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The evolution of diabetic ketoacidosis: An update of its etiology, pathogenesis and management

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ABSTRACT

The prognosis of diabetic ketoacidosis has undergone incredibly remarkable evolution since the discovery of insulin nearly a century ago. The incidence and economic burden of diabetic ketoacidosis have continued to rise but its mortality has decreased to less than 1% in good centers. Improved outcome is attributable to a better understanding of the pathophysiology of the disease and widespread application of treatment guidelines. In this review, we present the changes that have occurred over the years, highlighting the evidence behind the recommendations that have improved outcome. We begin with a discussion of the precipitants and pathogenesis of DKA as a prelude to understanding the rationale for the recommendations. A brief review of ketosis-prone type 2 diabetes, an update relating to the diagnosis of DKA and a future perspective are also provided.

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1. Background

Diabetic Ketoacidosis (DKA) is a potentially fatal metabolic complication of uncontrolled diabetes mellitus. In his first clinical description of diabetes mellitus in the 2nd Century A.D. Aretaeus gave a detailed account of subjects with hyperglycemic crises [1], but it was Julius Dreschfeld, a German pathologist who further characterized DKA in his lecture to the Royal College of Physicians in London in 1886. He reported on the main ketones, acetoacetate and β-hydroxybutyrate, and their chemical determination [2]. The incidence of DKA in developed countries is comparable with estimated annual incidence rate of 13.6 and 14.9 per 1000 type 1 diabetic patients in the UK [3] and Sweden [4] respectively and 13.4 per 1000 subjects younger than 30 years in the US [5]. Hospital admission for DKA has increased by about 75% over the last two decades in the USA from about 80,000 in 1988 to 140,000 in 2009 [6].

DKA was invariably fatal until the discovery of insulin in the 1920s; however, DKA related mortality has reduced significantly over the years. In the US, the age-adjusted mortality rate decreased 64% from 48.4 per 100,000 diabetic population in 1980 to 17.3 per 100,000 diabetic population in 2009 [6]. Mortality was also reported to be low in the Europe with one UK institution recording no deaths amongst 46 DKA patients between 1997 and 1999 [3]. Overall, the mortality in adults in the UK and USA is less than 1% [3,6], but may be higher than 5% in the elderly and patients with severe co-morbid conditions [7,8]. DKA remains a leading cause of mortality in children and young adults with type 1 diabetes [9,10]. Morbidity and mortality from DKA remain high in developing countries, with incidence of about 80 per 1000 diabetic admissions and mortality rate of 30% in Kenya [11] and incidence of 41.7 per 100,000 population and mortality rate of 11.7% in Libya [12]. DKA is economically burdensome with an average length of stay of 3.4 days, DKA is responsible

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Table 1 – Diagnostic criteria and typical total body deficits of water and electrolytes in diabetic ketoacidosis.

	Mild	Moderate	Severe
Diagnostic criteria and classification			
Plasma glucose (mg/dl) [+]	>250	>250	>250
Arterial pH	7.25–7.30	7.00- < 7.24	<7.00
Serum bicarbonate (mEq/L)	15–18	10- <15	<10
Urine ketone [*]	Positive	Positive	Positive
Serum ketone [*]	Positive	Positive	Positive
Effective Serum Osmolality [**]	Variable	Variable	Variable
Anion Gap [***]	>10	>12	>12
Mental Status	Alert	Alert/Drowsy	Stupor/Coma
Typical deficits			
Total Water (L)	6		
Water (ml/kg) [δ]	100		
Na + (mEq/kg)	7–10		
Cl- (mEq/kg)	3–5		
K+ (mEq/kg)	3–5		
PO4 (mmol/kg)	5–7		
Mg++ (mEq/kg)	1–2		
Ca++ (mEq/kg)	1–2		

[+] Euglycemic DKA has been reported.
[*] Nitroprusside reaction method.
[**] Calculation: Effective serum osmolality: 2[measured Na + (mEq/L) + glucose (mg/dl)/18 [mOsm/kg].
[***] Calculation: Anion Gap: $(Na^+)-(Cl^- + HCO_3^-$ (mEq/L) [normal =12 ± 2].
[δ] Per kg of body weight. Data adapted from ref [19].

for about half a million hospital days per year and an estimated annual direct and indirect cost of 2.4 billion USD [6,13].

DKA consists of the biochemical triad of hyperglycemia, ketonemia and metabolic acidosis (table 1) resulting from absolute or relative insulin deficiency in the presence of an increase in counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone). Although DKA is typically characterized by hyperglycemia, euglycemic DKA has been reported in patients with type 1 diabetes who were vomiting, fasting or had been treated with insulin prior to presentation, and in pregnancy [14,15]. Additionally, there has been recent reports of euglycemic DKA in subjects treated with sodium–glucose cotransporter 2 (SGLT2) inhibitors [16,17].

DKA is more common in subjects with type 1 diabetes; but can also occur in type 2 diabetes, especially in patients of African or Hispanic descent [18]. About 35% of DKA cases in the USA in 2006 occurred in people with type 2 diabetes [6]. Similarly, a study from Sweden noted that type 2 diabetes accounted for 32% of 26 episodes of DKA recorded in that Caucasian population, furthermore, in 50% of patients with type 2 diabetes, DKA was the initial manifestation of diabetes [4].

2. Precipitating Factors

A diligent investigation for the precipitating illness should be made in all cases of DKA, as effective treatment of these conditions contributes to better outcome. Mortality in DKA is usually related to the associated co-morbidity rather than the biochemical derangement. Omission or inadequate dosing of insulin and infection are the most common precipitants of DKA [19]. More recent reports may suggest that omission of insulin, which is preventable, is becoming a more frequent precipitant of DKA than infections. Intercurrent illness such as cerebrovascular accident, pancreatitis, myocardial infarction, trauma, and drugs are well known to trigger DKA. Drugs that affect carbohydrate metabolism such as corticosteroids, thiazides, and sympathomimetic agents like dobutamine and terbutaline as well as atypical antipsychotic agents could precipitate DKA in susceptible individuals [20]. Subjects with type 1 diabetes using amphetamine-like analogs may be predisposed to DKA due to elevated catecholamine levels [21]. Emerging data suggests Sodium-Glucose Cotransporter 2 Inhibition may increase the risk of DKA, prompting the FDA to issue a warning in this regard in May 2015 [16,22]. Twenty cases of DKA were reported with SGLT-2 inhibitors in patients with diabetes in the FDA Adverse Event Reporting System (FAERS) between March 2013 and June 6, 2014. The mechanism of DKA in subjects treated with SGLT2 is not known with certainty; putative mechanisms include reduced insulin dose, glucagon secretion and decreased excretion of ketone bodies [22]. In young patients with type I diabetes, psychological problems complicated by eating disorders may be a contributing factor in 20% of recurrent ketoacidosis. Other factors that may lead to insulin omission and DKA in younger patients include fear of weight gain and hypoglycemia, rebellion against authority and the stress of chronic disease [23]. Cocaine use was reported as an independent risk factor for recurrent DKA in a retrospective study of over 200 cases of DKA [24]. Another study of a large cohort of DKA patients observed that substance abuse especially cocaine but also alcohol and cannabis were associated with recurrent episodes of DKA [25]. A recent report [26], suggested a relationship between low carbohydrate dietary intake and metabolic acidosis. Additionally, mechanical problems with continuous subcutaneous insulin infusion devices (CSII) has also been associated with DKA [27]. Finally, DKA has also been reported as the initial manifestation of previously undiagnosed endocrine conditions like acromegaly [28] and pheochromocytoma [29,30].

