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Chapter 10

# Diabetic Ketoacidosis

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/53199

## 1. Introduction

A chronic autoimmune destruction of the pancreatic beta cells results in decreasing endogenous insulin secretion and the clinical manifestation of type 1 diabetes mellitus (T1DM). The clinical onset of the disease is often acute in children and adolescents and diabetic ketoacidosis (DKA) is present in 20-74% of the patients [1-7]. DKA is a serious condition that requiring immediate intervention. Even with appropriate intervention, DKA is associated with significant morbidity and possible mortality in diabetic patients in the pediatric age group [8]. Young age and female sex have been associated with an increased frequency of DKA [3,9]. The triad of uncontrolled hyperglycemia, metabolic acidosis and increased total body ketone concentration characterizes DKA [10]. In addition to possible acute complications, it may also influence the later outcome of diabetes [11].

## 2. Epidemiology

Worldwide, an estimated 65 000 children under 15 years old develop T1DM each year, and the global incidence in children continues to increase at a rate of 3% a year [12,13]. The current incidence in the UK is around 26/100 000 per year [14]. Patterson et al. were aimed to establish 15-year incidence trends for childhood T1DM in European centres with EURODIAB study. 29 311 new cases of T1DM were diagnosed in children before their 15th birthday during a 15-year period between 1989-2003. The overall annual increase was 3.9% and the increases in the age groups 0-4 years, 5-9 years, and 10-14 years were found to be 5.4%, 4.3%, and 2.9% respectively. If present trends continue, prevalent cases younger than 15 years will rise by 70% in 2020 [15].

The incidence of DKA was found to be 5-8% in large community-based studies [16]. Approximately 115 000 patients admitted to the hospital because of DKA in one year in USA

[17]. In a Turkish study conducted among the patients with diabetic adults who admitted to the hospital, the ratio of T1DM was found to be 6.6% and DKA was 38% of the group [18]. There is wide geographic variation in the frequency of DKA at onset of diabetes. The ratio inversely correlates with the regional incidence of T1DM. Frequencies range from 15 to 70% in Europe, Australia, and North America [11,19-25]. The most occurrence ages of DKA are between the 18-44 years (56%), than 45-65 years (24%) continues with only 18% of patients <20 years of age. Two-thirds of DKA patients are considered to have T1DM and 34% to have type 2 diabetes. DKA is the most common cause of death in children and adolescents with T1DM. Half of all deaths in diabetic patients younger than 24 years of age are caused from DKA [26,27]. In adult subjects with DKA, the overall mortality is usually given <1% (13), however mortality rates may increase over 5% in the elders and in patients with concomitant life-threatening illnesses [28,29].

## 3. Pathogenesis

There are some factors as a reason of acute metabolic complications in diabetic patiens. These factors are insulin deficiency as the initial primary event in progressive beta-cell failure, its failure in a patient with established disease or its ineffectiveness when insulin action is antagonized by physiological stress such as sepsis and in the context of counterregulatory hormone (catecholamines, cortisol, glucagon, and growth hormone) excess. These hormonal changes increase glucose production from glycogenolysis and gluconeogenesis and impair glucose utilization by peripheral tissues, resulting in hyperglycemia, osmotic diuresis, electrolyte loss, dehydration, decreased glomerular filtration (further compounding hyperglycemia) and hyperosmolarity. [26, 30-35].

The combination of insulin deficiency and increased counterregulatory hormones in DKA also leads to the release of free fatty acids into the circulation from adipose tissue (lipolysis). This is augmented by transient insulin resistance due to the hormone imbalance itself as well as the elevated free fatty acid concentrations [8,10,26,28-39]. Uncontrolled hepatic fatty acid oxidation in the liver to ketone bodies (beta-hydroxybutyrate and acetoacetate) results ketonemia and metabolic acidosis [40]. The pathogenesis causing to hyperglycemia and ketoacidosis are schematized in Figure 1 [30].

A number of clinical studies showed that the hyperglycemia in patients with hyperglycemic crises is associated with a severe inflammatory state characterized by an elevation of proinflammatory cytokines tumor necrosis factor alpha (TNF-$\alpha$) and interleukin-6, and -8 (IL-6,8), C-reactive protein, reactive oxygen species, and lipid peroxidation, as well as cardiovascular risk factors, plasminogen activator inhibitor-1 and free fatty acids in the absence of obvious infection or cardiovascular pathology. Insulin therapy and hydration recover these parameters to near-normal values within 24 hours [41]. Recent studies focused on the role of interleukin-1 beta (IL-1ß), interleukin-12 (IL-12) and interferon-gamma (IFN-$\gamma$). As demonstrated *in vitro,* these cytokines can directly influence beta cell function and viability [42]. Karavanaki et al. studied plasma levels of cytokines IL-1$\beta$, interleukin-2 (IL-2), IL-6, IL-8, and interleukin-10 (IL-10), TNF-

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α and also white blood cell count (WBC), high sensitivity C-reactive protein (hs-CRP), growth hormone (GH) and cortisol in 38 newly diagnosed T1DM children with DKA (mean age 7.68±3.07 years), prior to, during and 120 hours after DKA management, with the aim to monitor their levels at different time-points and in different degrees of DKA severity. Prior to DKA management the levels of IL- 6, IL-8, IL-10,WBC and cortisol were elevated, but all parameters were reduced within 120 hours after DKA management [43].

