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# Diabetic Ketoacidosis

**Rachael Proumen[1], Runa Acharya[1,2*]**

[1]SUNY Upstate Medical University, Syracuse, USA
[2]Joslin Diabetes Center, Syracuse, USA
Email: *acharyar@usptate.edu

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## Abstract

Diabetic ketoacidosis (DKA) is an acute metabolic disorder that occurs in those with Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) which presents with persistent hyperglycemia (≥250 mg/ dL) leading to a high anion gap metabolic acidosis with ketosis in the setting of either a relative or absolute insulin deficiency. Evaluation for the precipitating cause of DKA, such as trauma, infection, pump malfunction or medication non-compliance is essential. While DKA can be life-threatening, and hospitalizations for DKA are on the rise, adverse outcomes are minimal if promptly treated with aggressive fluid resuscitation, adequate insulin therapy and close monitoring of electrolytes. Prevention of future episodes of DKA is reliant upon adequate patient and caregiver education with a focus on treatment strategies in acute illness or with travel. The aim of this article is to provide a comprehensive overview of the epidemiology, clinical presentation, pathophysiology, treatment and prevention of DKA.

## Keywords

Diabetes Mellitus, Diabetic Ketoacidosis, Management

## 1. Introduction

Diabetic ketoacidosis (DKA) is an acute metabolic disorder which occurs in the presence of prolonged hyperglycemia due to the absence of insulin which leads to a significant increase in the amount of circulating ketone bodies, leading to ketoacidosis. DKA can develop in patients with Type 2 diabetes mellitus (T2DM) in the setting of relative insulin deficiency as well as in Type 1 diabetes mellitus (T1DM) due to relative or absolute insulin deficiency. In T1DM, DKA tends to occur at the onset of disease but may also occur because of lack of insulin either from withdrawal or omission due to a variety of factors not limited to but including pump malfunction or misuse, increased insulin requirements during

acute illness as well as social, economic, or psychiatric burdens [1]-[15]. Common triggers for the development of DKA and relative insulin deficiency in T2DM include infections, trauma, myocardial infarction, stroke, congestive heart failure, use of steroids as well as lack of adjustment of regimen in pregnancy and other conditions [1]. Use of sodium/glucose co-transporter 2 (SGLT2) inhibitors in patients with T2DM has also been associated with increased incidence of DKA and a subsequent FDA issued advisory regarding their use [16].

## 2. Epidemiology

A report published by the Centers for Disease Control and Prevention analyzed hospitalizations with DKA as the primary discharge diagnosis between 2000 and 2014 revealed a slight decrease in age-adjusted rates for hospitalization with DKA from 2000 to 2009 (1.1% annually), however this rate significantly increased by 54.9% from 2009 to 2014 and was consistent among both sexes and all age groups (<45, 45 - 64, 65 - 74, and ≥75 years), with rates highest in persons aged < 45 years [17].

The increase in the number of hospitalizations for DKA from 2000 (101,621) to 2014 (188,950) may be attributed to lower threshold for hospitalization (*i.e.* less severe DKA), increase in the number of patients with euglycemic DKA, and increased prevalence of diabetes in the population [17]. Despite the increased number of hospitalizations for DKA, the overall case fatality rates decreased among the same time period [17]. The Centers for Disease Control and Prevention recently published a 2016 update which revealed a crude-rate of hospital discharges for hyperglycemic crisis as 9.1 per 1000 adults with diabetes [17].

DKA occurs in patients with both T1DM and T2DM, although most clinicians associate DKA more commonly with T1DM. Studies regarding first-episode of DKA show that it occurs more often in those with T1DM (~65% - 70% of patients) rather than those with T2DM (30% - 35% of patients) [18]-[23]. Mortality due to DKA or its complications is rare in both children and adults, despite its serious and life threatening nature. The rate of mortality in patients presenting with hyperglycemic crisis (DKA and hyperosmolar hyperglycemic non-ketotic syndrome) in 2009 was reported to be only 0.02% in those patients with diabetes, younger than 45 years or age and 0.014% in older adults with diabetes [24]. Children experiencing cerebral edema during DKA occurred in 0.3% - 1% of episodes and edema accounted for 57% - 87% of all deaths due to DKA [25] [26]. [27] Patients at the extremes of age including geriatric patients are among those at the highest risk for complications due to DKA and mortality is increased with each subsequent decade of life [28]-[34]. Fortunately, pharmacological advances in insulin formulations, management protocols and improvements in insulin administration, closer monitoring of hemodynamic and metabolic parameters has led to a significant decrease in mortality from DKA, especially amongst the elderly [31].