3. Ketosis-Prone Type 2 Diabetes

African authors reported about temporary diabetes in adults in the 1960s, subjects who after an episode of DKA could maintain glycemic control for varying periods without insulin therapy [31,32]. More recently, an increasing number of DKA cases with no apparent precipitating factors have been reported in subjects with type 2 diabetes; studies have indicated that about half of previously undiagnosed adult African Americans (AAs) and Hispanic subjects with unprovoked DKA have type 2 diabetes [33–37]. The evidence for type 2 diabetes in these patients include obesity, family history of diabetes, relatively preserved insulin secretion, low prevalence of beta cell autoimmunity, and the ability to discontinue insulin therapy during the period of near-normoglycemia [38–40].

This variant of type 2 diabetes has been referred to as idiopathic type 1 diabetes, atypical diabetes mellitus, Flatbush diabetes, type 1.5 diabetes, and more recently as ketosis-prone type 2 diabetes [18,41]. Ketosis-prone type 2 diabetes was thought to be present in AA alone but has been reported in Caucasians, Hispanics, Chinese, South Asians, and sub-Saharan Africans; AAs and Hispanics have a higher risk than Caucasians [40]. During DKA, subjects with ketosis-prone type 2 diabetes exhibit profound impairment in insulin secretion and action, but they recover beta-cell function and insulin sensitivity after resolution of DKA. Thus they are able to discontinuing insulin therapy within a few months of achieving near-normoglycemia [18,34,35,40]. Predictors of remission include absence of autoimmunity with preserved beta cell function as determined by a fasting C-peptide level of >1.0 ng/dl (0.33 nmol/l) or a glucagon-stimulated C-peptide of >1.5 ng/dl (0.5 nmol/l) [34,40]. Remission is associated with a greater recovery of basal and stimulated insulin secretion; ten years after onset of diabetes, 40% of patients with ketosis-prone type 2 diabetes are still able to maintain glycemic control without insulin therapy [35].

The pathophysiologic reason for acute but transient ß-cell failure is not known with certainty. Postulated mechanisms include glucotoxicity, lipotoxicity and genetic predisposition. Sustained hyperglycemia is known to impair beta cell function and elevated free fatty acid level has been implicated in insulin resistance and inappropriate beta cell response [42,43]. However, subjects with ketosis-prone type 2 diabetes did not show any impairment in stimulated insulin secretion after 20 h of hyperglycemia achieved by glucose infusion [44]. Furthermore, intralipid infusion for 48 h, which increased blood free fatty acid level fourfold did not produce acute beta cell failure [45]. Diminished insulin action in ketosis-prone type 2 diabetes may be mediated through AKT-2. Insulin stimulated phosphorylation and protein expression was found to be reduced in muscle of subjects with ketosis prone type 2 diabetes, defects that improved at the time of remission of hyperglycemia [46]. Immunogenetic studies appear concordant on the lack of autoantibodies preponderance in subjects with ketosis-prone type 2 diabetes [33,38,48]; but reports are conflicting on HLA association. While two studies [33,38] found no association, another study reported association with HLA-DR3 and HLA-DR4 [48]. A few studies have investigated putative candidate genes that may be associated with ketosis-prone type 2 diabetes. A point mutation in the HNF-1 gene was suspected to be marker in AAs [49], but this finding was not replicated in adults of sub-Saharan and Afro-Caribbean descent who instead had high frequency of polymorphism in the transcription factor PAX4 [50]. Furthermore, a higher prevalence of glucose-6 phosphatase deficiency has been reported in subjects with ketosis-prone diabetes and there was a proportional relationship between β-cell functional reserve and erythrocyte glucose-6 phosphatase activity but increased prevalence of glucose-6 phosphatase mutation was not found in these patients [51].

Majority of patients with ketosis-prone diabetes achieve remission but become increasingly insulin dependent over time if treated with lifestyle modification alone. Recurrence of ketosis occurs within 12–24 months in nearly 60% of patients who are treated with lifestyle modification alone [36,40,47]. Small dose sulfonylureas such as glyburide 1.25 to 2.5 mg/day) [47] and glipizide 2.5 mg/day [48] and the thiazolidinedione pioglitazone 30 mg/day [40] have been shown to prolong remission and prevent recurrence of DKA.

4. Pathogenesis

DKA results in abnormal metabolism of carbohydrate, protein, fat and derangement of fluid and electrolyte homeostasis. The fundamental pathogenetic mechanism is a decrease in the net effective action of circulating insulin, in the presence of elevated counter-regulatory stress hormones such as glucagon, epinephrine, norepinephrine, cortisol, and growth hormone. Elevated glucagon level plays a major role in the pathogenesis of DKA but it is not indispensable in the development of this condition as totally pancreatectomized subjects developed DKA when deprived of insulin [52].

4.1. *Carbohydrate Metabolism*

In the presence of decreased net effective action of insulin, hyperglycemia results from increased gluconeogenesis, glycogenolysis and impaired peripheral glucose utilization due to insulin resistance [53,54]. The gluconeogenic enzymes fructose 1,6 biphosphatase, phosphoenolpyruvate carboxykinase (PEPCK), glucose 6 phosphatase and pyruvate carboxylase, are stimulated by increased glucagon:insulin ratio and hypercortisolism resulting in accelerated hepatic glucose production [55] (see Fig. 1). There is also an increase in gluconeogenic precursors such as the aminoacids alanine and glutamine, as a result of protein catabolism; lactate from increased muscle glycogenolysis and glycerol from increased lipolysis [53]. Hepatic gluconeogenesis is the main mechanism for hyperglycemia in ketoacidosis, however, recent studies indicate renal gluconeogenesis may be a contributing factor [56]. Hyperglycemia may be mild in subjects who maintain good renal function, which supports glycosuria; but as the disease process evolves, glucose-induced osmotic diuresis leads to volume depletion and a reduction in glomerular filtration thus impeding further glucose excretion [57].

4.2. *Lipid and Ketone Metabolism*

Reduced effective insulin action and increased concentrations of counterregulatory hormones, especially epinephrine, which activates hormone-sensitive lipase in adipose tissue leads to the increased production of non-esterified fatty acids (NEFA) and glycerol from breakdown of triglycerides in DKA [58]. Glycerol is used as a substrate for gluconeogenesis but the release of NEFA assumes pathophysiological prominence in the liver. NEFA are oxidized to ketone bodies in the liver, a process that is predominantly stimulated by glucagon. They are also used to synthesize diacylglycerol which may contribute to hyperlipidemia and increased very-low-density proteins (VLDL) [59]. Hyperglucagonemia results in ketogenesis via increased hepatic carnitine concentrations and decreased hepatic malonyl CoA, which stimulates carnitine acyltransferase (CAT1), the rate-limiting enzyme in ketogenesis. The clearance of ketone bodies is also impaired in DKA due to low insulin concentrations, increased glucocorticoids, and decreased peripheral glucose utilization [60].