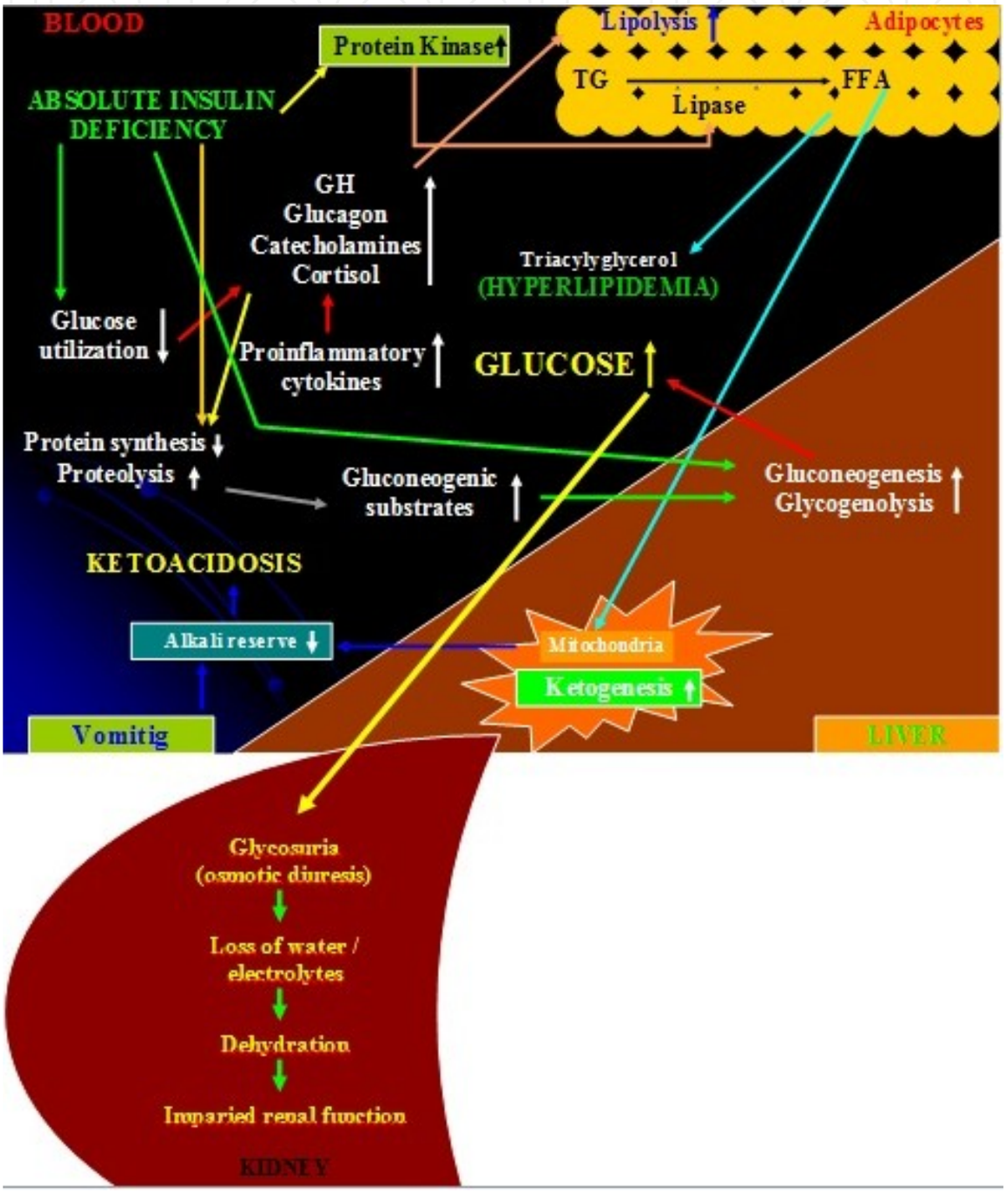


**Figure 1.** The pathogenesis causing to hyperglycemia and ketoacidosis in DKA (Data adapted from reference [17])

Recent studies have reported that an upregulated production of and interleukin-18 (IL-18) could be an important pathogenic event in the dysregulated production of IFN-γ and other type 1 cytokines thought to predispose T1DM [44-46] and the potential role of IL-18 in the pathophysiology of the chronic complications of diabetes mellitus [7-11]. But the potential role of IL-18 in the acute complications of diabetes mellitus such as DKA is controversial. Dong et al. compared serum IL-18 levels and other cytokines (IL-12 and IFN-γ) in newly diagnosed T1DM with DKA, T1DM without DKA and age/sex-matched healthy controls. Serum IL-18 levels were significantly higher in patients than those in healthy controls. Serum IL-12 and IFN-γ levels were not different between patients and controls. But there was a positive correlation between serum IL-18 and islet cell antibody (ICA) and C-peptide levels, but not between serum IL-18 and HbA1C, insulin and glucose in T1DM. Serum IL-18 levels also correlated positively with serum IL-12 levels. Serum IL-18 levels was significantly higher in patients with DKA than those in patients without DKA while C-peptide levels were markedly lower in patients with DKA. These results point that serum IL-18 levels are elevated and correlated with C-peptide levels and ICA in patients with T1DM, with marked increase in T1DM with DKA. Clinicans should be aware of the risk of DKA in diabetic patients with high serum IL-18 [47]. The procoagulant and inflammatory states may be due to nonspecific phenomena of stress and may partially explain the association of hyperglycemic crises with a hypercoagulable state [48].

## 4. Precipitating factors

A careful search for precipitating factors should be made, as correction of these contributes to improved outcomes and less frequent recurrences.

The most common precipitating factor in the development of DKA is infection [37,49,50] including viral syndromes, urinary tract infections, pelvic inflammatory disease, pneumonia, mucormycosis, malignant otitis externa (with pseudomonas aeruginosa), periodontal abscess and dental infection [51]. Other precipitating factors include discontinuation of, or inadequate insulin therapy, acute pancreatitis, myocardial infarction, stroke, major trauma and other severe/acute illnesses and drugs [30,32,37]. New-onset T1DM or discontinuation of insulin in T1DM frequently leads to the development of DKA. In young patients with T1DM, psychological problems complicated by eating disorders may be a contributing factor in 20% of recurrent ketoacidosis. In younger patients fear of weight gain and hypoglycemia, stresss of chronic disease may lead to insulin omission.

In the past, before the improvement in technology and sufficient education of patients continuous subcutaneous insulin infusion devices had also been associated with an increased frequency of DKA [52]; nowadays the incidence of DKA appears to have reduced in pump users [53]. Additional prospective studies are needed to document reduction of DKA incidence with the use of continuous subcutaneous insulin infusion devices [54].

Drugs that affect carbohydrate metabolism, such as corticosteroids, thiazides, sympathomimetic agents and pentamidine may precipitate the development of DKA [10]. The as-

http://dx.doi.org/10.5772/53199

sociation between antipsychotic drugs, especially with atypical antipsychotics and hyperglycemia and even DKA have been reported in some cases [55,56]. Arefi et al. reported the first case of DKA due to nalidixic acid overdosage [57]. It has been available for the treatment of urinary tract infections for many years [58]. There are reports of hyperglycemia, convulsions and glycosuria in overdosage of nalidixic acid [58-61]. Interferon-alpha (IFN-$\alpha$), a natural protein with anti-viral, anti-proliferative and immunomodulatory effects is routinely administered in chronic hepatitis C (CHC). Classical IFN-$\alpha$ has been correlated with the development of a variety of autoimmune disorders including Hashimoto thyroiditis, immune-mediated thrombocytopenia, hemolytic anemia, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, primary biliary cirrhosis and sarcoidosis. It is unclear whether IFN-$\alpha$ treatment is associated with the development of T1DM. The prevalence of diabetes mellitus development in patients receiving classical IFN-$\alpha$ for CHC is very low ranging from 0.08% to 0.7% [62,63]. Fabris et al. reviewed 9 relative studies; the prevalence of pancreatic auto-antibodies appeared to rise from 3% to 7% prior to and following initiation of IFN-$\alpha$ treatment [64]. Soultati et al. reported a 38 year-old female patient developed simultaneously DKA and hyperthyroidism 5 months following initiation of treatment with pegylated IFN-$\alpha$ and ribavirin for CHC. High titers of glutamic acid decarboxylase, antinuclear and thyroid (thyroid peroxidase and thyroglobulin) antibodies were detected [65]. Until 2005, 35 cases of IFN-$\alpha$ related T1DM had been reported in the medical literature [64,66-69]. DKA was reported in a few classical IFN-$\alpha$ related cases [70-73], in three pegylated IFN-$\alpha$ related cases [65,74,75]. The development of DKA and the permanent insulin dependency may be related with a rapidly developing T helper-1-mediated pathogenic mechanism [72]. Tacrolimus, a reversible calcineurin inhibitor, is known for its diabetogenic potential. The incidence of diabetes is less frequent among the patients of nephrotic syndrome in comparison to organ transplant recipients. DKA is even rarer. Sarkar et al. reported in a 12-year-old girl with steroid resistant nephrotic syndrome, DKA as the first presentation of new onset tacrolimus induced transient T1DM despite a lower dose range and low trough level of the drug is being [76].

Cocaine abuse causes recurrent DKA with several mechanisms, including therapeutic noncompliance, stimulation of adrenal release of epinephrine and norepinephrine and increased release of other counter regulatory hormones [30,77]. Cytomegalovirus infection [78,79], protease inhibitor treatment [80,81] and highly active antiretroviral therapy (via immune restoration) may precipitate DKA in HIV-infected patients [82].

