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Diabetic ketoalkalosis: the dark, torrid horse of diabetic emergencies

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Abstract

Diabetic ketoalkalosis (DKALK) is a rare but significant variant of diabetic emergencies, characterized by metabolic alkalosis rather than the typical acidosis seen in diabetic ketoacidosis (DKA). Despite its clinical importance, DKALK often goes unrecognized due to limited literature on its presentation and biochemical variables. This work examines the pathophysiology, clinical presentation, diagnostic challenges, management strategies, and implications for clinical practice of DKALK, drawing insights from case studies and research gaps in the field. Notable case studies underscore the diagnostic challenges and emphasize the importance of tailored management strategies for DKALK. Risk assessment involves recognizing predisposing factors such as severe vomiting, alcohol abuse, or concomitant diuretic use. Timely recognition and intervention are essential to prevent potentially life-threatening complications associated with DKALK. Continued research efforts are warranted to refine diagnostic criteria, optimize therapeutic approaches, and enhance early recognition of DKALK, ultimately improving patient outcomes in this challenging clinical scenario.

Keywords

Diabetic ketoalkalosis, metabolic alkalosis, diabetic emergencies, ketoacidosis, endocrinology

Introduction

First described in 1967 as a rare complication of diabetic ketoacidosis (DKA) [1], diabetic ketoalkalosis (DKALK), also known as "masked DKA" or "alkaline ketoacidosis" is actually an alternate version of DKA associated with mixed acid-base disorders [2] in which the anticipated acidosis is cloaked by an overriding alkalosis [2, 3]. This occurs in DKA patients with profuse vomiting via the loss of hydrogen ions from the intestinal tract and alkalotic contraction as a result of volume depletion [2]. Consequently, volume loss activates the renin-angiotensin-aldosterone system thus stimulating renal tubules to reabsorb sodium and bicarbonate while also generating new bicarbonates [4], both of which are facilitated by the release of hydrogen ions into the tubular lumen through secretory action [2, 4]. Hyperaldosteronism will consequently induce hypokalemia which induces metabolic alkalosis by moving hydrogen ions from the extracellular fluid compartment to the intracellular fluid compartment in exchange for potassium and by accelerating renal bicarbonate reabsorption [4, 5]. This multifactorial effect results in alkalaemia instead of the typical acidaemia that is seen in DKA where there is an accumulation of keto-acids [3, 5]. As there is limited literature on the clinical presentation and biochemical variables of DKALK, it is surmised that DKALK may be underdiagnosed and far more common than we think.

Significance in diabetic emergencies

DKA is defined as blood glucose > 250 mg/dL (although blood glucose levels can also be normal on some occasions), blood pH < 7.3, serum bicarbonate < 18 mEq/L, and the presence of elevated anion gap (AG) metabolic acidosis [6]. However, patients with DKALK present with blood pH > 7.4 and bicarbonate > 18 mEq/L [5, 6]. This limits their utility as diagnostic parameters and might mask or significantly delay diagnosis while other differentials of raised AG are investigated. DKA is a potentially deleterious complication of diabetes, and timely treatment relies on prompt recognition, hence novel assays like serum beta-hydroxybutyric acid (β-OHB), the major ketone body, makes it easier to use serum ketone measurement as an independent parameter for detecting ketoacidosis [2]. This facilitates speedy intravenous fluid therapy and electrolyte replacement which unmasks the underlying acidosis [6].

Pathophysiology of diabetic ketoalkalosis

DKALK is often regarded as a diagnostic misnomer due to its rarity and how it is often underreported. In clinical practice, there are numerous incidents where patients present with diabetes, positive serum ketones, and increased AG metabolic acidosis, but with pH > 7.3 or bicarbonate > 18 mmol/L, which fall beyond the current criteria for diagnosing DKA [7]. Interestingly, patients can even present with alkalemia with pH > 7.4, which is termed DKALK: an oddity of interesting proportions.

Ketoalkalosis is a state where there are circulating ketone bodies in the presence of alkalosis [1, 2]. In cases of diabetes complications such as DKA, acidosis is the norm, but there are situations where this acidosis is overridden to initiate alkalosis due to distinct pathophysiological mechanisms [6]. DKA can present with profuse vomiting, which leads to metabolic alkalosis due to hydrogen ion loss from the gastrointestinal tract and contraction alkalosis due to volume depletion [4, 5]. Increased aldosterone levels will, in turn, induce hypokalemia which contributes to the generation and increment of bicarbonates by shifting hydrogen ions from the extracellular fluid to the intracellular fluid in exchange for potassium and by increasing renal reabsorption of bicarbonates [5, 6]. This effect leads to alkalemia instead of the typical acidaemia seen in DKA as a result of ketone bodies [6].