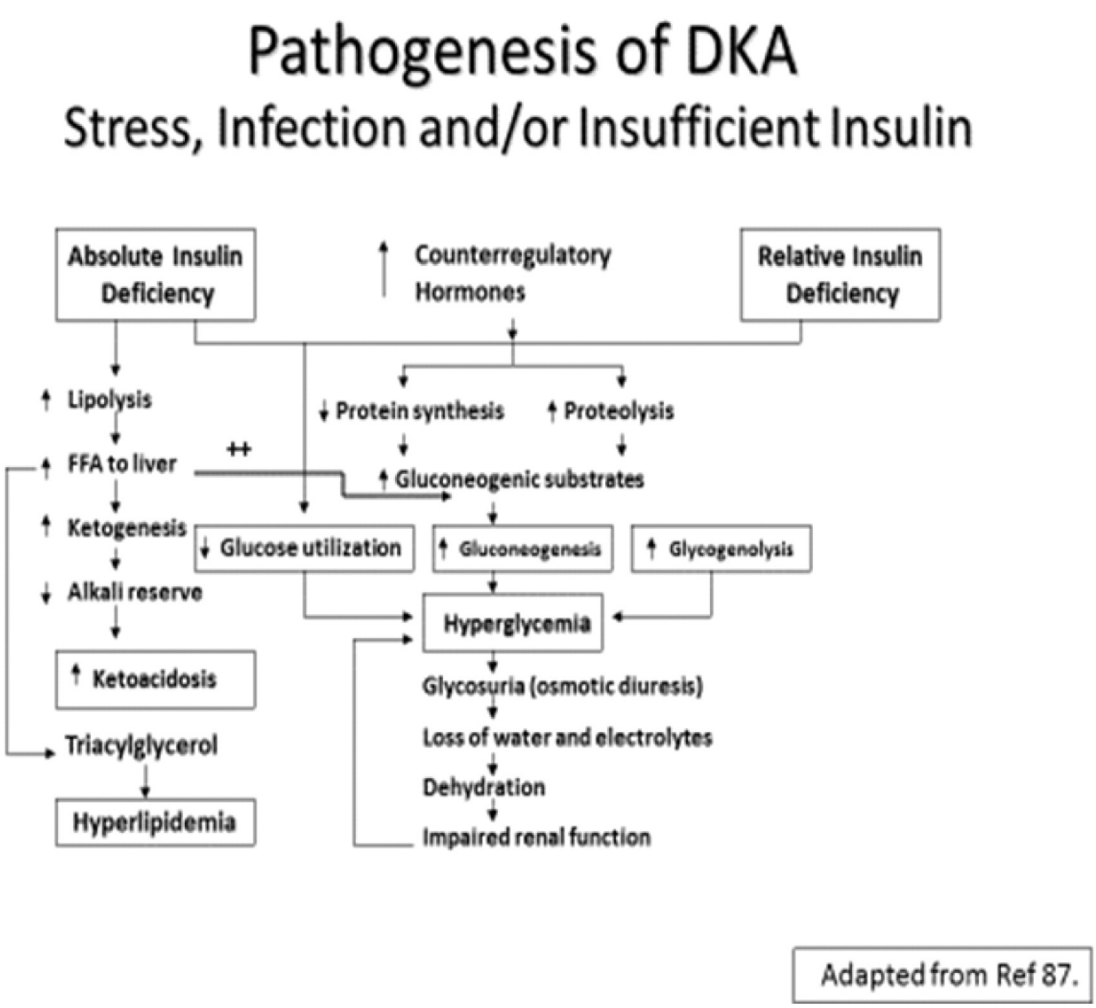

Fig. 1 – Pathogenesis of DKA.

Growth hormone may also play a prominent role in ketogenesis as physiological doses of growth hormone can increase circulating levels of NEFA and ketone bodies. [61] The ketoacids are buffered by extracellular and cellular buffers, resulting in their loss and subsequent anion gap metabolic acidosis. Elevated levels of other organic acids such as D-lactate have been demonstrated in DKA [62,63]; D-lactate has been shown to correlate with acidosis and anion gap in subjects with DKA [62].

4.3. *Water and Electrolyte Disturbances*

Estimated electrolyte deficits in DKA are shown in Table 1.

Osmotic diuresis resulting from hyperglycemia promotes net loss of multiple minerals and electrolytes such as sodium, potassium, calcium, magnesium, chloride, and phosphate. Some of these electrolytes (sodium, potassium and chloride) can be replaced rapidly during treatment, while others may require days or weeks to restore homeostasis [64–66]. Ketoanion excretion results in obligate urinary cation excretion in the form of sodium, potassium, and ammonium salts, which contributes to a solute diuresis. Insulin deficiency per se may also contribute to renal losses of water and electrolytes because of deficient water and salt resorptive effect of insulin in the renal tubule [66].

Abnormalities in serum potassium are common in DKA due to increased plasma tonicity, which results in intracellular water and potassium shifts into the extracellular space. Also, protein catabolism with resultant potassium shifts into the extracellular space, decreased potassium re-entry into the cell secondary to insulinopenia and significant renal potassium losses as a result of osmotic diuresis and ketonuria contribute to potassium dyshomeostasis. Progressive volume depletion leads to decreased glomerular filtration rate and a greater retention of glucose and ketoanions in plasma which elevates plasma tonicity. Thus, a considerable proportion of patients with DKA have concomitant hypertonicity [37,67]. Patients with better oral intake of food, salt and fluid during DKA have better preservation of kidney function, greater ketonuria and lower ketonemia, lower anion gap and less hypertonicity. During treatment with insulin, hydrogen ions are consumed in the metabolism of ketoanion, this regenerates bicarbonate which relieves metabolic acidosis and decreases the plasma anion gap. Therefore, the urinary loss of ketoanions, as sodium and potassium salts, represents loss of potential bicarbonate.

Emerging evidence indicate that hyperglycemic emergencies including DKA are associated with an inflammatory state marked by elevation in proinflammatory cytokines such as

tumor necrosis factor-α, interleukins and C-reactive protein. Also, reactive oxygen species, markers of lipid peroxidation and plasminogen activator inhibitor-1 are elevated [68]. All of these parameters return to normal with resolution of DKA. This inflammatory and procoagulant state may explain the relatively high incidence of thrombotic events in DKA. In-vivo and in-vitro activation of T-cells with emergence of insulin receptors has also been demonstrated [69,70].

5. Diagnosis

5.1. *History and Physical Examination*

DKA evolves rapidly over a short period, usually hours and patients may not be aware of the disease. Symptoms of hyperglycemia such as polyuria, polydipsia, polyphagia and weight loss are usually present. Other symptoms include vomiting, abdominal pain, dehydration, weakness and in severe cases altered mental status. Signs elicited on the physical examination include dehydration shown by poor skin turgor, Kussmaul respirations, and tachycardia. In severely ill patients, hypotension, shock and altered consciousness may be present. Mental status can vary from full alertness to profound lethargy or coma. The pathogenesis of altered sensorium in DKA is not known with certainty, while some studies suggest hyperosmolarity as the origin of altered mentation in DKA[67,71], others indicate acidosis may be the prime determinant of the level of consciousness in these patients [72,73]. However, in a retrospective analysis of over 200 cases of DKA we determined that acidosis was the prime determinant of altered sensorium, but hyperosmolarity played a synergistic role in patients with severe acidosis to precipitate depressed sensorium. Combination of severe acidosis and hyperosmolarity predicted altered consciousness with 61% sensitivity and 87% specificity [74]. Signs and symptoms of the precipitating illness may be present and should be sought in each case. Although infection is a common precipitating factor fever may not be present, patients can be normothermic or even hypothermic due to peripheral vasoconstriction arising from hypovolemia, and low fuel substrate availability. Abdominal pain, which usually correlates with the severity of acidosis and may be confused with acute abdomen in 50–75% of cases [75,76]. In the absence of acidosis, another etiology for abdominal pain should be pursued. Hematemesis could occur in up to 25% of patients, due to gastritis [57].

5.2. *Laboratory Evaluation*

Table 2 summarizes the admission biochemical data in patients with DKA.