## 3. Pathogenesis

Insulin is the major player in fuel homeostasis via its effects in the liver, muscle and adipose tissue. Insulin stimulates glycogen synthesis and conversion of free fatty acids (FFA) into triglycerides, thus fostering energy storage [34] [35]. Insulin decreases fuel expenditure via inhibiting gluconeogenesis, glycogenolysis and lipolysis, including triglyceride catabolism which leads to fewer circulating FFA and thus substrates for ketogenesis (**Figure 1**) [34] [35] [36]. Counter-regulatory hormones which oppose the action of insulin include glucagon, catecholamines, cortisol and growth hormone. Glucagon opposes the effects of insulin on fuel stores; glucagon's actions are inhibited by insulin, FFA and ketones, while it is stimulated by amino acids, catecholamines and cortisol. Glucagon's main action is to stimulate glucose production in the liver by means of both glycogenolysis and gluconeogenesis. Other counter-regulatory hormones (catecholamines, cortisol, growth hormone), aid in the glucagons' effects on protein, carbohydrate and lipid metabolism (**Figure 2**) [34] [35] [36]. The deficiency of insulin and subsequent increase in counter-regulatory hormones including glucagon ultimately results in stimulation of lipolysis and FFA release which is later converted into ketone bodies, chiefly acetoacetate and beta hydroxybutyrate, in the liver (**Figure 3**) [34] [35] [36].

The accrual of ketone bodies in circulation leads to the development of an elevated anion gap metabolic acidosis (pH < 7.2), leading to respiratory compensation resulting in deep, rapid respirations described as "Kussmaul" respirations, which promotes a compensatory respiratory alkalosis in attempt to bring pH back towards the normal range (**Figure 3**) [34] [35] [36].

The successful operation of most tissues in the body requires glucose as an essential substrate. Most organs and tissues additionally require insulin for glucose entry, with the exception of the central nervous system, red blood cells and the renal medulla. In DKA with a relative or absolute insulin deficiency, tissues are unable to utilize glucose, relying on ketones as an alternative fuel source [34] [35] [36].

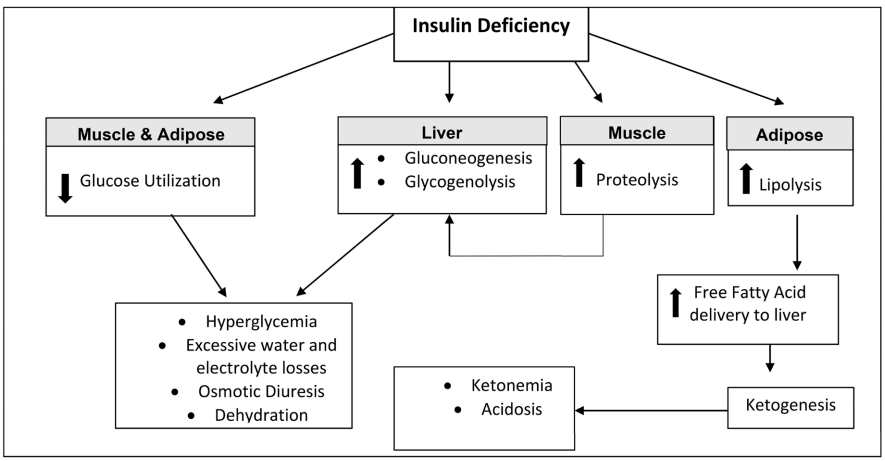


**Figure 1.** Pathogenesis of DKA.

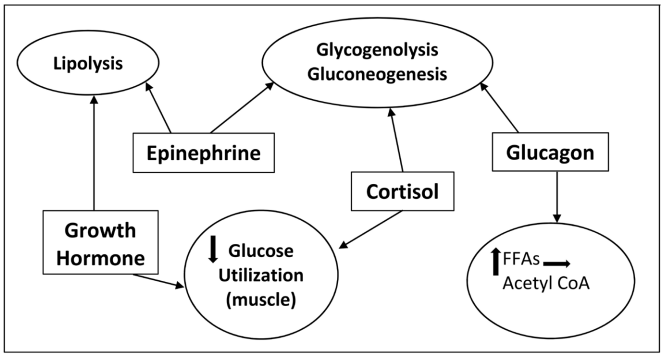


**Figure 2.** Counter-regulatory Hormones. Absolute insulin deficiency leads to a rise in the counter-regulatory hormones: Epinephrine, Cortisol, Growth Hormone and Glucagon. The key hormone is glucagon; actions of the counter-regulatory hormones are opposite to those of insulin.