## 5. Diagnosis

### 5.1. History and physical examination

The acute DKA episode in T1DM evoluation should be done rapidly. The symptoms of poorly controlled diabetes may be present for several days, but the metabolic changes typical of ketoacidosis usually occurs within a short time (typically 24 h). Occasionally,

the entire symptomatic presentation may evolve or develop more acutely and the patient may present with DKA with no prior clues or symptoms. For DKA, the typical clinical findings includes a history of polyuria, polydipsia, weight loss, vomiting, dehydration, weakness and mental status change. Physical examination may include poor skin turgor, Kussmaul respirations, tachycardia and hypotension. Mental status can vary from full alertness to profound lethargy or coma [10,37]. The symptoms and physical signs of DKA are listed in Table 1.

| MANIFESTATIONS OF DIABETIC KETOACIDOSIS | |
|---|---|
| Symptoms | Physical findings |
| Nausea / vomiting | Tachycardia |
| Thirst / polyuria | Dry mucous membranes / reduced skin turgor |
| Abdominal pain | Dehydration / hypotension |
| Shortness of breath | Tachypnea / Kussmaul respirations |
| | Abdominal tenderness |
| | Lethargy / obtundation / cerebral edema / possibly coma |

**Table 1.** The symptoms and physical signs of DKA

Although infection is a common precipitating factor for DKA, patients can be normothermic or even hypothermic. Severe hypothermia, if present, is a poor prognostic sign and could be fatal. The major complications of hypothermia are acute renal failure, aspiration pneumonia, rhabdomyolysis, acute respiratory distresss syndrome and acute pancreatitis [83]. The mechanism of hypothermia complicated by DKA is unclear, but the inability of glucose to endocytose due to insulin deficit which leads to a lack of substrate for cellular heat production has been proposed [84]. A characteristic elevated J point on the electrocardiogram (ECG) (Osborn wave) may be observed when markedly hypothermia occurs [85-87]. The thermoregulatory system could be impaired in diabetic patients with autonomic neuropathy and reduced muscle mass or adipose tissue related with malnutrition. Thus, become prone to hypothermia under certain conditions [88,89].

Nausea, vomiting, diffuse abdominal pain are frequent in patients with DKA (50%) [90]. Abdominal pain on presentation could be a result of the DKA or an indication of a precipitating cause of DKA, particularly in younger patients or in the absence of severe metabolic acidosis [91,92]. Further evaluation is necessary if this complaint does not resolve with successfull treatment, because this may indicate other underlying complications.

### 5.2. Laboratory findings

The initial laboratory evaluation should include determination of plasma glucose, blood urea nitrogen, creatinine, electrolytes (with calculated anion gap), osmolality, serum and urinary ketones and urinalysis, as well as initial arterial blood gases and a complete blood count [93]. If laboratory measurement of serum potassium is delayed an ECG should be performed for baseline evaluation of potassium status [94,95]. An increased

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WBC count is response to stress is characteristic of DKA and is not indicative of infection. If there is evidence of infection, chest X-ray and urine, sputum, throat or blood cultures should also be obtained [93].

The severity of DKA is classified as mild, moderate, or severe based on the severity of metabolic acidosis (blood pH, bicarbonate, and ketones) and the presence of altered mental status as shown in Table 2.

| | DKA | | |
|---|---|---|---|
| | Mild (plasma glucose >250 mg/dl) | Moderate (plasma glucose >250 mg/dl) | Severe (plasma glucose >250 mg/dl) |
| Arterial pH | 7.25–7.30 | 7.00 to <7.24 | <7.00 |
| Serum bicarbonate (mEq/l) | 15–18 | 10 to <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 |

*Nitroprusside reaction method.
†Effective serum osmolality: 2[measured Na+ (mEq/l)] + glucose (mg/dl)/18.
‡Anion gap: (Na+) − [(Cl− + HCO3− (mEq/l)].

**Table 2.** Classification of DKA

One of the major laboratory findings in DKA is the elevation of total blood ketone concentration. Assessment of increased ketonemia is usually performed by the nitroprusside reaction which provides a semiquantitative estimation of acetoacetate and acetone levels. The nitroprusside test (both in urine and in serum) is highly sensitive, but it does not recognize the main metabolic product in ketoacidosis; beta-hydroxybutyrate. In conclusion this assay is insufficient to determine the severity of ketoacidosis [10,31]. Measurement of serum ß- hydroxybutyrate may be an alternative to determine ketoacidosis [96). Ketoacids cause an increased anion gap metabolic acidosis. The anion gap is calculated by subtracting the sum of chloride(Cl) and bicarbonate (HCO3) concentration from the sodium (Na) concentration:

[Na - (Cl +HCO3)]. A normal anion gap is between 7 and 9 mEq/l and an anion gap 10–12 mEq/l indicates the presence of increased anion gap metabolic acidosis [10].

In clinical trials mixed acid–base disorders have been showed in DKA [97,98], but it is very rare the presentation of DKA with alkalaemia. The first case has been reported in 1970, defined as 'diabetic ketoalkalosis' [99] and it was followed by other case reports. The factors related with alkalemia in DKA were; recurrent vomiting which causes hydrogen and chloride ion loss (autonomic neuropathy such as delayed gastric emptying might have been related to recurrent vomiting), alkali ingestion and contraction alkalosis due to dehydration and/or diuretic use [100]. Treatment of diabetic ketoalkalosis does not differ from that of pure DKA.

Hyperglycemia is a key diagnostic criterion of DKA; but plasma glucose level varies in a wide range on admission. Recent studies have reported from normal or near normal [101] to elevated [31,3] hepatic glucose production rates. This factor possibly contributes to the wide range of plasma glucose levels in DKA that are independent of the severity of ketoacidosis [96]. In contrast to this 10% of the DKA patients presents with so-called 'true euglycemic DKA' [blood glucose <200 mg/dl (11.1 mmol/l)] [102]. Due to nausea or vomiting caused by a precipitating illness or by worsening ketoacidosis itself, a decrease in caloric intake occurs. If patients continue to take sufficient amounts of insulin in this situation may maintain euglycemia. But ketone body formation cannot be stopped, so they present as DKA accompanied with only mild elevations of blood glucose or normoglycemia [103-105]. Euglycemic DKA can be associated with other conditions such as; near total glycogen depletion [106,107], accelerated lipolysis [108] and free fatty acid production [109], less effectiveness of insulin suppressing lipolysis and ketogenesis during fasting and when there is sufficient circulating fluid volume to maintain glucose excretion [110]. In women with diabetes, pregnancy is also a condition that is associated with euglycemic ketoacidosis [111,112] as pregnancy is considered to be a state of accelerated starvation [113] with increased lipolysis and ketone body production in the presence of increased insulin insensitivity [114].

At presentation leukocytosis with cell counts in the 10,000 –15,000 $mm^3$ range is commonly seen in DKA and may not be indicative of an infection. But leukocytosis with cell counts 25,000 $mm^3$ may indicate infection and require further evaluation [115]. In ketoacidosis, leukocytosis may be correlated to elevated levels of cortisol and norepinephrine which is attributed to stress [116].

On admission serum sodium is usually low because of the osmotic flux of water from the intracellular to the extracellular space as a result of hyperglycemia. An increased or even normal serum sodium concentration in the presence of hyperglycemia indicates severe degree of free water loss. To assess the severity of sodium and water deficit, serum sodium may be corrected by adding 1.6 mg/dl to the measured serum sodium for each 100 mg/dl of glucose above 100 mg/dl [10,31]. In the calculation of effective osmolality, [sodium ion (mEq/l) x 2 + 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 [10].

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Serum potassium concentration may be increased because of an extracellular shift of potassium caused by insulin deficiency, hypertonicity and acidemia [117]. However, patients have severe total-body potassium deficiency. Treatment could be lowers serum potassium concentration and trigger cardiac arrhythmia. So patients with low normal or low serum potassium concentration should be monitored closely. If necessary appropriate potassium replacement should be done [93].

Insulin mainly affects glucose metabolism, but also protein and lipid metabolism. In the literature there are many cases of DKA presented with severe hyperlipidemia [118,119]. In patients with newly diagnosed T1DM presenting with DKA there is an absolute insulin deficiency that causes increased lipolysis and free fatty acid accumulation to the liver, decreased in utilization and excretion which results with hyperlipidemia. Severe hypertriglyceridemia can complicate DKA by the development of pancreatitis. As it is related with increased morbidity and mortality, clinicians must be aware of this complication. Children under the age of 5 years presenting with DKA have a higher rate of mortality. Therefore, these should be monitored for hyperlipidemia and if there is clinical evidence, for pancreatitis [120-123]. Pseudonormoglycemia [124] and pseudohyponatremia [125] may occur in DKA in the presence of severe chylomicronemia.