A good clinical history and physical examination along with bedside tests such as capillary blood glucose and ketones or ketonuria should clinch a tentative diagnosis of DKA; however, a definitive diagnosis must be verified by laboratory tests. The initial laboratory evaluation of patients with suspected DKA includes determination of plasma glucose, blood urea nitrogen/creatinine, serum ketones, electrolytes (with calculated anion gap), osmolality, urinalysis, urine ketones by dipstick, as well as initial arterial blood gases and complete blood count with differential. An electrocardiogram, chest x-ray and urine, sputum or blood cultures may be clinically indicated. Glycated hemoglobin may be needed to differentiate an acute decompensation from a previously undiagnosed or poorly controlled diabetes. The diagnostic criteria for DKA are shown in Table 1. Accumulation of ketoacids results in an increased anion gap metabolic acidosis. The anion gap is calculated by subtracting the sum of chloride and bicarbonate concentration from the sodium concentration [Na – (Cl + HCO3)]. The normal anion gap was previously reported to be 12 +/– 2 mEq/l, however, most laboratories currently measure sodium and chloride concentrations using ion-specific electrodes, which measure plasma chloride concentration 2–6 mEq/l higher than with prior methods [77,78]. Thus, the normal anion gap using the current methodology is between 7 and 9 mEq/l, therefore, an anion gap >10–12 mEq/l may indicate the presence of anion gap acidosis. DKA is classified as mild, moderate, or severe based on the severity of metabolic acidosis (blood pH, bicarbonate, ketones) and the presence of altered mental status [79].

Arterial blood gas analysis is recommended for the initial evaluation of patient with DKA, but this requires an expensive equipment which may not be available in some institutions; especially in developing countries where the morbidity and mortality from DKA are high. Secondly, arterial blood sampling could be painful and technically difficult. Therefore, studies have investigated the use of venous blood to assess metabolic acidosis in subjects with DKA [79–82]. In a recent analysis of nearly 400 DKA cases we demonstrated that arterial pH could be reliably estimated from serum bicarbonate concentration using the following formula: arterial pH = 6.97 + (0.0163 x bicarbonate), by applying this equation, serum venous bicarbonate concentration of ≤20.6 mEq/L predicted

Table 2 – Admission biochemical data in patients with DKA.

Parameters measured	
Glucose (mg/dl)	616 ± 36
Na + (mEq/l)	134 ± 1.0
K+ (mEq/l)	4.5 ± 0.13
BUN (mg/dl)	32 ± 3
Creatinine (mg/dl)	1.1 ± 0.1
pH	7.12 ± 0.04
Bicarbonate (mEq/l)	9.4 ± 1.4
ß-hydroxybutyrate (mmol/l)	9.1 ± 0.85
Total osmolality (mosm/kg)	323 ± 2.5
IRI (nmol/l)	0.07 ± 0.01
C-peptide (nmol/l)	0.21 ± 0.03
FFA (nmol/l)	1.6 ± 0.16
Human growth hormone (ng/l)	6.1 ± 1.2
Cortisol (ng/l)	500 ± 61
IRI (nmol/l) *	0.09 ± 0.01
C-peptide (nmol/l) +	0.25 ± 0.05
Glucagon (pg/l)	580 ± 147
Catecholamines (ng/l)	1.78 ± 0.4
Anion gap	17

Data are presented as mean ± SEM.
* Immunoreactive insulin.
+ Response to intravenous tolbutamide. Data adapted from ref [86].

arterial pH ≤7.3 with over 95% sensitivity and 92% accuracy. Thus a gas analyzer may not be a necessity for managing most patient with DKA [83]. Another cross-sectional prospective study evaluated the utility of end-tidal carbon dioxide measured by capnography as a surrogate for arterial blood gas in 181 patients suspected to have DKA in the emergency room. Capnography values higher than 24.5 mmHg excluded DKA with a sensitivity and specificity of 90% [84].

Patients with DKA could have leukocytosis, which may be proportional to the severity of acidosis, hypercortisolemia and elevation of catecholamines [85]. However, leukocytosis greater than 25,000/μL may suggest a concurrent infection which warrants further evaluation [86]. The admission serum sodium is usually low because of the efflux of water from the intracellular to the extracellular space in the presence of hyperglycemia. An increase in serum sodium concentration in the presence of hyperglycemia indicates a rather profound degree of water loss. The measured value can be corrected by adding 1.6 mmol/l (1.6 mEq/L) of sodium for every 5.6 mmol/l (100 mg/dl) of glucose above 5.6 mmol/l (100 mg/dl). Measured serum sodium and glucose concentrations may be falsely lowered by severe hypertriglyceridemia in laboratories using volumetric testing or dilution of samples with ion–specific electrodes [87,88]. Unless the plasma is cleared of chylomicrons, pseudonormoglycemia and pseudohyponatremia can occur.

Serum potassium concentration may be elevated because of an extracellular shift of potassium caused by insulin deficiency, hypertonicity, and acidemia [89,90]. Patients with low normal or low serum potassium concentration on admission have severe total-body potassium deficiency and require very careful cardiac monitoring and more vigorous potassium replacement as treatment can lower serum potassium further, thus predisposing to cardiac dysrhythmia. The total body deficit of sodium and potassium might be as high as 500–700 mEq [90,91]. Therefore, treatment with insulin should not be commenced until the serum potassium is greater than or equal to 3.3 mmol/l (3.3 mEq/L). Measured serum creatinine may be falsely elevated due to dehydration or interference with the assay by elevated acetoacetate [92,93]. Serum creatinine should be monitored during hydration and resolution of acidosis.

A significant proportion of patients with DKA may have elevated plasma tonicity, which in the presence of severe acidosis contributes to altered mentation; about 7% of patients may have severe acidosis and hypertonicity and are therefore at the risk of developing altered state of consciousness and poorer prognosis [74]. Perhaps the term Diabetic hyperosmolar ketoacidosis (DHKA) could be applied to this subset of patients. In the calculation of effective osmolality [2[measured Na (mEq/L)] + glucose (mg/dl)/18], the urea concentration is not taken into account because it is freely permeable and its accumulation does not induce major changes in intracellular volume or osmotic gradient across the cell membrane. Elevation in amylase and lipase levels may occur in 16–25% of patients with DKA [94,95]. Although amylase level may correlate with the severity of acidosis in such patients [95], its origin may be the parotid gland [94]. Therefore, pancreatic enzymes may not be specific for the diagnosis of pancreatitis in patients with DKA [96]; hence, patients with elevated serum amylase and lipase and abdominal pain may require imaging to exclude pancreatitis. Ketone bodies are usually measured by the nitroprusside method which detects acetoacetate but not ß hydroxybutyrate (BOHB), the more abundant ketone body. During treatment of DKA, BOHB is converted to acetoacetate, therefore, the follow-up measurement of ketones with the use of nitroprusside is not recommended because the ketones test may show high values which erroneously suggests that the condition of ketonemia is worsening. Newer glucose meters have the capability to measure BOHB, which overcomes this problem. Furthermore, studies have investigated the use of BOHB in the management of DKA and this metabolite is increasingly being used by laboratories to evaluate ketonemia [96].

Drugs that have sulfhydryl groups can interact with the reagent in the nitroprusside reaction, thus giving a false positive result [97], captopril, an angiotensin converting enzyme inhibitor used for the treatment of hypertension and diabetic nephropathy is an important example. Clinical judgment and other biochemical considerations may be relevant in interpreting the value of positive nitroprusside reaction in patients taking captopril who are suspected to have DKA.