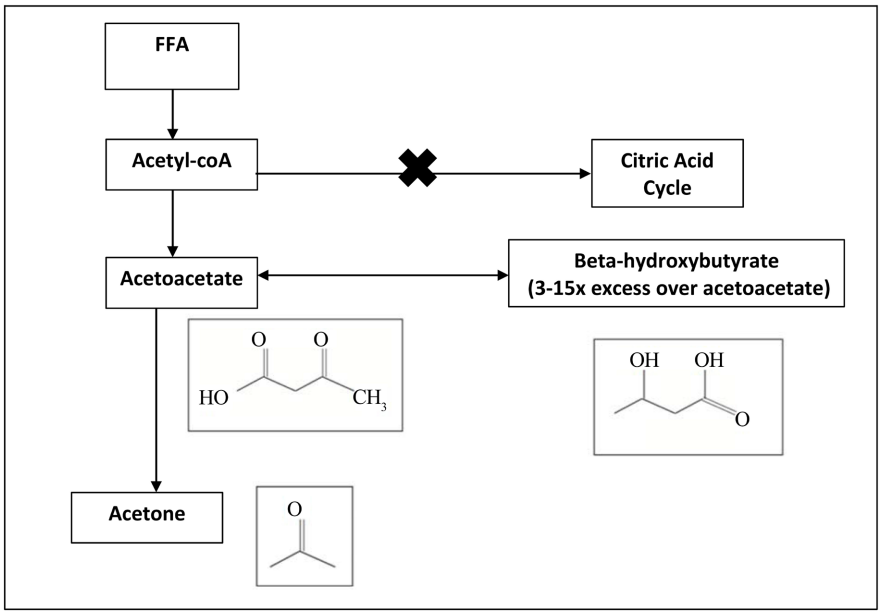


**Figure 3.** Ketone Production. DKA leads to increased lipolysis in adipose tissue which causes release of free fatty acids (FFA). FFAs then undergo beta-oxidation in the liver to form acetyl-CoA. Typically, acetyl-coA would then enter the Citric Acid cycle, however in DKA, intermediates (mainly oxaloacetate) have been depleted by entry into the gluconeogenesis pathway. Acetyl Co-A accumulation then causes increased ketone production and ketoacids.

Marked hyperglycemia in DKA causes an increase in serum osmolality leading to a fluid shift from the intracellular to the extracellular component. This fluid shift then signals the cerebral thirst center to increase fluid intake to maintain fluid balance between the extra- and intracellular compartments. Ketoacidosis-induced nausea and vomiting in the setting of this osmotic diuresis compounded by inability to communicate or ambulate to achieve adequate hydration during critical illness subsequently leads to worsening of dehydration, hyperosmolality and diuresis. Sizable fluid losses then lead to decreased renal blood flow

causing less glucose excretion which therefore promotes a greater elevation in plasma glucose and thus osmolality [37] [38] [39].

High anion gap metabolic acidosis is not the only acid-base disturbance that can be seen in DKA. The presence of other contributing acid-based disorders is established by comparing the difference between the patient's anion gap and the normal anion gap (ΔAG) to the difference between normal serum bicarbonate and patient's serum bicarbonate ($\Delta HCO_3^-$). In a complete DKA without additional acid/base disturbances, the ΔAG is approximately equal to $\Delta HCO_3^-$. If the ΔAG is less than $\Delta HCO_3^-$, there is a greater decline in serum bicarbonate than expected compared to the size of increase in the anion gap. In this circumstance, there is often another measured anion contributing, leading to hyperchloremic acidosis in the presence of the anion gap metabolic acidosis in DKA. Dehydration can cause decreased renal perfusion and may lead to renal injury with the development of a hyperchloremic tubular acidosis. Hyperchloremic tubular acidosis is one of the most common causes of normal anion gap acidosis with concurrent DKA as an additional fall in serum bicarbonate is due to further buffering of an acid that does not contribute to the anion gap.

Likewise, if the ΔAG > $\Delta HCO_3^-$ this suggests the bicarbonate did not decrease as much as expected in the presence of an elevated anion gap. This can be explained by the concurrent presence of metabolic alkalosis, often induced from dehydration and vomiting as well as other processes that increase the serum bicarbonate such as primary hypercortisolism, hyperaldosteronism or compensatory metabolic alkalosis in presence of chronic respiratory acidosis in patients with chronic lung disease. Occasionally an elevated anion gap metabolic acidosis may occur due to the accrual of multiple measured and/or unmeasured anions; e.g. lactic acidosis in presence of septic shock, acute myocardial infarction or diminished tissue perfusion from severe dehydration or critical illness (**Table 1**).

## 4. Clinical Presentation

The acute metabolic derangements of DKA occur quickly and typically happen within 24 hours of absolute insulin deficiency. Patients with T1DM then may have a gradual decline with progression of symptoms over time. However, in clinical practice, DKA is often the initial manifestation of diabetes, especially in children with T1DM, possibly due to lack of recognition of illness by patients and caretakers [40]-[46]. DKA is rarely the initial manifestation of T1DM or latent autoimmune diabetes of adults (LADA) in teens and adults [47]-[52]. These patients generally present with hyperglycemia without evidence of ketosis, as they recognize symptoms of polyuria, polydipsia and weight loss and seek earlier evaluation and treatment. Patients diagnosed with LADA are often initially misdiagnosed as T2DM, resulting in successful management with lifestyle interventions and oral medications, without insulin for a short period of time. Unfortunately, hyperglycemia often recurs within 6 - 12 months as conservative measures fail and most patients ultimately require long-term insulin administration.

