perioperative recommendations advise discontinuing SGLT2 inhibitors at least 3–4 days before elective surgical procedures to reduce the risk of perioperative euDKA. In emergency surgical settings where discontinuation was not possible, clinicians should maintain a high index of suspicion and closely monitor for high-anion gap metabolic acidosis and ketosis despite normal glucose levels.

SGLT2 inhibitors should only be restarted once the patient is clinically stable, eating reliably, adequately hydrated, and free of ongoing precipitating factors such as infection or surgical stress.

Clinical Vigilance

Clinicians must maintain a high index of suspicion for euDKA, particularly in patients presenting with unexplained metabolic acidosis. Routine assessment of ketones is essential, even in the presence of normal glucose levels, to facilitate early diagnosis. (Table 4). Summarised the prevention of Euglycemic DKA.

Table 4: summarizes the prevention strategies of euglycemic DKA

Prevention Strategy	Recommendation
Surgery	Stop SGLT2 inhibitor 3–4 days prior
Acute illness	Hold medication
Fasting	Avoid prolonged fasting
Symptoms	Check ketones early

Future Directions

Future research should focus on developing predictive risk models to identify patients at increased risk of euDKA prior to initiation of SGLT2 inhibitors. The identification of reliable biomarkers for early detection may further improve clinical outcomes. Standardized protocols for perioperative and sick-day management are needed to reduce variability in care. Additionally, advances in artificial intelligence-based monitoring systems hold promise for real-time risk assessment and early intervention, potentially transforming the prevention and management of this emerging complication.

Conclusion

Euglycemic diabetic ketoacidosis (euDKA) represents a significant and evolving challenge in the management of Type 2 Diabetes Mellitus and reflects a paradigm shift in the clinical presentation of diabetic ketoacidosis. The increasing use of SGLT2 inhibitors has contributed to the rising incidence of this atypical and often underrecognized condition, characterized by ketoacidosis in the absence of marked hyperglycemia.

The pathophysiology is complex, involving reduced insulin activity, increased glucagon secretion, enhanced lipolysis, accelerated hepatic ketogenesis, and glycosuria-induced normoglycemia. These mechanisms create a metabolic environment in which significant acidosis may develop despite near-normal glucose levels, often leading to misdiagnosis and delayed treatment.

The clinical implications are substantial, as delayed recognition can result in severe metabolic decompensation and potentially life-threatening outcomes. A high index of suspicion is therefore essential, particularly in patients receiving SGLT2 inhibitors who present with unexplained gastrointestinal or respiratory symptoms.

Prevention remains central to minimizing risk. Careful patient selection, structured patient education, adherence to sick-day management protocols, and appropriate perioperative discontinuation of SGLT2 inhibitors are key strategies. In addition, clinicians must adopt a broader diagnostic approach that includes routine assessment of ketones and acid–base status, even in the absence of significant hyperglycemia.

In conclusion, while SGLT2 inhibitors provide substantial therapeutic benefits, their safe use requires heightened clinical awareness of euDKA. Early recognition, prompt management, and proactive risk mitigation are essential to optimize patient outcomes while preserving the advantages of this important drug class.

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