5.3. *Differential Diagnosis*

DKA consists of the biochemical triad of hyperglycemia, ketonemia and anion gap metabolic acidosis, each of these components can be seen in other metabolic conditions (Fig 2). Therefore, physical and laboratory evaluation to differentiate other causes of metabolic acidosis is warranted. For example, in alcoholic ketoacidosis (AKA), total ketone bodies are much greater than in DKA with a higher BOHB to acetoacetate ratio of 7:1 versus a ratio of 3:1 in DKA [98]. Patients with AKA seldomly present with hyperglycemia. Patients with poor oral intake could present with mild ketoacidosis, (starvation ketosis), but this may not occur in individuals on prolonged fasting, except they have a problem with ketone metabolism. Thus, patients with starvation ketosis rarely present with serum bicarbonate concentration less than 18 mEq/L, and do not exhibit hyperglycemia. DKA should be distinguished from high anion gap acidosis including lactic acidosis, advanced chronic renal failure as well as ingestion of drugs such as salicylate, methanol and ethylene glycol. Isopropyl alcohol which is commonly available as rubbing alcohol can cause considerable ketosis and high osmolar gap without metabolic acidosis, however, it has a tendency to cause hypoglycemia rather than hyperglycemia. These conditions with their laboratory findings are summarized in Table 3 [99].

6. Treatment

The goals of therapy in DKA are 1) Improvement of circulatory volume and tissue perfusion; 2) Gradual correction of hyperglycemia and hyperosmolality; 3) Correction of electrolyte imbalance, and resolution of ketosis; 4) Identification and adequate treatment of comorbid conditions. The recommended protocol for the treatment of DKA is provided in Fig. 3 [78,100]. Successful treatment of DKA demands frequent monitoring by clinical and laboratory parameters to ensure the goals of therapy are being achieved.

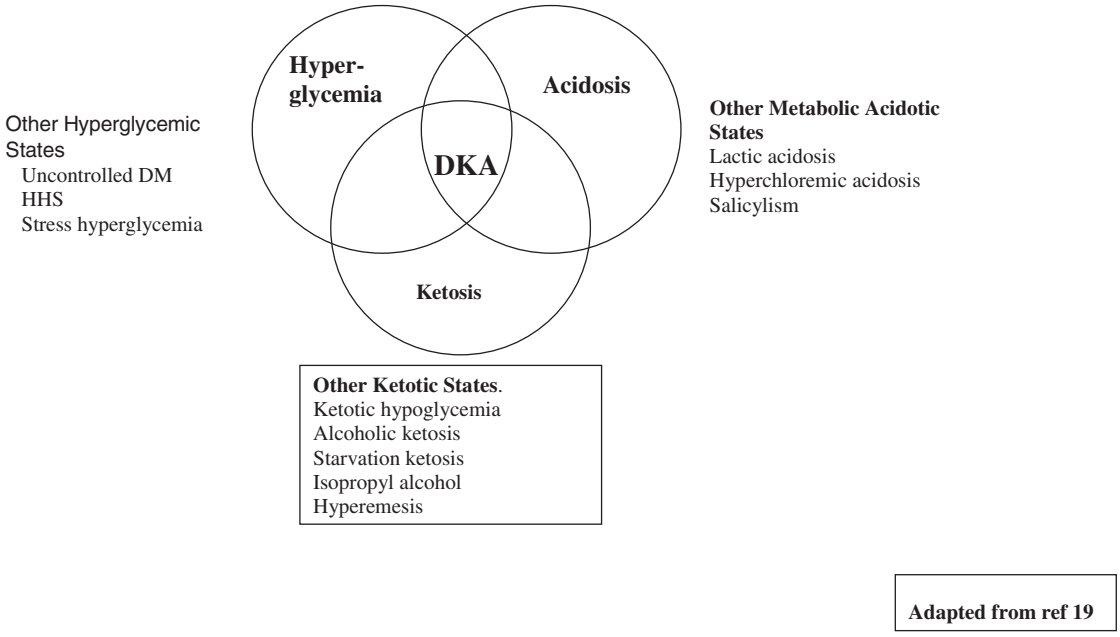

Fig. 2 – Differential diagnosis of DKA. Data adapted from ref [19].

6.1. *Fluids*

DKA is a volume-depleted state [89,101] water deficit may be up to 6 l (Table 1); Initial fluid therapy is aimed at expanding interstitial and intravascular volume and reestablishing adequate renal perfusion. Although the benefits of proper rehydration is unequivocal, the fluid of choice for resuscitating the critically ill patient was a subject of controversy. A prospective study which investigated the effects of hypotonic, isotonic and hypertonic fluids in patients with severe diabetic ketoacidosis reported no significant difference in the volume of fluid retained when solutions of varying tonicity were administered. However, hypertonic fluids worsened hypertonicity, hypernatremia and hyperchloremia [102]. Additionally, some patients treated with hypotonic fluids developed diuresis; hence, rapid repletion of the plasma and extracellular volume with isotonic fluids is indicated in subjects with DKA. Furthermore, there was controversy as to which fluid is superior in the critically ill: colloids such as dextran vs crystalloids such as normal saline. A meta-analysis of prospective randomized studies comparing colloids and crystalloids in critically ill patients reported that colloids were more expensive but did not confer any mortality benefit [103]. Another prospective randomized study investigated the optimal rate of hydration in patients with DKA. Subjects were randomized to receive either 1000 ml/h or 500 ml/h of 0.9% saline solution. Both groups were biochemically similar at baseline and in the rate of resolution of biochemical abnormalities [104]. Lastly, a prospective randomized study which evaluated fluids for maintenance of adequate glycemic level for the resolution of DKA (5% versus 10% dextrose along with continued insulin infusion), found that 10% dextrose was associated with significantly lower level of ketonemia and higher level of hyperglycemia, but did not confer any advantage in the rate of resolution of acidosis [105].

The initial fluid of choice is isotonic saline which should be infused at the rate of 15–20 ml/kg body weight per hour or 1–1.5 l during the first hour. This expands the extracellular volumes. The subsequent choice for fluid replacement depends on the state of hydration, serum electrolyte levels, and urinary output. In general, 0.45% NaCl infused at 4–14 ml/kg/h is appropriate if the corrected serum sodium is normal or elevated; 0.9% NaCl at a similar rate is appropriate if corrected serum sodium is low (See Fig. 3). Adequate fluid replacement is assessed by hemodynamic monitoring (improvement in blood pressure and pulse), measurement of fluid input and output, blood chemistry and clinical examination. Half of the estimated water deficit should be replaced over 12–24 h. An effective serum osmolality >320 mOsm/kg indicates severe dehydration, which would require aggressive fluid replacement therapy. In patients with hypotension, aggressive fluid repletion with isotonic saline should continue until blood pressure is stable. The administration of insulin without fluid replacement in hypotensive patients could worsen circulatory collapse. Hydration in the first hour of therapy before insulin has the following advantages: a) it allows opportunity to obtain serum potassium value before insulin administration, b) it prevents potential deterioration of hypotension, which could occur with the use of insulin without adequate hydration, c) it improves insulin action [106] and may reduce the concentration of counter regulatory hormones and hyperglycemia [107]. Hydration has been shown to reduce blood glucose, BUN, hemoconcentration and potassium concentration without significant reduction in pH or HCO3 concentration [67]. Reduction in blood glucose level is thought to result from osmotic diuresis [93,107]. Energy is required for the metabolism of ketone bodies, therefore, as soon as blood glucose falls below 200 mg/dl, the sodium chloride solution should be replaced with 5% glucose containing saline solution and the rate of insulin infusion should be reduced until acidosis and ketosis

Table 3 – Laboratory evaluation of metabolic acidosis and coma.