**Table 1.** High anion gap metabolic acidosis and the delta gap.

| $\text{Anion Gap}(AG) = \left[Na^+\right] - \left[Cl^- + HCO_3^-\right]$ | |
|---|---|
| $\Delta AG = \Delta HCO_3^-$ | Pure high anion gap metabolic acidosis |
| $\Delta AG < \Delta HCO_3^-$ | High anion gap metabolic acidosis PLUS additional non-anion gap metabolic acidosis (*i.e.* RTA) |
| $\Delta AG > \Delta HCO_3^-$ | High anion gap metabolic acidosis PLUS concurrent metabolic alkalosis (*i.e.* vomiting, hypercortisolism, hyperaldosteronism, contraction alkalosis) |
| $\Delta AG \gg \Delta HCO_3^-$ | High anion gap metabolic acidosis PLUS primary respiratory alkalosis (*i.e.* severe lactic acidosis, septic shock, etc.) |

In T2DM, the onset of DKA is often preceded by a prodrome of symptoms of poor glycemic control (polyuria, nocturia, polydipsia, weight loss) for the preceding days or months, unless acutely triggered by severe illness or infection. Rapid occurrence of symptoms of abdominal pain, nausea, vomiting, muscle cramps, respiratory distress heralds the onset of ketonemia and frequently occurs about 24 - 48 hours prior to presentation. Often, patients mistake their gastrointestinal symptoms as a separate gastrointestinal disorder that precipitates DKA.

The clinical presentation of patients in acute DKA reveals hyperventilation, ketotic breath, tachycardia, profound dehydration, orthostasis, abdominal pain and sometimes hypothermia and/or impaired consciousness or coma [33]. Elderly patients or those at extremes of age are more susceptible to changes in mental status, which correlate more so with marked increases in serum osmolality rather than acidosis. It is known that in the geriatric population a serum osmolality ≥ 340 mOsm/L can induce a markedly altered mental state, including confusion, convulsion, and coma. [53] During the recovery of DKA, a hyperchloremic acidosis may occur and persist, oftentimes more profoundly in patients with T2DM manifesting DKA than in patients with T1DM (**Table 2**).

The diagnosis of DKA requires a high anion gap metabolic acidosis in presence of elevated serum ketones (beta-hydroxybutyrate, acetoacetate, or acetone) in addition to hyperglycemia (≥250 mg/ dL). DKA can be classified into mild, moderate, or severe depending on clinical presentation and level of acidosis (**Table 3**). Hyperglycemia alone nor ketonemia or ketoacidosis alone is sufficient for diagnosis. Historically, testing for ketoacidosis was performed by checking the urine for ketones via the nitroprusside reaction. However, this only detects acetoacetate and not beta-hydroxybutyrate, the primary ketone present in DKA, often present in 3 - 5 times excess of other ketones [46]. Serum testing of beta-hydroxybutyrate is more sensitive and specific than urine ketones and thus is the preferred ketone for rapid diagnosis of DKA. The advent of urine ketone sticks and blood capillary point-of-care glucose meters that can also measure ketones has been instrumental for patients to utilize at home in times of illness

Table 2. Differences in DKA in T1DM & T2DM.

| Type 1 Diabetes Mellitus (T1DM) | Type 2 Diabetes Mellitus (T2DM) |
|---|---|
| Majority of cases (65% - 70%) | 30% - 35% of total DKA cases |
| pH ≤ 7.2 | pH > 7.2 |
| BMI ≤ 27 kg/m$^2$ | BMI > 27 kg/m$^2$ |
| Less time to achieve urine without ketones (~29 hours) | More time to achieve urine without ketones (~36 hours) |
| Infection as a precipitating factor (21.6%) | Infection as a precipitating factor (48.4%) |

Table 3. Classification of DKA severity.

| | MILD | MODERATE | SEVERE |
|---|---|---|---|
| Arterial pH | 7.25 - 7.30 | 7.00 - 7.24 | <7.00 |
| Serum Bicarbonate (meq/L) | 15 - 18 | 10 - 15 | <10 |
| Anion gap (meq/L) | 10 - 12 | 12 - 14 | >15 |
| Mental status | Alert | Alert/drowsy | Stupor/coma |

and likely reduces hospitalizations in adults when combined with advice by telephone [46]. Confirmation of acidosis was traditionally done via arterial blood gas sampling however in recent years there has been a transition to largely utilizing venous blood gas for assessment of acidosis as pH is largely comparable [46] [54].