On the admission in patients with DKA, serum phosphate level is usually elevated because of an extracellular shift of phosphate caused by insulin deficiency, hypertonicity and increased catabolism. Thus, serum concentration does not reflect an actual body deficit [31,126,127]. Typical total body deficits of water and electrolytes in DKA are seen in Table 3.

| Typical deficits | |
|---|---|
| Total water (L) | 6 |
| Water (ml/kg)* | 100 |
| $Na^+$ (mEq/kg) | 7-10 |
| $Cl^-$ (mEq/kg) | 3-5 |
| $K^+$ (mEq/kg) | 3-5 |
| $PO_4$ (mmol/kg) | 5-7 |
| $Mg^{++}$ (mEq/kg) | 1-2 |
| $Ca^{++}$ (mEq/kg) | 1-2 |

**Table 3.** Typical total body deficits of water and electrolytes in DKA (*Per kg of body weight)

Increased amylase and lipase has been reported in 16-25 % of patients with DKA. The mechanism of elevated enzymes in DKA remains unclear. Amylase elevations could be related with subtle injury to pancreatic acinar cells which causes release of this enzyme to the circulation, release of salivary gland amylase or suboptimal excretion in the urine [128]. There is little correlation between the presence, degree or isoenzyme type of hyperamylasemia and the presence of gastrointestinal symptoms (nausea, vomiting, and abdominal pain) or pancreatic imaging studies [129]. Increase in lipase may be related with release of nonpancreatic lipolytic enzymes into the circulation due to malignant tumors, to acute cholecystitis or esophagitis. Other possible mechanism are; renal insufficiency, delayed blood withdrawal, hypertriglyceridemia or subclinical pancreatitis [130]. Pancreatic enzyme levels reach a peak 12-24 hours after initiation of treatment for DKA [131]. Hyperlipasemia is less reliable for diagnosing acute pancreatitis, but elevated lipase is more spesific.

### 5.3. Differential diagnosis

Other causes of metabolic acidosis and ketosis must be differentiated from DKA. Differantial diagnosis of DKA can be seen in Table 4.

| | DKA | Starvation or high fat intake | Lactic acidosis | Uremic acidosis | Alcholic ketosis | Methanol or ethylenglycol intoxication | Salicylate intoxication |
|---|---|---|---|---|---|---|---|
| Ph | ↓ | N | ↓ | Mİld ↓ | ↓ ↑ | ↓ | ↓ ↑ |
| Plasma glucose | ↑ | N | N | N | ↓ or N | N | N or ↓ |
| Total plasma ketones | ↑ ↑ | Slight ↑ | N | N | Slight to moderate ↑ | N | N |
| Anion gap | ↑ | Slight ↑ | ↑ | Slight ↑ | ↑ | ↑ | ↑ |
| Osmolality | ↑ | N | N | ↑ | N | ↑ ↑ | N |
| Uric acid | ↑ | Mİld ↑ | N | N | ↑ | N | N |
| Glycosuria | ++ | - | - | - | - | - | - |

*Acetest and Ketostix measure acetoacetic acid only, thus misleading low values may be obtained because the majority of 'ketone bodies' are ß-hydroxybutyrate.
*(Data adapted from reference 10)

**Table 4.** Differantial diagnosis of DKA

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Acute renal failure can be seen in ~5-7% of all adult hospitalizations [132,133]. It shares the common feature of an increased anion gap metabolic acidosis but can be easily differentiated from DKA by the absence of hyperglycemia or ketonemia. On the other hand, severe DKA can lead to prerenal azotemia and secondary acute kidney injury [134,135].

Severe uremic acidosis, characterized by an extremely high blood urea nitrogen, often >200 mg/dL (71.4 mmol/L) and creatinine >10 mg/dL (884 umol/L) causes acidosis via retention of anionic solutes in the patient with chronic kidney disease. The pH and anion gap can be found usually mild abnormal, however blood sugar is typically normal. Severe uremia typically occurs when creatinine clearance falls to <10 mL/min (0.1669 ml/s) in irreversible renal disease [136].

Lactic acidosis occasionally contributes to metabolic acidosis in patients hospitalized for either uncomplicated diabetes or DKA [137]. The main reason of lactic acidosis is tissue hypoxia [138]. It occurs in the setting of decreased tissue oxygen delivery which triggers non-oxidative metabolism of glucose to lactic acid. When co-existent with DKA, the anion gap typically exceeds that attributable to lactate alone. If lactic acidosis, with a serum lactate ≥5 mmol/L (45 mg/dL), occurs accompanied with DKA or hyperosmolar hyperglycemic state, severe volume depletion affects cardiac output negatively and also pre-existent cardiovascular disease increases this risk. Underlying liver disease with reduced lactate clearance and sepsis may also contribute more frequent/severe lactic acidosis in hyperglycemic emergencies. For main therapy it should be performed to optimise tissue perfusion and to treat underlying conditions [17,136].

When there is insufficient carbohydrate availability, starvation ketosis may occur by result of physiologically appropriate lipolysis and ketogenesis to provide fuel substrates. Blood glucose and arterial pH are found to be usually in normal level and the anion gap is at most mildly elevated. Although ketonuria may be apparent in urine analysis, modest ketonemia is typical in blood examination [17,136].

Chronical alcohol abuse may be the reason of alcoholic ketosis for ethanol is the predominant caloric source for days or weeks. Ketosis happens in sudden decrease of alcohol and caloric intake. Patients are usually present in normoglycemic or hypoglycemic state on submission, although some have rarely mild hyperglycemia [136].

Toxic ingestions sometimes need to be differentiated and history of the patients with laboratory studies may help for the differantial diagnosis. Salicylate, methanol and ethylene glycol each produce an increased anion gap metabolic acidosis without hyperglycemia or ketosis. Methanol and ethylene glycol will also cause a serum osmolal gap [17,136]. Measurement of suspicious drug/toxin concentrations with high index of suspicion, usually confirms the diagnosis of acute intoxication [139-142].

If there are some gastrointestinal or renal losses for any reason, non-anion gap metabolic acidosis may occur. It is characterized by a low serum bicarbonate concentration with subsequent chloride retention. Diarrhea and renal tubular acidosis are frequent causes of this condition. Carbonic anhydrase inhibitor therapy, rapid dilution of plasma bicarbonate by infused saline may be considered as the other varying reasons [143,144]. DKA can

be easily differentiated from this condition by the presence of an increased anion gap and hyperglycemia. In complicated diabetics, especially in diabetic nephropathy, if there is hypoalbunemia, it can affect the apparent anion gap, since albumin is negatively charged protein contibuting 50-60% to the normal anion gap. If albumin is below the normal value of 4 g/dL (40 g/L), the calculated anion gap should be corrected by adding 2.5 for every 10 g/L (1 g/dL) to determine whether excessive abnormal anions are present [145-147].

## 6. Treatment

Successful treatment of DKA requires correction of dehydration, hyperglycemia and electrolyte imbalances, identification of comorbid precipitating events and above all, frequent patient monitoring. Protocols for the management of patients with DKA is summarized in Fig. 2 [10].

### 6.1. Fluid therapy

The most important initial therapeutic intervention is fluid replacement followed by insulin administration. DKA is a volume depletion state with water deficit, varying widely but averaging 6 L [51]. Initial fluid therapy is directed toward expansion of the intravascular, interstitial and intracellular volume (all of which are reduced in hyperglycemic crises), to establish tissue perfusion for insulin to reach cells [148] and restoration of renal perfusion. The goal of fluid resuscitation is to replace half of the estimated water deficit over the first 12-24 hours and adding for the ongoing losses (eg: vomiting) [51]. Replacement fluids may decrease the blood glucose by up to 23% because of increased renal perfusion and loss of glucose in urine [149] Hyperglycemia can reduce serum sodium by causing an osmotically driven shift of water from intracellular to extracellular compartments. In the previous estimated models; each 5.5 mmol/L (100 mg/dL) increase in glucose above normal resulted in a decrease of 1.6 mmol/L (1.6 mEq/L) in measured serum sodium [150], Hillier et al. suggested that 2.4 mmol/L (2.4 mEq/L) per 5.5 mmol/L (100 mg/dL) glucose increase is more accurate [151].