	Starvation or high fat intake	DKA	Lactic acidosis	Uremic acidosis	Alcoholic ketosis (starvation)	Salicylate intoxication	Methanol or ethylene glycol intoxication	Hyperosmolar coma	Hypoglycemic coma	Rhabdomyolysis	Isopropropyl alcohol
pH	Normal	↓	↓	Mild ↓	↓↑	↓↑	↓	Normal	Normal	Mild ↓ may be ↓↓	Normal
Plasma glucose	Normal	↑	Normal	Normal	↓ or normal	Normal or ↓	Normal	↑↑ >500 mg/dl	↓↓ <30 mg/dl	Normal	↓
Glycosuria	Negative	++	Negative	Negative	Negative	Negative †	Negative	++	Negative	Negative	Negative
Total plasma ketones*	Slight ↑	↑↑	Normal	Normal	Slight to moderate ↑	Normal or	Normal	Normal or slight ↑	Normal or slight ↑	Normal	↑
Anion gap	Slight ↑	↑	↑	Slight ↑	↑	↑	↑	Normal	Normal or slight	↑↑	↑↑
Osmolality	Normal	↑	Normal	↑	Normal	Normal	↑↑	↑↑ >330 mOsm/kg	Normal	Normal or slight ↑	↑
Uric Acid	Mild (starvation)	↑	Normal	Normal	↑	Normal	Normal	Normal	Normal	↑	Normal
Miscellaneous	False-positive	May give lactate for ethylene glycol	Serum >200 >7 mmol/l	BUN mg/dl	salicylate	Serum levels positive	Serum positive		hemoglobinuria	Myoglobinuria	

resolve. It should be emphasized that the replacement of urinary losses is also important as failure to do this leads to delay in the restoration of sodium, potassium, and water deficits.

6.2. *Insulin Therapy*

DKA was invariably fatal before the discovery of insulin in the early 1920s; with the introduction of insulin, mortality was reduced to less than 50% and subsequently to less than 20% as antibiotics and adequate hydration were incorporated into the treatment of DKA [3,108]. In the 1950s, the mortality of patients treated with high doses of insulin was reported to be less than 10% but in more recent years, the use of standardized treatment guidelines has reduced mortality rate to less than 1% in good centers [3,108]. In the beginning of insulin therapy, small amounts of insulin were used to treat DKA with good results, but high-dose insulin therapy became the standard of care when insulin became more available; between the 1950s and early 1970s, up to 100 U/h or more were given due to perceived insulin resistance, but prospective randomized studies did not show any advantage of high-dose insulin compared with low-dose [108]. Landmark studies in the 1970s established low or physiologic dose regular insulin as the optimal therapy for DKA [109,110]. A prospective randomized controlled trial by Kitabchi et al. investigated the effect of low-dose vs high-dose insulin therapy in 48 patients with DKA [110,110]. The baseline biochemical characteristics were similar in the two arms, which were comparable in the rate of resolution of biochemical defects and the counter-regulatory hormones glucagon and cortisol declined at the same rate in both groups. However, hypoglycemia and hypokalemia were more frequent in subjects treated with high-dose vs physiologic dose insulin (25 vs 0% and 30 vs 4% respectively).

In moderate to severe DKA or DKA with mental obtundation (as defined in Table 1), intravenous regular insulin by continuous infusion is the treatment of choice. Previous treatment protocols have recommended the administration of an initial bolus of 0.1 U/kg followed by the infusion of 0.1 U/kg/h [19,85], however, a more recent prospective randomized trial demonstrated that a bolus is not necessary if patients are given hourly insulin infusion at 0.14 U/kg body wt/h [100]. Low-dose insulin infusion protocols decrease plasma glucose concentration at a rate of 50–75 mg/dL/h. If blood glucose does not fall by 10% in the first hour, an intravenous bolus of 0.14 U/kg should be administered followed by continuous infusion at the previous rate [78]. When the plasma glucose reaches 200 mg/dl, the insulin infusion rate should be reduced to 0.02–0.05 U/kg/h. Also, dextrose should be added to the intravenous fluids at this point. The rate of insulin administration or the concentration of dextrose may be adjusted to maintain blood glucose concentration between 150 and 200 mg/dl until resolution of DKA.

Several prospective randomized open label trials have demonstrated the efficacy and cost effectiveness of subcutaneous rapid-acting insulin analogs (lispro, aspart and glulisine) in the treatment of uncomplicated mild to moderate DKA [111–115]. In one of these studies [111], the patients received subcutaneous insulin lispro at a dose of 0.3 U/kg

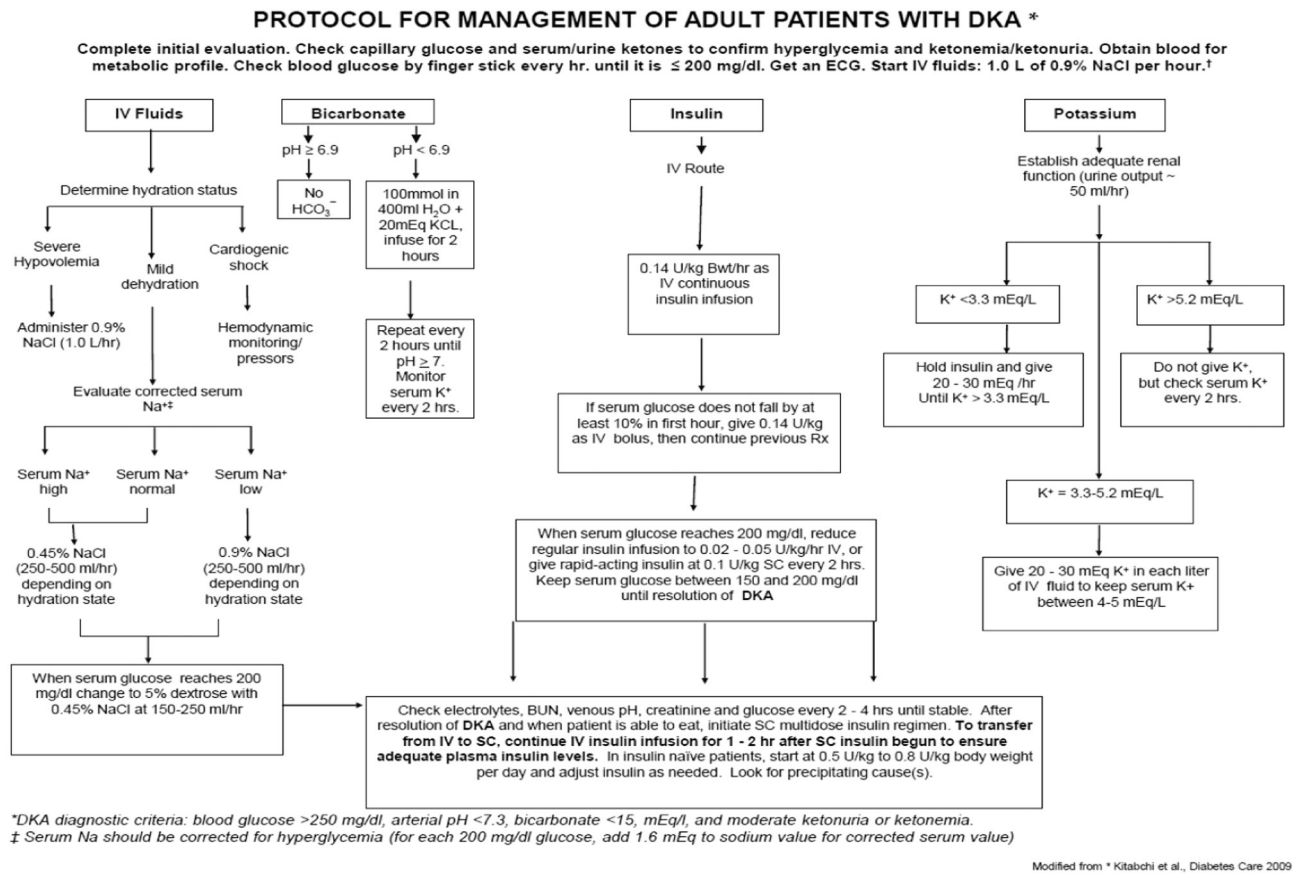

Fig. 3 – Treatment of DKA.