Patients who present to the hospital after treatment with insulin may have milder hyperglycemia but will still possess significant ketoacidosis. There are numerous causes of ketoacidosis other than DKA, due to alcohol use as well as pancreatic involvement, and are important in the differential [55] [56] [57] [58]. The differential diagnosis of DKA includes various other types of metabolic acidosis (**Table 4**) that leads to ketosis and/or ketoacidosis [35] [36] [55] [56] [57] [58]. Important differentials to consider include alcoholic ketoacidosis, starvation ketosis and pancreatic ketoacidosis in the setting of severe acute pancreatitis. In pancreatic ketoacidosis, a positive association has been shown between the serum anion gap, pH and serum lipase levels (**Table 5**) [57] [58].

## 5. Management of DKA

DKA management is centered on aggressive fluid resuscitation, IV insulin administration, electrolyte repletion and correction and treatment of the underlying precipitant of DKA.

**Fluid Resuscitation.** Marked fluid losses occur in patients with DKA, up to approximately 6 - 9 L in adults (**Table 6**). Fluid losses should be aimed to be replaced within 24 - 36 hours, with approximately half given in the first 8 - 12 hours [59]. A current approach recommends rapid infusion of 0.9% sodium chloride (normal saline) at a rate of 15 - 20 ml/kg (1 - 2 L) for the first hour, followed by a rate at 250 ml/hr. When the blood glucose declines to under 250 mg/dL, the IV fluids are changed to a dextrose-containing fluid, such as 5% dex-

trose with 0.45% sodium chloride (normal saline) [59]-[64]. Additional electrolyte solutions may need to be added to the IV fluids, administered orally, or via nasogastric tube in those with difficult IV access secondary to volume depletion.

**Table 4.** Differential diagnosis of metabolic acidosis.

| High Anion Gap Metabolic Acidosis | Non-Anion Gap Metabolic Acidosis |
|---|---|
| **Common Causes** | **Low Potassium** |
| • Lactic Acidosis<br>• Ketoacidosis<br>• Acute kidney injury<br>• Chronic kidney disease<br>• Ethylene glycol poisoning<br>• Methanol poisoning<br>• Salicylate overdose/poisoning | • Renal Tubular Acidosis<br>• GI losses/Diarrhea<br>• Ureteral diversions<br>• Surgical drainage or fistula<br>• Post-hypocapnic acidosis |
| **Uncommon Causes** | **Normal or High Potassium** |
| • Diethylene glycol poisoning<br>• Propylene Glycol poisoning<br>• 5-oxoproline acidosis<br>• d-lactic acidosis | • Renal tubular acidosis<br>• Early renal failure<br>• Hydronephrosis<br>• Hypoaldosteronism<br>• Drug-induced<br>• Addition of inorganic acids<br>• Sulfur toxicity<br>• Cholestyramine<br>**Other**<br>• Excessive fluid administration/expansion acidosis<br>• Cation exchange resin |

**Table 5.** Laboratory findings in acute pancreatitis. Serum lipase concentrations, anion gap $\left[Na^{+}-\left(Cl^{-}+HCO_{3}^{-}\right)\right.$ and arterial pH values in 18 subjects with acute pancreatitis divided into three groups: $K_0$ with neither ketonuria nor ketonemia, $K_1$ with ketonuria alone without ketonemia, and $K_2$ with both ketonuria and ketonemia.

| Group | No. of Subjects | Serum Lipase (u/L) | Anion Gap (nm/L) | Arterial pH |
|---|---|---|---|---|
| Neither ketonuria nor ketonemia | 5 | 304 ± 22 | 11.6 ± 1.3 | 7.42 ± 0.03 |
| Ketonuria without ketonemia | 6 | 438 ± 64* | 17.7 ± 1.4* | 7.33 ± 0.03* |
| Both ketonuria and ketonemia | 7 | 779 ± 110$^{\ddagger=/}$<br>(23 - 190)$^{\$}$ | 27.6 ± 2$^{\ddagger=/}$<br>(12 - 15)$^{\$}$ | 7.27 ± 0.02$^{\ddagger=/}$<br>(7.35 - 7.45)$^{\$}$ |

* $P < 0.01$ vs. $K_0$; $^{\ddagger}$ $P < 0.001$ vs. $K_0$; $^{=/}$ $P < 0.01$ vs. $K_1$; $^{\$}$ Normal range in parenthesis.