The presence of concurrent primary metabolic alkalosis, primary respiratory alkalosis, and primary respiratory acidosis can cause changes in pH and bicarbonate [2] and the presence of coincident primary metabolic alkalosis, respiratory alkalosis, and respiratory acidosis can cause changes in pH and bicarbonate [2] and the subtle nuances between these salient respective parameters alongside ketones and hyperglycemia form the structures of comparison between DKALK and DKA [8] (Table 1).

Table 1. Comparison between DKA and DKALK

Characteristics	DKA	DKALK
Diabetes (RBS > 14 mmol/L)	Present	Present
Serum and urine ketones	Present (> 3 mEq/L)	Present (> 3 mEq/L)
Anion gap	> 18 mEq/L	> 18 mEq/L
Arterial pH	< 7.3	> 7.4
Bicarbonate	< 18 mEq/L	> 18 mEq/L

RBS: random blood sugar; DKA: diabetic ketoacidosis; DKALK: diabetic ketoalkalosis

Clinical presentation

Emergency complications of diabetes which almost always lead to hospitalizations are not uncommon in medical emergencies [8, 9]. DKA is commonly complicated by mixed acid-base disorders whose biochemical values (pH > 7.3 or bicarbonate > 18 mmol/L), fall outside the parameters defined by traditional DKA (pH ≤ 7.3 or bicarbonate ≤ 18 mmol/L) resulting in DKALK [2]. DKALK may be identified by calculating the delta ratio (DR), which may illustrate the possible discordance between the changes in AG over the changes in bicarbonate, in combination with additional symptoms and signs from a medical history and physical examination of the patient [8, 10]. This medical condition is easily misdiagnosed and is probably more common than is generally recognized [11].

Symptoms and signs

One of the defining features of the condition is profuse and or intractable vomiting [12, 13]. The patient may also have a history of self-medication with absorbable alkalis [14, 15]. Other symptoms and signs are in keeping with those of traditional DKA.

Diagnostic challenges

DKALK, being one of the conditions in the spectrum of metabolic disorders, though common in presentation, often goes without being recognized by practitioners. Alkalosis may be present in several children and adults with DKA when the serum bicarbonate and pH are relatively normal [10]. Since many factors can alter the acid-base milieu in a background of straightforward features of hyperglycemia, increased AG, presence of ketones, and an appropriately decreased bicarbonate [10, 16], it is highly likely that a concomitant primary alkalosis will be missed if the values are not strikingly unusual [10]. There is also the possibility of gastroparesis, an autonomic dysfunction seen in poorly controlled DM that can pose a dilemma in achieving a precise diagnosis [7]. Thus, a diagnosis of DKALK requires patience, attention to history, particularly, of intractable nausea and vomiting, biochemical values, and a step forward to calculate the DR (though not always necessary) between the changes in the AG divided by the changes in serum bicarbonate. A correct diagnosis of DKALK is crucial because it could be potentially dangerous to treat hyperglycemic patients with alkali if their condition is otherwise ketoalkalosis instead of ketoacidosis which is not uncommon although the likelihood of this scenario is rare as the use of alkali is almost never indicated in the management of DKA/DKALK.

Risk factors and predisposing conditions

Infection is the most frequent precipitating cause of DKA and DKALK globally, accounting for 30–50% of cases. Most infections are caused by pneumonia and urinary tract infections. Psychological stress, non-compliance with insulin therapy, and concurrent diseases (e.g., surgery, trauma, myocardial ischemia, pancreatitis) are additional triggering reasons [17]. To reiterate, the most prominent clinical feature of DKALK is vomiting, with the depletion of potassium, chloride, and hydrogen ions. Self-medication with absorbable alkaline substances may also contribute to alkalosis [12].

Comparison with other diabetic emergencies

DKA usually manifests with acidaemia, however, it may occur as an alkalaemia in strange presentation with diuretics, intractable vomiting, and hyperaldosteronism [6].