The initial fluid of choice is isotonic saline, generally given for the first 4 hours of therapy (Table 4). Subsequent choice for fluid replacement depends on hemodynamics, the state of hydration, serum electrolyte levels and urinary output. Fluid resuscitation should be individualized according to the patient's degree of dehydration, mental status and underlying diseases such as congestive heart failure or renal failure [51]. Glucose, an osmotic diuretic, may produce a high urine output even in severely dehydrated patients. The threshold for glycosuria in healthy adults occurs at plasma glucose concentration of approximately 180 mg/dL (9.99 mmol/L), though adults with long-standing diabetic nephropathy may have considerably higher thresholds. As a result, urine output should not be considered a reliable predictor of volume status in hyperglycemic states [152].

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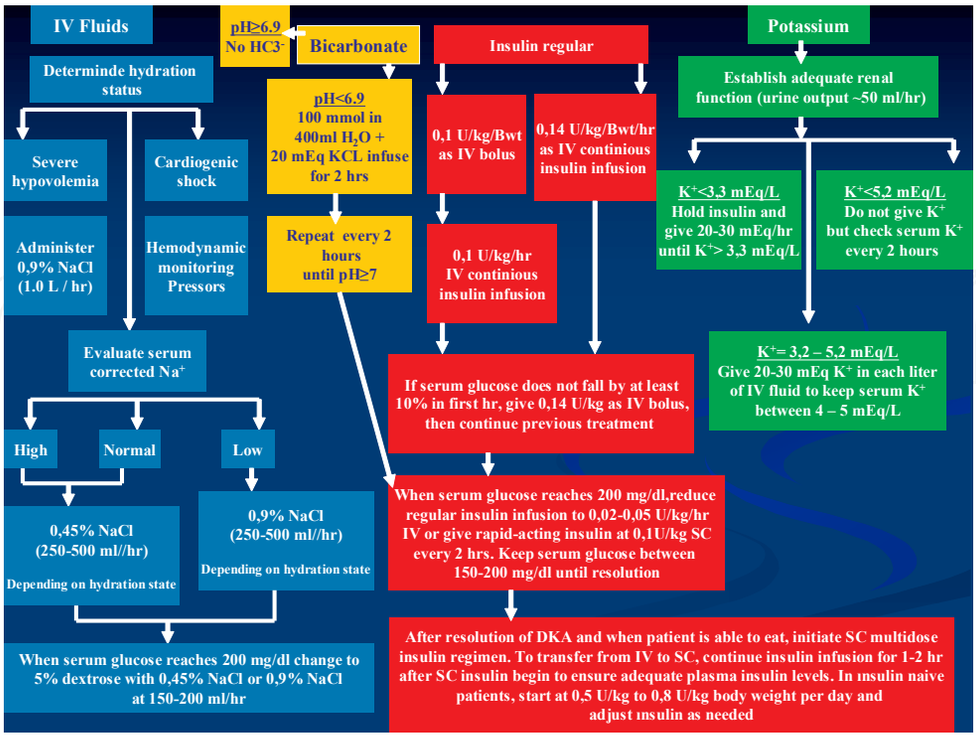


**Figure 2.** Protocols for the management of patients with DKA (Data adapted from reference 10)

| Hours | Volume |
|---|---|
| 1st hour | 1,000 – 2,000 mL |
| 2nd hour | 1,000 mL |
| 3rd-5th hours | 500 – 1,000 mL/hour |
| 6th-12th hours | 250 – 500 mL/hour |

**Table 5.** Suggested average initial replacement rate of fluid in DKA (after hemodynamic resuscitation with normal saline when indicated)

Many guidelines recommend initial fluid resuscitation with colloid in hypotensive patients. However, the hypotension results from a loss of electrolyte solution and it is more physiological to replace with crystalloid. A recent Cochrane review did not support the use of colloid in preference to crystalloid fluid [153]. In the absence of cardiac compromise, isotonic saline (0.9% NaCl) is infused at a rate of 15–20 ml kg/body wt/h or 1–1.5 L during the first hour. In general, 0.45% NaCl infused at 250–500 ml/hour 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 (Fig. 2). That total fluid administered should not exceed 4 L/m²/24 hour for fear of causing cerebral edema is most often the mainstay of therapy in many pediatric critical care unit protocols [154,155]. Successful treatment with fluid replacement can be evaluate by hemodynamic monitoring (improvement in blood pressure), measurement of fluid input/output, laboratory values and clinical improvement. In patients with renal or

cardiac failure, monitoring of serum osmolality and frequent assessment of cardiac, renal and mental status must be performed during fluid resuscitation to avoid iatrogenic fluid overload [10,37,148]. During treatment of DKA, hyperglycemia is corrected faster than ketoacidosis. The mean duration of treatment until blood glucose is <250 mg/dl and ketoacidosis (pH>7.30; bicarbonate >18 mmol/l) is corrected is 6 and 12 hours [36,156]. Once the plasma glucose falls to <200-250 mg/dL (11.1-13.88 mmol/L), 5% dextrose should be added to replacement fluids to allow continued insulin administration until ketonemia is controlled while at the same time avoiding hypoglycemia [93,135]. In hypotensive patients, aggressive fluid resuscitation with isotonic saline should be continued until blood pressure normalized [51].

### 6.2. Insulin therapy

Insulin lowers the serum glucose concentration (by decreasing gluconeogenesis and glycogenolysis, increasing tissue glucose uptake) and arrests ketone production (by reducing lipolysis and glucagon secretion). The most important point in the treatment of DKA involves insulin administration. There was major concern about; physiologic or low dose insulin therapy was superior to pharmacologic dose regimen and the administration of regular insulin via continuous intravenous infusion or by frequent subcutaneous or intramuscular injections [10,157-160]. Several randomized controlled studies have shown that physiologic or low dose insulin therapy was superior to pharmacologic dose regimen and low-dose insulin therapy is effective regardless of the route of administration in DKA [118,159,160]. In clinical practice most patients are treated with low dose, intravenous regular insulin until resolution of DKA [30]. The administration of continuous intravenous infusion of regular insulin is preferred because of its short half-life and easy titration and the delayed onset of action and prolonged half-life [107,127,160].

Previous treatment algorithms have recommended the administration of an initial intravenous bolus of regular insulin (0.1 unit/kg) followed by the infusion of 0.1 unit/kg/h [10,17], but a recent prospective randomized study showed that a bolus dose is not required if patients are given hourly insulin infusion at 0.14 unit/kg body weight [161]. Low-dose insulin infusion protocols decrease plasma glucose concentration at a rate of 50–75 mg/d/ h. If plasma glucose does not decrease by 50–75 mg in the first hour, the insulin infusion should be increased every hour until a steady glucose decline is achieved. When the plasma glucose reaches 200 mg/dl in DKA, the insulin infusion rate may decrease to 0.02–0.05 units/kg/h, at the same time dextrose should be added to the intravenous fluids for avoiding hypoglycemia. The rate of insulin administration or the concentration of dextrose may need to be adjusted to maintain glucose values between 150 and 200 mg/dl until DKA resolved [90]. Resolution of ketoacidosis includes these criteria; 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 in normal range. Once hyperglycemia is corrected, 12-24 hours of intravenous insulin treatment is sufficient to clear ketones from the circulation [51].

Subcutaneous rapid-acting insulin analogs (lispro and aspart) offer an efficacious and cost-effective alternative to continuous intravenous infusions in the treatment of DKA [162-164].

Umpierrez et al. used subcutaneous rapid-acting insulin (insulin lispro or aspart) 0.2 units/kg initially followed by 0.1 unit/kg every hour or an initial dose of 0.3 units/kg followed by 0.2 units/kg every 2 hours, until blood glucose is ≤ 250 mg/dL; the insulin dose is then decreased by half (to 0.05 or 0.1 unit/kg, respectively) every 1-2 hours until resolution [162,163]. There were no differences in 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% [162-164]. This approach is not widely used for many reasons, including titration difficulties with longer half-life preparations, requirement for hourly nursing interventions and lack of staff experience compared to that with standard insulin infusions. However, until these studies are confirmed outside the research arena, patients with severe DKA, hypotension, anasarca or associated severe critical illness should be managed with intravenous regular insulin in the intensive care unit [93].