initially, followed by 0.1 U/kg every hour until blood glucose was <250 mg/dl, when insulin dose was decreased to 0.05 or 0.1 U/kg given every hour until resolution of DKA. In the second study [112], insulin aspart was given at an initial dose of 0.3 U/kg followed by 0.1 U/kg every hour until blood glucose was <250 mg/dl when dose was reduced to 0.05 U/kg hourly until resolution of DKA. The second arm of the aspart study administered 0.3 U/kg as a loading dose followed by 0.2 U/kg an hour later and every 2 h until blood glucose was <250 mg/dl. At that time, insulin dose was reduced to 0.1 U/kg every 2 h. In comparison with intravenous regular insulin, there were no differences in the length of hospital stay, total amount of insulin needed for resolution of hyperglycemia or ketoacidosis. Patients treated with insulin analogs were managed in the open medical wards which reduced cost of hospitalization by 30%. In another study which investigated the efficacy of insulin analogs, patients were randomly assigned to receive intravenous regular or glulisine insulin until resolution of DKA [114]. Thereafter, patients treated with regular insulin were transitioned to subcutaneous NPH and regular insulin given twice daily, while subjects treated with glulisine insulin were transitioned to subcutaneous glargine given once daily and prandial glulisine. Both arms were equally effective but patients treated with NPH and regular insulin had a higher rate of hypoglycemia than the glargine and glulisine group (41% vs 15%). Insulin analogs have not been investigated in complicated or severe DKA, therefore, it would be prudent to treat patients with severe DKA, hypotension, anasarca, or associated severe critical illness with intravenous regular insulin in the ICU [78].

Patients with DKA should be treated with regular insulin or insulin analog until resolution. Criteria for resolution of ketoacidosis include a blood glucose <200 mg/dl and two of the following criteria: a serum bicarbonate level ≥ 15 mEq/l, a venous pH >7.3, and a calculated anion gap ≤12 mEq/l. Patients can be transitioned to subcutaneously administered multiple dose insulin when DKA has resolved and they are able to eat. Those previously treated with insulin may be recommenced on their home dose if they had been well controlled. Insulin-naïve patients should receive a multi-dose insulin regimen beginning at the dose of 0.5–0.8 U/kg/day [78]. To prevent recurrence of ketoacidosis in the transition period, insulin infusion should be discontinued 2 h after commencement of subcutaneous insulin. If the patient is unable to eat, intravenous insulin and fluid replacement may be continued. Use of long-acting insulin analogs during the initial management of DKA may facilitate transition from intravenous to subcutaneous insulin therapy. It may also avoid rebound hyperglycemia and ketogenesis, which could occur on discontinuation of intravenous insulin [116]. This hypothesis, which looks plausible has not been verified by prospective studies. A recent pilot study investigated this approach in a prospective, randomized, controlled trial comparing coadministration of insulin glargine and intravenous insulin vs intravenous insulin alone [117]. The outcome was similar in both arms of the study. All patients received intravenous

insulin while the glargine arm received subcutaneous insulin glargine in addition within two hours of diagnosis. Upon resolution of DKA, patients treated with intravenous insulin alone were transitioned to long-acting insulin while daily insulin glargine was continued in the glargine group. During the follow up period, blood should be drawn every 2–4 h for determination of serum electrolytes, glucose, blood urea nitrogen, creatinine, osmolality, and pH. Determination of pH can be done by venous rather than arterial puncture because arterial blood gases are seldomly needed in such patients. An equivalent arterial pH value is calculated by adding 0.03 to the venous pH value [80]. In facilities where blood gas analysis is not available, venous serum bicarbonate could be used to estimate arterial pH. [83]. Ketonemia typically takes longer to resolve than hyperglycemia. Direct measurement of BOHB in the blood is the preferred method for monitoring DKA and is becoming increasingly available [118].

6.3. *Potassium replacement*

Close attention should be paid to repletion of potassium in patients with DKA. Although total-body potassium is depleted [119,120], mild to moderate hyperkalemia is frequently seen in these patients, due to acidosis which displaces potassium from the cell to the extracellular space, proteolysis and insulin deficiency [85]. Insulin therapy, correction of acidosis, and volume expansion would decrease serum potassium concentration. To prevent hypokalemia, potassium replacement should be initiated when serum levels fall below 5.3 mEq/l in patients with adequate urine output (50 ml/h). Generally, 20–30 mEq potassium in each liter of infusion fluid is sufficient to maintain a serum potassium concentration within the normal range of 4–5 mEq/L. Occasionally patients with DKA may present with hypokalemia, especially if they have been vomiting or had been taking diuretics. In such cases, potassium repletion should begin with fluid therapy, and insulin treatment should be delayed until potassium concentration is restored to >3.3 mEq/L to avoid arrhythmias or cardiac arrest and respiratory muscle weakness [78]. A prospective study of 29 consecutive cases of DKA reported normokalemia or hyperkalemia in 82% of the patients, but 63% of them developed hypokalemia in course of treatment, the correction of which required 145 mEq of potassium on the average (59–239 mEq) [102]. Cardiac monitoring would be indicated in subjects with severe hypokalemia.

6.4. *Bicarbonate therapy*

Bicarbonate therapy in DKA is controversial. While some workers believe that insulin therapy would correct ketoacidosis without use of bicarbonate, others argue that severe acidosis is associated with impaired myocardial contractility, cerebral vasodilatation, coma, and gastrointestinal sequelae, which warrants bicarbonate therapy. Prospective randomized studies have demonstrated no benefits of bicarbonate therapy in DKA patients with pH ≥6.9 [121–123]. In a randomized study of 21 adults [121], administration of bicarbonate conferred no benefits in the rate of resolution of DKA or increase in pH or serum bicarbonate concentration in the blood or cerebrospinal fluid. Furthermore, it was observed that the pH level was higher in the CSF than the blood indicating the brain has some protection against severe acidosis. In another randomized study of 32 patients, bicarbonate therapy was associated with delay in the fall of total ketone bodies, blood lactate and lactate: pyruvate ratio [123]. Delay in the resolution of ketosis was also observed in human and animal experiments in another small prospective study [124]. Lastly, a more recent systematic review which investigated the benefits and risks of bicarbonate therapy in DKA reported increased risk of cerebral edema and prolonged hospitalization in pediatric patients but no benefit [125]. No prospective randomized studies investigating the use of bicarbonate in DKA with pH values <6.9 have been reported [78], therefore, the decision to use bicarbonate should be based on the clinical state of the patient. Subjects who are clinically well compensated may not require administration of bicarbonate, while it would be prudent to use bicarbonate in individuals with severe acidosis who may deteriorate without bicarbonate therapy. Adults with pH <6.9 who may deteriorate without bicarbonate therapy may be given 100 mmol sodium bicarbonate in 400 ml sterile water (an isotonic solution) with 20 mEq KCI administered at a rate of 200 ml/h for 2 h until the venous pH is >7.0. If the pH is still <7.0 after infusion, we recommend repeating infusion every 2 h until pH reaches >7.0 [78].