Although signs of DKA (acidosis or alkalosis) might appear for several days prior to the development of ketoalkalosis or ketoacidosis, the condition often manifests itself within less than 24 hours. The history of the hyperglycaemic hyperosmolar state (HHS) spans several days to weeks. In addition, persons living with type 1 diabetics who are younger and slimmer tend to experience DKA, and persons living with type 2 diabetes who are older and obese are more likely to experience HHS [18]. Physical manifestations include Kussmaul breathing, elevated respiratory rate, fruity breath from acetone in diabetic keto-alkalosis and ketoacidosis, and indications of dehydration accompanying hypotension. Though fairly common in HHS, confusion is an uncommon manifestation of DKA. It is important to look into possible explanations as in HHS high serum osmolality (> 340 mOsm/kg) correlates better with confusion than blood glucose does [18]. A substantial proportion of patients with DKA also exhibit hyperosmolality and are classified under the combined condition known as DKA-HHS [19].

Another diabetic emergency is euglycemic diabetic ketoacidosis (EDKA). EDKA, is a tetrad comprising metabolic acidosis, increased AG, ketonemia or ketonuria, and normal blood glucose levels (< 200 mg/dL) [14]. Triggered by states like fasting, this condition presents a significant diagnostic challenge due to the euglycemic state concealing the presence of underlying DKA. The normal blood glucose levels can be misleading, masking the critical metabolic disturbances characteristic of DKA and thereby complicating timely diagnosis and appropriate intervention [14].

Diagnostic approaches

DKALK is a severe and potentially life-threatening complication of DM, characterized by hyperglycemia, ketosis, and metabolic alkalosis [6, 18]. Timely and accurate diagnosis is crucial for effective management and prevention of complications. Thus, we foray into the diagnostic strategies for DKA, focusing on laboratory tests and imaging techniques.

Laboratory tests

1. Blood glucose levels: Elevated blood glucose levels (> 250 mg/dL) are a defining feature of DKA and are typically assessed using a glucometer or laboratory assay [19].
2. Serum ketones: Measurement of serum ketones, particularly 3-hydroxybutyrate in confirming ketosis, a critical aspect of DKA [13].
3. Arterial blood gas (ABG) analysis: ABG analysis reveals metabolic acidosis, characterized by a decreased pH (< 7.3), reduced bicarbonate levels (< 15 mEq/L), and an increased AG (> 12 mEq/L) [20].
4. Electrolyte levels: Evaluation of serum electrolytes, including potassium, sodium, and chloride, is essential to identify electrolyte imbalances like hyperkalemia or hyponatremia [21].
5. Renal function tests: Assessment of renal function through blood urea nitrogen (BUN) and creatinine levels assists in detecting renal impairment, which can complicate the management of DKA [13].

Imaging modalities

1. Chest X-ray (CXR): CXR may be conducted to investigate potential precipitating factors of DKA, such as pneumonia or pulmonary edema, which can worsen respiratory distress [22].
2. Abdominal ultrasound: Abdominal ultrasound can help in evaluating concurrent conditions like pancreatitis or cholelithiasis, which may present similar symptoms to DKA or contribute to its development [13].
3. Computed tomography (CT) scan: In severe cases of DKA, CT imaging may be necessary to assess for cerebral edema, a rare but life-threatening complication characterized by altered mental status and focal neurological deficits [23].
4. Magnetic resonance imaging (MRI): MRI can be employed to conduct a comprehensive assessment of cerebral edema and distinguish it from various other intracranial disorders [22, 23].

Ultimately, the identification of DKALK requires a blend of clinical assessment, laboratory examinations and imaging techniques. Timely detection of DKA using suitable diagnostic methods is essential to promptly commence treatment and decrease the negative health outcomes linked with this metabolic disorder.

Clinical management

Treatment of DKALK does not differ from the conventional management of DKA. There are five mainstays of DKA management: fluid resuscitation and maintenance, hyperglycemia correction, electrolyte replacement, treating the precipitating cause, and supportive care [13, 15].

It is however essential to maintain strict vigilance for any concomitant disease process, such as infections, cerebrovascular accident, myocardial infarction, sepsis, or deep venous thrombosis [15]. Underlying or concomitant infections is one of the commonest precipitating factors of DKALK in the setting of DKA, in susceptible individuals [13]. Diagnosing it and other possible causes is central to the management and recovery of DKA patients.

Fluid resuscitation

There is universal agreement that the most important initial therapeutic intervention in keto-alkalosis, like in ketoacidosis, is appropriate fluid replacement followed by insulin administration [24].