**Table 6.** Fluid and electrolyte losses in DKA.

| | |
|---|---|
| **Water** | 100 ml/kg (60 - 110) |
| **Sodium** | 6 meq/kg (5 - 13) |
| **Potassium** | 5 meq/kg (4 - 6) |

**Insulin Administration.** As an essential treatment in DKA, insulin acts to inhibit glycogenolysis and gluconeogenesis and promotes glucose uptake by the peripheral tissues, thereby lowering the serum glucose level. Insulin also inhibits lipolysis and triglyceride breakdown, thus reducing the substrate, such as FFA, therefore limiting further ketoacidosis. [65] [66]

An important tenet in the administration of insulin in DKA is that it must only be given when the serum potassium is greater than 3.3 mEq/L and should be initiated after initial fluid resuscitation. If fluids and electrolytes are not properly resuscitated, insulin will act to cause a shift of fluid from the extracellular space back into the cells leading to intravascular dehydration and likely persistent hypotension. Simply giving insulin to reduce the plasma glucose without appropriate administration of fluids may lead to persistence of acidosis via induced renal tubular acidosis by means of suppression of aldosterone and plasma renin activity.

Insulin administration should enable a gradual decline in the plasma glucose level and improvement of ketoacidosis. While administering insulin, blood glucose should be monitored hourly via a point-of-care glucose meter with a goal of reducing serum glucose at a rate of 10% per hour. IV is the preferred route of insulin administration [65]-[76]. Other routes of administration, such as intramuscular or subcutaneous can have decreased absorption in critical illness and are thereby less effective. The use of IV insulin also allows for adjustments to rate and ability to provide additional boluses as necessary to achieve desired blood glucose level. Various types of insulin have a similar serum profile when given intravenously [67] [77].

Prior to the discovery of insulin, DKA was often fatal; however, now the mortality rate is about 1% in most hospitals if treated appropriately. Initially management of DKA was focused on small doses of insulin alone without significant fluid resuscitation, however in the mid 20th century, standard treatment of DKA shifted to high-dose insulin infusions [78]. In the 1970s, milestone studies revealed that better outcomes were achieved with low-dose insulin regimens as well as aggressive fluid replacement and thus that became the standard of care [78].

The current standard of practice recommends an initial insulin regimen that is weight based (0.1 unit/kg), with an IV insulin bolus followed by continuous infusion typically at a rate of 0.1 unit/kg/hour [72] [73]. Some studies however have called into question the need for bolus versus continuous insulin infusion alone at two different hourly rates [71] [72]. Kitabchi *et al.* evaluated the efficacy of an insulin priming dose followed by continuous insulin infusion versus continuous infusion alone [74]. The study had three groups: 1) 12 patients with priming dose of IV regular insulin 0.07 units/kg body weight with subsequent infusion of regular insulin at 0.07 units/kg/hour; 2) 12 patients without a priming IV dose, on continuous IV infusion of regular insulin at 0.07 units/kg/hour; and 3) 13 patients without a priming dose on an IV infusion of regular insulin at 0.014 units/kg/hour (double the rate of group 2). While there was not a signifi-

cant difference in time to reach desired blood glucose < 250 mg/dL between groups, numerous patients who did not receive a priming dose did require supplemental insulin to achieve goal of initial serum glucose reduction by 10% [72]. Wagner et al suggested that a lower insulin dose (0.5 - 4 units/hour) may be as effective as current recommended dose of 0.1 units/kg/hour, however the time to resolution of ketoacidosis was longer in these patients with likely longer duration to achieve desired serum glucose level [75].

A limiting factor of these studies [73] [74] [75] is the relatively small sample size and only a mild-to-moderately high (<500 mg/dL) blood glucose level, which makes it difficult to draw conclusions. Bradley and Tobias conducted a retrospective study on DKA management over a 10-year-period in children admitted to pediatric intensive care unit [76]. This retrospective study compared two protocols, 1) administration of IV bolus dose of insulin 0.24 ± 0.27 units/kg body weight followed by continuous infusion of insulin versus 2) continuous insulin infusion alone. Similar to previous studies, a longer duration of therapy was required in order to achieve the desired blood glucose value as well as a greater time to resolution of DKA in those with continuous insulin infusion alone [75]. Thus, we recommend that insulin therapy should be individualized depending on the severity of hyperglycemia and ketoacidosis. As expected, a patient with a blood glucose value of 330 mg/dL may be effectively managed by continuous insulin infusion alone versus a patient with a blood glucose of 950 mg/dL will likely require IV bolus of insulin followed by infusion to achieve desired effect.

Blood glucose values should be monitored hourly and the rate of the insulin infusion should be adjusted accordingly. The insulin rate can be adjusted per the following formula: Units of regular insulin/hour = (glucose − 60) × 0.01 or 0.02. Per the American Diabetes Association (ADA), rate of IV insulin should be gradually reduced and when blood glucose reaches ≤ 200 mg/dL, subcutaneous insulin should be initiated, when at least two of the following criteria are met: serum anion gap <12 mEq/l (or local laboratory's upper limit of normal), serum bicarbonate ≥ 15 mEq/L, arterial blood pH > 7.30, and consuming oral intake [1].