In patients younger than 4 years of age there is a prolonged time lag for plasma glucose levels to reach 12 to 14 mmol/L, because young children and adolescents who have high growth velocity and higher levels of the human growth hormone, a diabetogenic hormone. In addition to this, patients with fever or infections and higher metabolic requirements may need 15% to 20% more insulin than the usual dose [165].

In rare cases of patients with allergy to human insulin presenting with hyperglycemic crisis, desensitization to human insulin may be performed before treatment with human insulin. A recent case report documented the successful treatment of a woman with allergy to human insulin and its analogs with continuous subcutaneous infusion of human insulin [166].

### 6.3. Potassium

Despite a total body potassium deficit resulting from the glycosuric osmotic diuresis, mild-to-moderate hyperkalemia is common in patients with hyperglycemic crises upon initial presentation because of proteolysis, acidosis, and insulin deficiency [10,167]. Insulin therapy, correction of acidosis and volume expansion decrease serum potassium concentration [10].

Occasionally patients with DKA may present with significant hypokalemia, in which case insulin therapy should be delayed until potassium concentration is corrected to >3.5 mequiv./l to avoid arrhythmias and respiratory muscle weakness [168,169]. To prevent hypokalemia, potassium replacement is initiated after serum levels fall below the upper level of normal for the particular laboratory (5.0-5.2 mEq/l) in patients without renal impairment. The treatment goal is to maintain serum potassium levels within the normal range of 4–5 mEq/l. Generally, 20–30 mEq potassium in each liter of infusion fluid is sufficient to maintain serum potassium concentration within the normal range but additional doses may be necessary [10,30].

The rare patient with severe hyperkalemia (>6.0 mEq/l) on admission with concomitant electrocardiographic changes may benefit from bicarbonate therapy [170].

### 6.4. Bicarbonate therapy

The hepatic metabolism of free fatty acids generates ketoanions, such as beta-hydroxybutyrate and acetoacetate [171,172]. Impaired tissue perfusion due to volume contraction and the adrenergic response to the often severe underlying precipitating illness result in lactate production [173]. Acute kidney injury leads to accumulation of other unmeasured anions, such as sulphate, urate and phosphate [174]. All these, together with hyperchloremia which predominates during the recovery phase of DKA [175], contribute to the development of acidemia, which often is severe [176,177].

Metabolic acidemia can impair myocardial contractility, reduce cardiac output, affect oxyhemoglobin dissociation and tissue oxygen delivery, inhibit intracellular enzymes, such as phosphofructokinase, alter cellular metabolism, and result in vital organ dysfunction [178-181]. In the past, therapy in DKA has placed importance on the rapid reversal of acidemia. But based on currently available evidence, several deleterious effects of bicarbonate therapy have been reported, such as increased risk of hypokalemia, decreased tissue oxygen uptake, cerebral edema and development of paradoxical central nervous system acidosis [182]. The use of bicarbonate in DKA remains a controversial subject.

Since severe acidosis may be associated with adverse effects, patients with pH <6.9 or when pH is <7.1 and hemodynamic instability or hyperkalemic electrocardiographic changes are present [93,135], bicarbonate should be given. A choice is to give 100 mmol sodium bicarbonate (two ampules) in 400 ml sterile water with 20 mEq KCI at a rate of 200 ml/h for 2 hours. If the pH is stil <7.0 after infusion, we recommend repeating infusion every 2 hours until pH reaches >7.0 [17,93]. Potassium replacement should be considered before administering bicarbonate or KCL should be added in the bicarbonate solution at 40 mmol (40 mEq) KCl/L to avoid precipitous hypokalemia [93,135].

### 6.5. Phosphate

In patients with DKA there is about 1 mmol/kg body weight phosphate depletion. At presentation serum phosphate levels are usually normal or elevated. But with insulin therapy these levels rapidly decrease [90,132]. Randomized studies showed that phosphate replacement have no any additional benefit on the clinical outcome [126,183] and in contrast, phosphate replacement may trigger hypocalcemia and hypomagnesemia [183,184]. Hypophosphatemia can cause hemolysis, refractory acidosis, reduced cardiac output, respiratory muscle weakness, rhabdomyolysis, central nervous system depression, seizures, coma or acute renal failure. Careful phosphate replacement should be planned to the patients with these findings and severe hypophosphatemia (serum phosphate <1 mg/dL) [10,90,132]. In severe deficiency, the amount, added to intravenous replacement fluids can be 20–30 mEq/l potassium phosphate. Secure replacement rate that can correct hypophosphatemia is 4.5 mmol/h (1.5 ml/h of K2 PO4) [185]. In less severe deficiencies 80-110 mmol (2.5-3.5 g) daily in 2-3 divided doses oral phosphate can be given [93,135,186].

### 6.6. Transition to subcutaneous insulin

When DKA has resolved, patients who are appropriate for oral intake can be started on a multiple dose insulin regimen with a long acting insulin (e.g. glargine or detemir) to cover basal insulin requirements and short/rapid acting insulin (lispro, aspart or glulisine) given before meals to control plasma glucose. To ensure adequate plasma insulin levels and to avoid hyperglycemia and ketonemia intravenous insulin infusion should be continued for 1–2 hours after the subcutaneous insulin is given. Patients who are inappropriate for oral intake the treatment should be continued with an infusion of intravenous fluids and insulin [10,17,49,93,187]. A multiple-dose subcutaneous combination regimen is preferred, as it is related with less hypoglycemia and provides a better physiologic pattern of control than other regimens. In insulin-naïve patients, a multidose insulin regimen should be started at a dose of 0.5-0.8 units/kg body weight per day. Patients with known diabetes, whose blood glucose monitoring are in the normal ranges before DKA, may start with dose of insulin they are receiving [160].

In the past human insulin (NPH and regular) were usually given in two or three doses per day. With the development of new analogue insulins, basal-bolus regimens with basal (glargine and detemir) and rapid-acting (lispro, aspart, or glulisine) insulin treatments became a major concern in the treatment of DKA. A prospective randomized trial compared with a split mixed regimen of NPH plus regular insulin twice daily treatment and a basal-bolus regimen, including glargine once daily and glulisine before meals following the resolution of DKA. Glycemic control were similar between the two groups but the study showed that treatment with basal-bolus insulin regimen was associated with a lower rate of hypoglycemic events (15%) than the rate in those treated with NPH and regular insulin (41%). This trial showed that analogue insulins may offer a more physiologic effect [156].

### 6.7. Somatostatin therapy in the management of resistant diabetic ketoacidosis

As a inhibiting hormone for counterregulatory hormones, somatostatin may be used in the treatment of DKA. Somatostatin analogues have been successfully used in the treatment of diabetes associated autonomic neuropathy and they have also been shown to decrease the requirements for insulin [188,189]. Continuous subcutaneous octreotide infusion suppresses counterregulatory hormones, increases insulin-mediated glucose metabolism by enhancing glucose storage and reduces energy expenditure [189]. There are limiting data in the literature about somatostatin use in DKA. Diem et al. were assessed preventive effects of octreotide on diabetic ketogenesis during insulin withdrawal. Octreotide led to a marked suppression of beta-hydroxybutyrate, acetoacetate and glucagon levels and an associated diminution of bicarbonate consumption and the fall in pH [190]. Anthony et al. reported a case of DKA with glucagonoma who was unresponsive to conventional therapy and treated with octreotide [191]. In conclusion, for patients who do not respond to conventional DKA treatment, somatostatin could be added to therapy. More data and further randomized controlled clinical trials should be made with the use of somatostatin in treatment of DKA.