The main aims for fluid replacement are as follows [24]:

1. Restoration of volume loss.
2. Excretion of ketone bodies.
3. Correction of electrolyte imbalance and alkalemia.

As it stands, the bulk of the available literature regarding fluid therapy is based on consensus guidelines and expert opinions [25]. Normal saline is recommended as the initial IV fluid replacement. Initial IV fluid replacement starts with 0.9% sodium chloride at a rate of 15–20 mL/kg (about 1–1.5 L) over one hour [25, 26]. Thereafter, the rate and type of fluids are determined by assessment of the stability of the clinical state [26].

Electrolyte replacement

DKA is associated with a significant total body deficit of serum electrolytes, especially potassium, sodium, and chloride [24–26]. Particular attention should be paid to potassium correction in the alkalotic state as hypokalemia is a common finding. In a case study, it was reported that adding potassium to an IV saline solution aids in quickly reversing the alkalotic state [27].

The alkalosis is usually corrected with the treatment of the precipitating condition, as IV fluids improve tissue perfusion and renal function, thereby increasing the excretion of organic acids [28]. However, bicarbonate-based therapy has been disputed in several randomized control trials and is strictly contraindicated in the management of DKALK [29].

Correction of hyperglycemia

Insulin therapy is a crucial component of DKALK management as it reduces hepatic gluconeogenesis and suppresses ketogenesis. Continuous insulin infusion (CII) is recommended and widely accepted as the standard of care for the treatment of DKA. IV regular insulin infusion has a rapid (15 min) onset of action and allows for titratable drug administration to match changing glucose levels [30].

Long term management

Revision of the patients' insulin and hyperglycaemic medications is central to the long-term care for DKA patients. Education and follow-up on adherence reduce the risk of missed or wrong dosing, which is one of the commonest precipitants of DKA [15, 30]. Continuous follow-up of patients can help to minimize adverse

outcomes. Preventive measures include patient counseling, education, and laying down instructions for the patient to present to the physician as early as possible.

Case studies

Literature review of notable cases

DKALK has courted interest in current literature as a rare manifestation of diabetic emergencies, characterized by metabolic alkalosis rather than the typical acidosis seen in DKA [6]. Notable case studies have highlighted the clinical significance of this condition, often occurring in patients with complicating factors such as severe vomiting, alcohol abuse, or concurrent diuretic therapy [14].

The purpose of this literature review is to bring to awareness and remembrance the incidences of DKALK and the treatment approach employed in each circumstance.

One notable case demonstrated the diagnostic challenge posed by DKA, where a patient presented with severe vomiting and metabolic alkalosis, initially misdiagnosed as gastrointestinal illness [15]. Another case study underscored the importance of recognizing DKA in patients with unexplained metabolic alkalosis, leading to timely intervention and improved outcomes [16].

Table 2 summarises some notable reported case studies of DKA.

Table 2. Notable studies of DKA

Study (year)	Study design	Case presentation
Nanavati et al. (2018) [6]	Case series	This case series examined six patients with DKA, all presenting severe nausea and vomiting.
Jaramillo et al. (2020) [14]	Case series	The case series examined instances of DKA presenting with elevated pH levels, contrary to the typical acidic pH associated with DKA. They reported three cases of DKA with paradoxical alkalosis, emphasizing the importance of recognizing this atypical presentation to avoid misdiagnosis and delay in treatment. The study underscores the need for clinicians to consider DKA even in cases with alkalotic pH, especially in diabetic patients with metabolic derangements. Early recognition and management are crucial to prevent complications and improve patient outcomes.
Kumar et al. (2018) [15]	Literature review	A case of a 25-year-old female with DKA exhibiting intractable vomiting, alkalotic pH, and high AG.
Brill et al. (2024) [16]	Case report	Another case report highlighted a 52-year-old female with insulin-dependent diabetes mellitus type 2 who presented with abdominal pain, nausea, and vomiting, which are common symptoms of DKA.
Svart et al. (2015) [7]	Case series	A case series involving six patients with DKA, three of such cases presented with keto-alkalosis in patients with type 1 diabetes mellitus, all presenting severe symptoms like nausea and vomiting and two of them had severe GES-treated gastroparesis. All patients had high levels of 3-OHB and a high AG.