Prior to discontinuation of IV insulin, there should be at least 1 - 2 hours of overlap with subcutaneous insulin. Overlapping subcutaneous and IV insulin prevents a rapid decline in insulin levels and recurrence of hyperglycemia and possibly ketosis [65]-[76] [79] [80] [81] [82]. When selecting the appropriate maintenance insulin therapy in diabetes, it is important to mimic physiologic insulin secretion, which is done by using basal plus prandial insulin dosing [83]. Basal insulin ensures normoglycemia during the fasting state as well as controls hyperglycemia between meals, whereas short-acting insulin works to limit postprandial glycemic elevations. Current basal insulin regimens in use include insulin glargine and insulin detemir as well as intermediate-acting NPH insulin [83] [84] [85] [86] Total daily insulin dosage is typically allocated into 50% basal insulin and 50% rapid- or short-acting insulin, which is then divided into three

mealtime doses.

When choosing a subcutaneous insulin regimen after resolution of DKA, those with a prior established diagnosis of T1DM who were optimally treated at home, can be resumed on their home subcutaneous insulin regimen once tolerating oral intake [1]. Patients with newly diagnosed T1DM without prior treatment with insulin should be initiated on a basal-bolus insulin regimen with multiple daily subcutaneous insulin injections, at a dose at 0.5 - 0.6 units/kg per day, and adjusted as needed until optimal dose is identified. There are various basal insulins to choose from including insulin detemir or insulin glargine, however utilizing insulin detemir may be associated with less glycemic control, increased number of daily injections to achieve adequate control and subsequently increased cost in those with T1DM, thus insulin glargine is preferred [87]. As an example, a 60 kg female may need a total daily dose of 30 units of insulin, half of which (15 units) will be basal insulin (*i.e.* insulin glargine) and the other half (15 units) would be rapid-acting insulin (*i.e.* insulin aspart) separated into three 5 unit dosages given with each meal. An alternative to this regimen would be to provide mealtime insulin based on carbohydrate counting and administering a rapid acting bolus of insulin based on carbohydrate intake. Management with a basal-bolus regimen prevents marked hyperglycemia and/or wide excursions in blood glucose levels and has been shown to be more effective than a subcutaneous sliding-scale regular insulin regimen alone given every 6 hours, thus a basal-bolus regimen in strongly recommended [80] [81] [82].

Patients with T2DM can be initiated on their current inpatient insulin regimen but will require close outpatient follow-up to reassess the need for alterations (or discontinuation) of insulin regimen, addition of oral hypoglycemic agents and education on lifestyle modification.

## 6. Electrolytes

The osmotic diuresis that occur secondary to hyperglycemia during DKA contributes to major electrolyte losses, of which the major electrolytes depleted are sodium and potassium (**Table 6**). Other electrolytes are also lost, including chloride, phosphate and magnesium. Serum sodium values during DKA may either be low or high, and may be falsely low due to intracellular shift in setting of hyperosmolarity. Thus, the serum sodium should be "corrected" when hyperglycemia is present. While there is some debate on how best to correct this, the most common formula is as follows: Corrected Serum sodium = Measured serum Sodium + 0.016 × (Serum Glucose (mg/dL) − 100).

Likewise, the osmotic diuresis in DKA also depletes total body potassium levels. Interestingly, serum potassium levels can be quite variable at presentation. High serum potassium levels can occur due to insulin deficiency and acidosis, leading to a shift of potassium from the extracellular to intracellular space. Alternatively, the severe depletion of total body potassium due to osmotic diuresis can also cause a low or normal potassium upon presentation. Treatment with

fluid administration and IV insulin causes an influx of potassium, magnesium and phosphate into the cells, thus leading to the development of a decline in the electrolytes serum concentrations [37] [38] [39] [88]. Aggressive fluid resuscitation with normal saline will cause increased renal perfusion which will promote urinary excretion of chloride, potassium, magnesium, and phosphate [37] [38] [39] [89], thus frequent monitoring of electrolytes, especially potassium, is imperative as hypokalemia can induce cardiac arrhythmias and even death.

Typically, in DKA there is a striking total body potassium deficit, on average about 3 - 5 mEq/Kg body weight though may be as large as 10 mEq/kg body weight in some patients. Potassium should be supplemented when the serum level declines below 5 mEq/L with a goal serum potassium between 4 - 5 mEq/L. [1] IV administration of potassium at a rate of 10 meQ/hour is preferred, although in resource-limited settings oral/enteral supplementation is suitable; supplementation via nasogastric tube is an acceptable alternative if patient is unable to consume oral intake due to persistent nausea and vomiting.