### 6.8. Monitoring

Successful management and early intervention for complications require close monitoring. Timeline in DKA management are listed in Figure-3 [165]. The clinicians should be made a flow chart to obtain all relevant incidents regarding the patient's condition and clinical outcome [192].

| Time | Evaluation | Laboratory | Intervention |
|---|---|---|---|
| 0-1 st hour | GCS on admission, check pupils, monitor vitals (HR, BP, temperature and pulse oximetry) | CBC, electrolytes (Na, Cl, K, HCO3, PO4, Mg), BUN, Cr, ß- hydroxybutyrate, urine ketones, venous pH, blood glucose, lactic acid level, ECG | Calculate total fluid deficit; start careful fluid ressuciation; plasma volume expanders, goal to achieve normal blood pressure; check urine output (may need catheter)<br><br>Start insulin (with prior check on K levels) and replace fluids; may need bicarbonate; GCS<8 or CE: intubate and ventilate, |
| 2 nd hour | Check BP and ensure urine output; check GCS every hour for first 8 hours | Check lactic acid in second hour and follow up on labs | nasogastric tube for suction |
| | High fever | Suspect infection; check WBC (>15000mm3), CRP (high) and urine (WBCs and for nitrates, leukoesterases) | Send appropriate cultures (blood and urine), chest radiograph, use antibiotics with broad spectrum |
| 3-8 th hour | GCS as above; check for ongoing losses | Venous blood pH every 2 hours; electrolytes; and ß- hydroxybutyrate every 4 hours; may check urine ketones | While continuing insulin; reasses adequecy of fluids and ascertain complete rehydration |
| | Continued abdominal pain | Serum amylase and lipase levels; ultrasound abdomen and abdominal X-ray | May need to manage acute abdominal pain (pancreatitis)<br><br>May need to switch dextrose if serum glucose level is ≤250 mg/dL; continue to check response to ongoing hydration |
| 9-24 th hour | Check GCS every 2 hours | Can change to labs every 8/12 hours at end of 24 hours | Complete rehydration at 48-hour period;transition to pump or subcutaneous insulin |
| 24-48 hours | Check GCS every 2 hours if hypernatremia was initially present | Check for pH, electrolytes, and ß-hydroxybutyrate as above and stop if pH, ß- hydroxybutyrate and HCO3 are normal | |

**Figure 3.** Timeline in DKA management. GCS:Glascow Coma Scale, CBC:Complete Blood Counting, ECG:Electrocardiogram, HR:Heart Rate, BP:Blood Pressure, BUN:Blood Urea Nitrogen, Cr: Creatinine, WBC:White Blood Cell, CRP:C-reactive protein, CE:Cerebral edema (adapted from reference 165)

http://dx.doi.org/10.5772/53199

Recommendations for laboratory monitoring include; hourly vital signs and neurologic checks; hourly blood glucose levels for the first 4-6 hours and then to continue with 2 hour intervals in the following period; venous blood gases every 2 hours for 6 hours, then every 4 hours, Na, K and ionized calcium every 2 hours for 6 hours then every 4 hours; magnesium and phosphorus every 4 hours; blood urea nitrogen and creatinine levels (every 4 hours) should also be monitored until stable; basic metabolic profile at admission and then every morning. Fluid intake and urinary output should be monitored [193-195]. These are the minimum requirements and should be revised for special situations. For example, patients with initially low potassium, more frequent (hourly) K measurements should be made with ECG monitoring [194,195] or if patient's neurological status is unstable and has a high risk of cerebral edema, more frequent neurologic and vital sign checks (20-30 minutes) should be made [192].

Serum bicarbonate and anion gap are good markers of therapeutic response. Close monitoring of arterial blood gases and serum or urine ketones should not be used as predictor of clinical improvement. Despite of successfull treatment by arresting ketogenesis, ketone levels may be considered unchanged or high, as beta-hydroxybutyrate converts to acetoacetate and conventional (nitroprusside) testing detects only acetoacetate and acetone [135]. For avoid this problem laboratory measurement or the use of a bedside fingerstick sample monitor for beta-hydroxybutyrate can be made. It is reasonable to reduce laboratory monitoring frequency when acidosis resolves, the anion gap falls to near normal limits while response to glycemic therapy becomes noticeable [135]. In the presence of persistent acidosis, despite of successfull treatment; sepsis, concomitant illness or inadequate insulin dosing should be kept in mind and further evaluation and intervention should be made [135,193].

## 7. Complications of diabetic ketoacidosis or it's treatment

Most of the diabetes-related morbidity and mortality in T1DM can be attributed to complications of DKA.

### 7.1. Hypoglycemia

Decrease in the plasma glucose concentration rate should be kept in the range of 50–75 mg/dl/hour. As ketoacidosis is corrected, a rapid decline in plasma glucose levels can be occur and this may cause the blood glucose drop to hypoglycemia levels. Hypoglycemia leads to the release of counter-regulatory hormones and this results with rebound ketosis which can lengthen the duration of treatment. In addition to this, severe hypoglycemia can cause cardiac arrhythmias, seizure or loss of consciousness, brain injury including coma or death. The insulin infusion rate should be checked every hour until a steady glucose decline is achieved and once the plasma glucose falls to <200-250 mg/dL (11.1-13.88 mmol/L), dextrose should be added to replacement fluids to allow continued insulin administration and avoid hypoglycemia [93].

### 7.2. Rhabdomyolysis and renal failure

Acute renal failure (ARF) is an uncommon complication of DKA and rarely requires renal replacement therapy and it may be severe and potentially life threatening [196,197]. The etiology of ARF associated with DKA is multifactorial. The most commonly cited causes are hypovolemia, hypotension and rhabdomyolysis [196]. Prolonged profound ketoacidosis and insulin infusions can lead to severe hypophosphatemia, mainly as a result of intracelluar phosphate shifting [198-201]. Hypophosphatemia can be resulted with rhabdomyolysis. Other risk factors for rhabdomyolysis are severe hyperglycemia and high osmolality. But the pathogenic mechanism leading to rhabdomyolysis in DKA remains unclear. There are few reported cases in literature which had rhabdomyolysis in DKA. There may be no symptoms or the condition can present with a mild increase of creatine kinase or rarely significant acute renal failure necessitating hemodialysis [202-205].

### 7.3. Peripheral venous thrombosis

In DKA treatment, patients may require central vascular access for intensive fluid replacement. However, this route of vascular access causes many complications [206] like venous thromboembolism (VTE) [207]. Children with thrombophilia, malignancy, congenital cardiac disease, acute infection, trauma and surgery have a high risk for complications of central venous catheter (CVC) related VTE [206]. In the medical literature there have been few reported cases CVC related VTE in DKA children without known risk factors. [208-210]. Thus, DKA and its treatment may promote a prothrombotic state and activation of vascular endothelium, predisposing to thrombosis. Whilst, DKA has not been identified as an isolated risk factor for CVC-related VTE in adults [211]. Where essential for, intensive fluid replacement in DKA, these lines should be removed as soon as possible, particularly as CVC-related VTE appears to occur within the first 24-48 hours after insertion [210].

### 7.4. Pancreatitis

Acute pancreatitis is a well known complication of DKA in adults [212] but is unusual in childhood. In children with DKA, abdominal pain and vomiting are common. In addition to this, patients with DKA also have elevated serum pancreatic enzyme (amylase/lipase) concentrations without clinical signs or symptoms and without radiographic evidence of pancreatitis [213,214]. Although hypertriglyceridemia is a known cause of acute pancreatitis and elevated triglyceride concentrations are frequent during DKA, an association between elevated triglyceride concentrations in DKA and pancreatic enzyme elevation or pancreatitis have not be showned in the previous studies [213,215]. The mechanism responsible for pancreatic enzyme elevation in DKA has thus remained unclear. Physicians should be aware of this phenomenon so that patients with DKA who have abdominal pain and elevated pancreatic enzymes are not erroneously diagnosed with acute pancreatitis unless in the presence of persistent abdominal pain, which does not resolve with a successful treatment.