GES: gastric electrical stimulation; 3-OHB: 3-hydroxybutyrate; DKA: diabetic ketoacidosis; AG: anion gap

These meld of case reports and studies emphasize the need for heightened clinical suspicion and a comprehensive understanding of DKA as a potential "dark horse" among diabetic emergencies. Furthermore, they highlight the importance of tailored management strategies addressing both the underlying precipitating factors and the metabolic derangements unique to DKA. Continued research efforts are enjoined and warranted to refine diagnostic criteria, optimize therapeutic approaches, and enhance early recognition of DKA, ultimately improving patient outcomes in this challenging clinical scenario.

Implications for clinical practice

The implications of DKALK in clinical practice demand attention and are significant, emphasizing the need for heightened awareness and tailored management strategies. Recognition of DKALK as a distinct entity from DKA is crucial, as it presents with metabolic alkalosis rather than acidosis [2, 6]. Clinicians must maintain a high index of suspicion, particularly in patients with atypical presentations or complicating

factors such as severe vomiting, alcohol abuse, or diuretic use. Prompt diagnosis and appropriate management are essential to prevent potentially life-threatening complications [6]. Furthermore, healthcare providers should ensure comprehensive evaluation and treatment addressing both the underlying precipitating factors and the metabolic abnormalities unique to DKA. Continued research efforts are necessary to refine diagnostic criteria and therapeutic approaches, ultimately optimizing clinical outcomes for affected individuals [14].

Risk assessment

Risk assessment of DKALK involves recognizing predisposing factors such as severe vomiting, alcohol abuse, or concomitant diuretic use, which can precipitate this condition [6]. Additionally, patients with poorly controlled diabetes or a history of insulin non-compliance are at increased risk [7]. Clinicians should maintain a high index of suspicion in these individuals and consider DKALK in the differential diagnosis of diabetic emergencies. Timely recognition and intervention can mitigate the risk of severe complications associated with DKALK.

Research gaps

The entity of DKALK is readily misdiagnosed and is probably more common than generally recognized [13]. This has been attributed to the factors that alter the acid-base ecosystem in the presence of ketonemia and hyperglycemia [16]. The unavailability of striking clinical criteria for diagnosis, and the paucity of literature on the subject has left golf in the perception of DKALK [13, 14]. Continued research efforts are necessary to refine diagnostic criteria and therapeutic approaches to optimize clinical outcomes [14, 15].

Advances in DKALK diagnosis and management

Huggins et al. [9] proposed a revision of the diagnostic criteria for DKALK to identify cases, facilitate prompt management and reduce misdiagnosis [9, 13]. The proposed diagnostic criteria (an extension of the existing accepted criteria) posits that when the elevated DR is above 1.2 or when the bicarbonate is variably elevated, the diagnosis is DKALK until proven otherwise. The DR is a ratio between the rise in the AG (> 12) and the drop in bicarbonate (< 18 mEq/dL) [9].

Conclusions

DKALK is a misnomer albeit a not-so-uncommon scenario. DKALK is a state in which there are circulating ketone bodies in the presence of alkalosis. An outstanding feature of DKALK is intractable vomiting [11, 12] that may have been preceded by intake of absorbable alkali [9]. Most frequently precipitated by infection [17], it is straightforward to diagnose with rapid availability of electrolytes, pH, glucose, and ketone tests, although it remains essential to calculate the AG and DR as well as have an awareness of the full clinical picture [9]. The management involves fluid resuscitation, restoration of euglycemia and electrolyte balance, treating the precipitant, and managing concomitant disease processes. A review of the patient's antidiabetic medications, thorough risk assessment as well as education and follow-up on adherence to prescribed medications are necessary measures to consider for an optimal treatment outcome. Overall, a high index of suspicion despite atypical presentation is required to identify DKALK and improve clinical outcomes as highlighted in case reports [15, 16]. Further research is advocated as we chart the course of diabetology and construct a standardized approach toward clinical management.

Abbreviations

AG: anion gap

DKA: diabetic ketoacidosis

DKALK: diabetic ketoalkalosis

DR: delta ratio

HHS: hyperglycaemic hyperosmolar state

Declarations

Author contributions

PA: Conceptualization, Writing—original draft, Writing—review & editing, Validation. NM, SB, EO, AE, EE, AOE, ASA, CBO, and PNO: Writing—original draft, Writing—review & editing. All authors gave approval to the final submission.

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The authors declare no conflicts of interest.

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