Some have suggested the use of bicarbonate therapy in DKA, however the use of bicarbonate for management of acidosis has not illustrated improved patient outcomes and may be harmful, inducing hypokalemia, delayed improvement in hyperosmolarity and ketosis as well as rebound metabolic alkalosis [89] [90] [91]. In patients who present with an initial pH < 7.0, treatment with IV bicarbonate has not been shown to shorten duration of hospitalization or accelerate resolution of acidosis. In children, bicarbonate therapy has been noted to be a risk factor for cerebral edema [92]. Similarly, altered mental status in adults can be exacerbated if bicarbonate is given [92] [93]. Given the numerous potential adverse effects with bicarbonate therapy in DKA, it is only recommended for use when the serum pH is less than 6.9 in attempt to facilitate a timely correction to pH of 7.0 - 7.1 and/or in the presence of a concurrent lactic acidosis [1].

The pursuit of an underlying source that triggered DKA and its appropriate management is imperative once treatment for DKA has been initiated (**Table 7**). There are several possible adverse outcomes that should be expected during the management of DKA with administration of aggressive IV fluid resuscitation, insulin and monitoring of electrolytes (**Table 8**). Common complications include altered electrolytes (*i.e.* hypokalemia), hyperchloremic metabolic acidosis, fluid overload, cerebral edema, and acute respiratory distress syndrome [93]. The profound dehydration that exists in DKA can cause hyperviscosity and ultimately lead to vascular events including coronary and mesenteric thrombosis, peripheral vascular occlusion, myocardial infarction and stroke. Cerebral edema is thought to be secondary to rapid glucose lowering and typically occurs in both the very young and very old.

## 7. Prevention

Prevention of future episodes of DKA is centered on patient education provided by physicians, nurses and diabetic educators to the patient and the caregivers.

Table 7. Common precipitants of DKA.

| |
|---|
| Non-compliance with insulin or inadequate insulin treatment |
| New-onset diabetes (20% - 25%) |
| **Acute Illness:**<br>• Infection (30% - 40%)<br>• Stroke<br>• Myocardial infarction<br>• Acute pancreatitis |
| **Medications:**<br>• Clozapine, Olanzapine<br>• Cocaine<br>• Lithium<br>• Terbutaline |

Table 8. DKA Complications.

| Complications due to DKA | Complications due to DKA Management |
|---|---|
| • Acute vascular occlusion-myocardial infarction, cerebrovascular accident, mesenteric, etc.<br>• Acute renal failure<br>• Acute pancreatitis<br>• Erosive gastritis<br>• Acute gastric distention | • Cerebral edema<br>• Hypokalemia<br>• ARDS<br>• Fluid overload<br>• Hyperchloremic metabolic acidosis<br>• Hypoglycemia<br>• Acute line infection or thrombosis<br>• Recurrence of DKA upon transfer out of ICU |

Patients and caregivers should be instructed in frequency of monitoring of blood glucose and administration of rapid-acting insulin to achieve recommended blood glucose goals. The ADA recommends a preprandial capillary plasma glucose range of 80 - 130 mg/dL and a peak postprandial capillary plasma glucose level of <180 mg/dL [94] [95] [96] [97].

It should be noted that during acute illness rapid-acting insulin should not be withheld, especially if patients have poor oral intake. Blood glucose should be monitored at an increased frequency in times of reduced oral intake and/or significant gastrointestinal distress and rapid-acting insulin should be given based on current blood glucose values. It is essential to have close monitoring of blood glucose as ongoing severe hyperglycemia may ultimately develop into hyperglycemic non-ketotic state or DKA.

Patients using an insulin pump should be educated that in times of illness or during pump malfunction, they may need to discontinue the pump and administer basal/bolus insulin. Patients should have the requisite supplies at home in back-up and be knowledgeable about how to perform long- and rapid-acting subcutaneous insulin injections, if necessary. Education should also be provided on when to seek medical care, *i.e.* >5% loss of body weight, marked tachypnea (respiratory rate > 36/min), persistently elevated blood glucose, altered mental

status, uncontrolled fever, nausea or vomiting [1]. Emphasis should be made on prompt medical evaluation in times of illness to prevent progression of illness and development of hyperglycemic emergencies such as DKA.

## 8. Conclusion

DKA is an acute metabolic disorder characterized by persistent hyperglycemia in the setting of ketosis and/or ketoacidosis that occurs in patients with both T1DM and T2DM. The diagnosis requires swift recognition of the disorder and appropriate evaluation for underlying cause to prevent adverse outcomes. Management should be focused on aggressive fluid resuscitation, adequate insulin therapy and close monitoring and replacement of electrolytes. Prevention of future episodes is reliant upon adequate patient and caregiver education on routine diabetes management as well as during times of stress such as acute illness or during travel. While DKA can be life-threatening, with the appropriate treatment mortality is minimal in adults.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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