### 7.5. Mucormycosis

Mucormycosis is an acute, rapidly progressing, and often fatal facultative fungal infection occurs in patients with diabetes who have poor glycemic control and DKA, which have been well established as predisposing factors for fungal growth. Mucormycosis can be classfied; cutaneous, rhino-cerebral, pulmonary, gastrointestinal, central nervous system and disseminated [216]. The rhino-cerebral forms develops in patients with diabetes, particularly with the complication such as DKA. The most common symptoms are; facial pain, headache, fever, and mental obtundation [217]. In the Figure 4 there is a patient of us, firstly diagnosed T1DM with DKA infected by mucormycozis [218].

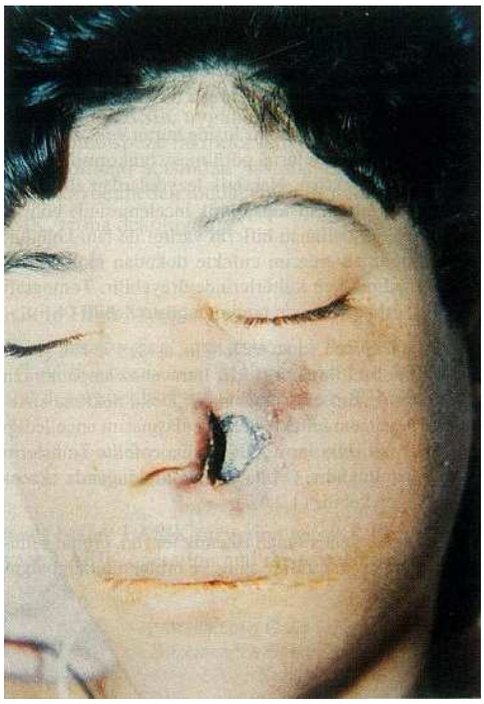

**Figure 4.** A 15 years old male patient firstly diagnosed T1DM with DKA infected by rhino-orbita-cerebral mucormycozis (Picture from the reference [218])

### 7.6. Pulmonary oedema

Pulmonary oedema is a rare, iatrogenic complication of DKA. Usually occurs within a few hours of initiation of treatment related with rapid infusion of crystalloids over a short period of time. Elderly patients and those with impaired cardiac/renal function are at high risk and monitoring of central venous pressure should be considered [219].

### 7.7. Pneumomediastinum

Spontaneous pneumomediastinum is a rare pulmonary complication of DKA [220]. Kussmaul breathing and repeated vomiting increases the intra-alveolar pressure; that leads to alveolar rupture; then, the air penetrates peribronchial and perivascular spaces and reach

the mediastinum. Extension into neck and subcutaneous tissue could be seen. The most common sypmtoms include chest pain and dyspnoea. Treatment is mostly supportive; management of nausea/vomiting along with correction of acidosis to break Kussmaul breathing is should be considered. Patients should be carefully monitored in intensive care settings [221-223].

### 7.8. Cerebral edema

Symptomatic cerebral edema (CE) is rare in adults treated for DKA, although asymptomatic CE may be occur [224] and may be present before treatment [225]. In contrast to this, CE occurs in ~0.3–1.0% of DKA episodes in children [224,226) and is associated with a mortality rate of 20–40% [226] and accounts for 57–87% of all DKA deaths [224,226]. Because of possible delay in diagnosis and more susceptibility to metabolic and vascular changes, children <5 years of age have higher risk for the development of CE. The recognized risk factors for development of CE are acidosis, hypocapnia and elevated serum urea nitrogen (indicator of severity of ketoacidosis and dehydration) [227]. The etiology of CE is unknown; many mechanisms have been proposed including cerebral hypoperfusion with subsequent re-perfusion [228,229], the generation of various inflammatory mediators [230], increased cerebral blood flow, disruption of cell membrane ion transport and a rapid shift in extracellular and intracellular fluids resulting in changes in osmolality. Thus the etiology of DKA-related CE is multifactorial and results of an interplay of complex pathophysiological processes involving the brain [231-235]. The time of onset is not the same in all affected individuals; two-thirds of patients develops signs and symptoms in the first 6-7 hours and the rest from 10-24 hours after start of the treatment with the early-onset individuals tending to be younger [182,236,237].

Muir et al. suggested a model for early detection. The system allowed 92% sensitivity and 96% specificity for the recognition of CE early enough for intervention. One diagnostic criterion, two major criteria or one major plus two minor criteria is suitable to establish CE [236]. Diagnostic criteria, major criteria and minor criteria are shown in Table 6.

| Diagnostic criteria | Major criteria | Minor criteria |
|---|---|---|
| 1. Abnormal motor or verbal response to pain<br>2.Decorticate or decerebrate posture<br>3.Cranial nerve palsy (especially III, IV, VI)<br>4.Abnormal neurogenic respiratory pattern<br>(eg: grunting, tachypnea, Cheyne-Stokes, apneustic) | 1.Altered mentation and fluctuating level of consciousness<br>2.Sustained heart rate deceleration (decline more than 20 per minute) not attributable to improved intravascular volume or sleep state<br>3. Age inappropriate incontinence | 1.Vomiting following initial treatment and its cessation, if present at admission<br>2. Headache (recurrent and more severe than on admission)<br>3.Lethargy or not easily aroused from sleep<br>4. Diastolic blood pressure greater than 90 mmHg<br>5. Age <5 years |

**Table 6.** Diagnostic criteria, major criteria and minor criteria for Cerebral Edema

To prevent the development CE the following should be made; avoiding excessive hydration and rapid reduction of plasma osmolarity, a gradual decline in serum glucose and maintenance of serum glucose between 250–300 mg/dl until the patient's mental status is improved [238].

First of all the rate of fluid administration should be decreased and head of the bed lifted up [236]. Administration of IV mannitol in a dosage of 1.0 g/kg over 20 minutes when repeated as necessary in 1-2 hours shows an improvement in clinical outcome [224,227,228,239]. Patients who do not respond adequately to mannitol of a dose of 1 g/kg, 5-10 mL/kg 3% saline infusion is an alternative treatment [240].

### 7.9. Intracerebral complications other than CE

Neurologic collapse during DKA can cause other intracerebral complications, with or without associated edema, but defined not idiopathic CE [227]. These include; subarachnoid hemorrhage, basilar artery thrombosis [224], cerebral venous thrombosis [241,242], meningoencephalitis [243] and disseminated intravascular coagulation [244,245].

## 8. Prevention

DKA can be prevented by access to a 24-hours telephone helpline for emergency advice and treatment, sufficient patient education and easier access to medical care. Especially patients should be educated about a clinical condition which increases the risk of developing DKA and the changes in the treatment at this situations.

These are includes the following;

1. Patients should be educated about what are the precipitating factors of DKA.
2. Early contact with a 24-hours telephone helpline or the health care provider should be obtained in an acute illness.
3. The importance of insulin during an acute illness should be emphasized.
4. Patients should be advised never to discontinue insulin before contact with health care provider.
5. Patients should be informed about blood glucose goals, the use of additional dose short or rapid acting insulin and the medications available to suppress a fever and treat an infection.
6. In the case of nause and vomiting an easily digestible liquid diet containing carbohydrates and salt should be initiated.
7. Family members should be educated about sick day management and record keeping including assessing and documenting temperature, blood glucose, and urine/blood ketone testing, insulin administration, oral intake and weight [93].

Home measurement of blood glucose-ketone levels may allow early recognition of hyperglycemia and ketosis. Adjusment of insulin therapy based on these findings may prevent hospitalization for DKA [246].

## 9. Conclusıon

DKA is a life-threatening condition which is the most common cause of death in children and adolescents with T1DM and a mortality rate <1% in adult subjects. DKA is a preventable complication of T1DM. Education about the precipitating factors of DKA and rapid access to health care providers contributes to better outcomes and fewer recurrences. DKA can be controlled in a period of 12-36 hours with an appropriate treatment. Thus, complications can be prevented and reduction in mortality rates can be achieved.

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