6.5. *Phosphate therapy*

Phosphate moves along with potassium from the intracellular to the extracellular compartment in response to acidosis and osmotic diuresis leads to urinary phosphate loss. Although, whole body phosphate deficits may average about 1.0 mmol/kg of body weight in DKA, serum phosphate at presentation is typically normal or high due to shifts across the cell membrane [126–128]. During insulin therapy, phosphate re-enters the intracellular compartment leading to a fall in serum phosphate concentrations. Adverse complications of hypophosphatemia are uncommon but could occur in severe cases. Potential complications include respiratory and skeletal muscle weakness, hemolytic anemia, and poor cardiac performance [128]. Phosphate depletion may also contribute to decreased concentrations of 2,3-diphosphoglycerate (2,3-DPG), thus shifting the oxygen dissociation curve to the left and limiting tissue oxygen delivery [128]. Prospective randomized studies have shown no benefit of phosphate replacement on clinical outcome in DKA [126,127] and overzealous phosphate therapy may be associated with hypocalcaemia [127]. To avoid the sequalae of hypophosphatemia, careful phosphate replacement may be indicated in patients with cardiac dysfunction, anemia, respiratory depression, and in those with serum phosphate concentration lower than 0.32 mmol/l (1.0 mg/dl). To replace phosphate stores and to avoid hyperchloremia, intravenous potassium repletion can be administered in a ratio of two-thirds potassium chloride and one-third potassium phosphate. The maximal rate of phosphate replacement generally regarded as safe to treat severe hypophosphatemia is 4.5 mmol/h (1.5 ml/h of K_2PO_4) [129].

7. Complications

The most frequent complications of DKA are hypoglycemia and hypokalemia, which result from overzealous treatment with insulin. Hypokalemia may also complicate bicarbonate therapy.

A transient hyperchloremic non-anion gap acidosis could occur in the recovery phase of DKA [130,131]; due to the loss of large quantities of ketoanions. Ketoanions are metabolized with regeneration of bicarbonate, their loss in the urine hinders regeneration of bicarbonate during treatment thus predisposing to acidosis. Administration of intravenous fluids containing chloride that exceeds the plasma chloride concentration and the intracellular shifts of NaHCO3 during correction of DKA also contribute to hyperchloremic acidosis [131]. This complication is usually of little clinical consequence.

Cerebral edema is a rare but serious complication of DKA, occurring in 0.7–1.0% of children with DKA; especially in those with newly diagnosed diabetes. Cerebral edema can also occur in patients with previously diagnosed diabetes and in very young adults under 20 years of age [132,133]. Headache, the earliest symptom of cerebral edema is followed by lethargy and altered sensorium. Neurological deterioration may occur rapidly with seizures, incontinence, pupillary changes, bradycardia, and respiratory arrest setting in as brain stem herniation occurs. Papilledema may be absent if onset is rapid. Mortality rate may be >70% if neurological symptoms are established, with only 7–14% of patients recovering without sequalae. Postulated mechanisms for cerebral edema include osmotically-driven movement of water into the central nervous system when plasma osmolality declines too rapidly during the treatment. [132–135]. A study, which assessed cerebral water diffusion and cerebral vascular perfusion during the treatment of children with DKA using magnetic resonance imaging, reported that cerebral edema was due to increased cerebral perfusion [134]. Another putative mechanism for cerebral edema involves the cell membrane Na+/H+ exchanger, which is activated in DKA. The high H+ level allows more Na + into the cell, which attracts water into the cell leading to edema [136]. The ketone bodies acetoacetate and β-hydoxybutyrate may also play a role in the pathogenesis of cerebral edema [137]. Ketone bodies have been shown to affect vascular integrity and permeability and contribute to edema formation. Measures that may reduce the risk of cerebral edema in high-risk patients include gradual replacement of sodium and water deficits in patients who have hypertonicity and the addition of dextrose to the correction fluid once blood glucose reaches 250 mg/dl.

Hypoxemia and, rarely, noncardiogenic pulmonary edema may complicate the treatment of DKA. Hypoxemia is due to a reduction in colloid osmotic pressure that results in increased lung water content and decreased lung compliance [19]. Patients with DKA who have a widened alveolo-arteriolar oxygen gradient noted on initial blood gas measurement or with pulmonary rales on physical examination appear to be at higher risk for the development of pulmonary edema. Thrombosis including disseminated intravascular coagulation has been reported in DKA [138] and high levels of pro-inflammatory cytokines and plasminogen activator inhibitor-1 (PAI-1) have been demonstrated in DKA, which resolve with insulin therapy and correction of hyperglycemia [68], therefore, prophylactic use of heparin may be indicated.

8. Prevention

Although mortality from DKA is <1%, all course mortality in subjects surviving DKA may be high; a retrospective analysis of over 600 episodes of DKA in nearly 300 patients seen in a hospital in the UK from 2007 to 2012 recorded no inpatient mortality. However, 14% of the patients died within 5 years of follow up and mortality was higher in subjects who had recurrent DKA [139]. Predictors of mortality during follow up included psychological issues, peripheral neuropathy, ischemic heart disease, alcoholism and prior admission to intensive care. Therefore, measures to prevent recurrent DKA should be pursued vigorously. Subjects with diabetes have increased cardiovascular morbidity and mortality; although SGLT-2 inhibitors have been associated with DKA, empagliflozin, an SGLT-2 inhibitor was recently reported to reduce all-cause and cardiovascular mortality in patients with type 2 diabetes at high risk for cardiovascular events [140]. Prospective clinical studies have identified poor adherence to insulin therapy as the major precipitant of DKA in some populations [141,142]. Education of the patient and care giver about diabetes care especially sick day management would be beneficial in preventing DKA. An interventional study in teen age patients with type 1 diabetes, which incorporated frequent outpatient clinics, reported better diabetes control and less diabetes related hospitalization in the intervention group [143]. Again, a home-based psychotherapy program reduced hospital admission for DKA over 24 months in a prospective randomized study of 127 youths [144]. Illicit drug use is associated with recurrent DKA [24,145,146], therefore, rehabilitation should be helpful in drug addicts. A significant proportion of DKA occur in subjects with type 2 diabetes; adoption of healthy lifestyle and maintenance of ideal body weight would contribute in reducing the surging incidence of DKA.

9. Future perspective

Over the years, remarkable improvement has been made in the prognosis of DKA, however, the recent observation of increased all course mortality in survivors of DKA merits a prospective investigation. Furthermore, some questions remain to be answered; the use of bicarbonate in patients with pH < 6.9 is yet to be investigated in a prospective randomized study. The mechanism for the induction of proinflammatory and prothrombotic state in DKA remains unclear. Understanding this pathway may be useful in preventing cardiovascular morbidity associated with hyperglycemic crises. Fast-acting insulin analogs have been shown to be as effective as intravenously administered regular insulin in mild to moderate DKA, but it is not known if subcutaneously administered regular insulin would be equally efficacious in such patients. Using regular insulin by subcutaneous route would be more economical than insulin analogs especially in developing countries. The rising prevalence of DKA could be due to its incidence in patients with ketosis-prone type 2 diabetes. The mechanism for acute severe β-cell function failure leading to ketoacidosis remains a subject for further investigation. The pathogenesis of altered mentation in DKA is yet to be conclusively elucidated. A retrospective study suggests acidosis may be the major determinant of sensorium [74], but a prospective randomized study is needed to validate this observation. The role of other organic acids such as lactate in the pathogenesis of DKA may also need to be evaluated further. Lastly, recent reports of DKA in subjects treated with SGLT2 inhibitors certainly deserves further inquiry.

Contribution of Authors

EAN – draft of manuscript and review for intellectual content; AEK – critique of manuscript and review for intellectual content.

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