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Diabetic Ketoacidosis Complications in Pediatrics: A Narrative Review

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ABSTRACT

Introduction: Around the world type I diabetes mellitus (T1D) is becoming more prevalent among pediatrics. The most common cause of mortality in children is diabetic ketoacidosis (DKA). It affects up to one-third of people with T1D. The most common complication of pediatric diabetic ketoacidosis is cerebral edema; however, it is not the only adverse effect of DKA that necessitates continuous observation.

Methods: This study was conducted as a narrative review obtaining all applicable data on complications of diabetic ketoacidosis (DKA) in the pediatrics age group.

Conclusion: This review of literature discusses the effects of DKA on different body systems including neurological, coagulopathy, pulmonary, gastrointestinal, infectious, and renal effects.

Aim: To educate families and healthcare professionals about the significance of strict glycemic control and early identification of DKA in order to prevent the onset of those consequences, we examine each of those multisystem impacts in children.

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Introduction

Diabetes mellitus (DM) is a metabolic disorder affecting blood glucose levels. It has two main types: type I is characterized by reduced or absent insulin release from pancreatic beta cells, and type II is characterized by reduced insulin sensitivity from body tissues [1, 2].

Type I usually manifests in pediatrics at the ages of 7 to 15 years; however, it can manifest in any age group. It results from an autoimmune attack to pancreatic beta cells that is associated with hereditary and environmental causes. Diabetic children may undergo delayed puberty and ultimately grow shorter compared to their peers. This complication has been significantly improved after administering insulin regimens to those children [3].

Diabetic Ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) is the most common complication of type 1 DM and the main cause of morbidity and mortality in type 1 diabetic patients. It usually manifests with a triad of acidosis, ketosis, and hyperglycemia. Among patients who develop DKA, cerebral edema is the most frequent cause of mortality. Recurrent episodes of DKA can result in short- and long-term disturbance in the structure and function of different body systems [3, 4].

The treatment of DKA consists of fluid resuscitation, insulin replacement, and electrolyte restoration along with monitoring for complications (Figure 1).

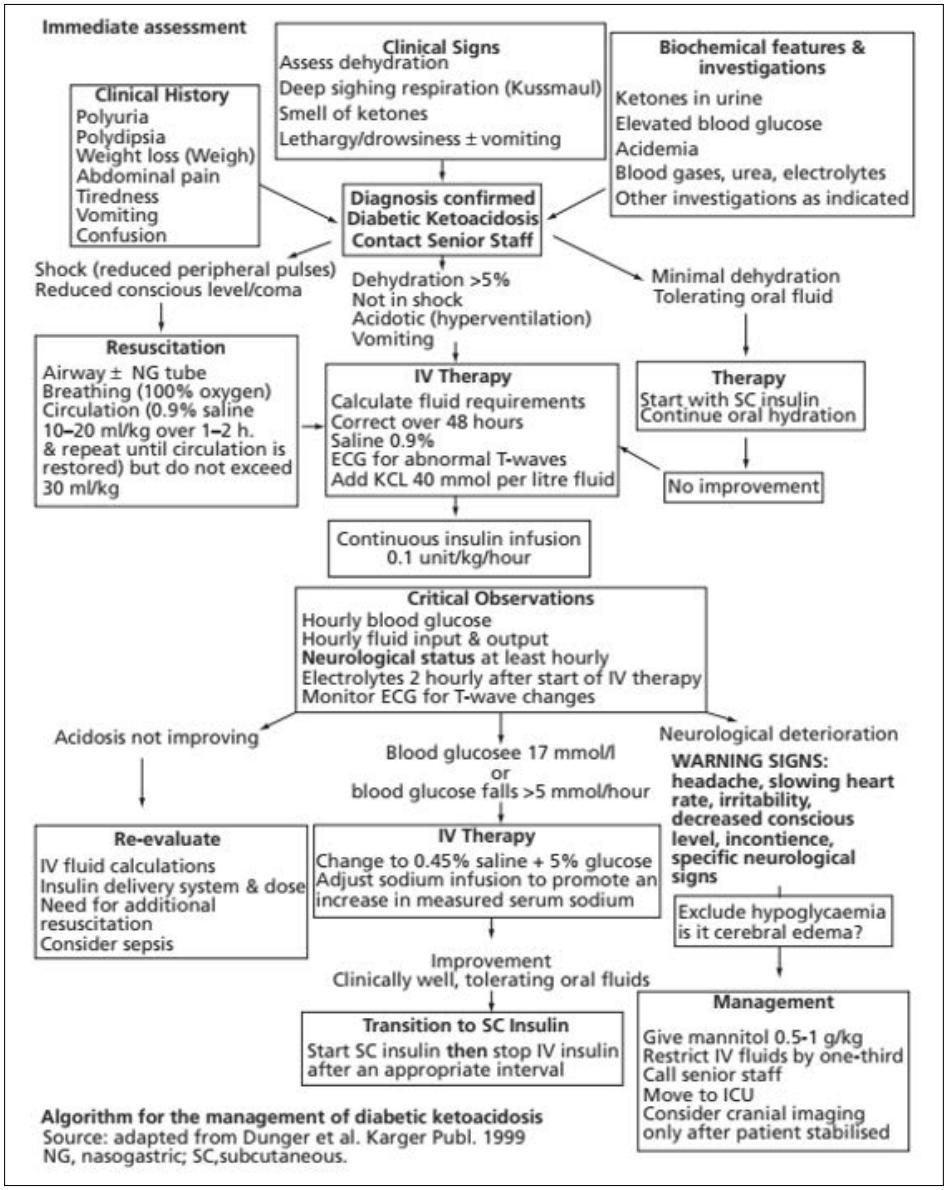

Figure 1

Epidemiology of DKA

DKA manifests at the time of the initial presentation in about one patient out of 30–40% of newly diagnosed type 1 DM patients both at the time of diagnosis and three months thereafter. Cerebral edema, which is the most common complication of type of DKA, affects 0.5% to 0.9% of DKA patients. Therefore, DKA has case fatality rates in the US ranging from 0.15% to 0.31% and is responsible for up to 40% of the condition's fatalities. Death is the most serious effect of DKA, and it strikes 0.15–0.30% of children with type 1 diabetes. Despite a steady decline in mortality due to cerebral edema, children with type 1 diabetes who simultaneously have bradycardia, hypertension, and coma still die from the condition 60–90% of the time [5, 6].

Methods

We gathered available information regarding complications of Diabetic ketoacidosis (DKA) in the pediatric age group. A comprehensive literature search was conducted using the terms "critical care," Diabetic ketoacidosis “DKA" "complication of DKA," and "DKA in pediatrics" in order to accomplish these goals by collecting several research questions. We used the keywords to search in the databases (PubMed and Google Scholar) and found 100 articles, out of which we chose 16 articles that met the inclusion criteria. The inclusion criteria are human studies that were published between 2008 and 2023 which included pediatric age groups who developed DM type I and had experienced at least one DKA episode. There was no restriction on study designs. In order for the narrative review to be as bias-free as feasible, in the second screening we chose which relevant studies are evidence-based and of the best possible quality.

Results

Cerebral & Neural Injuries

Cerebral edema (CE) is the most serious possible consequence of DKA therapy. It is the cause of 60–90% of DKA deaths. Despite being uncommon, it supervenes with a mortality rate of 21-24%. Additionally, 10 to 25 percent of cerebral edema survivors still have serious persistent morbidity. Cerebral edema often develops 4–12 hours following the start of therapy, although it can also happen prior to treatment beginning or, in rare cases, as late as 24-48 hours.

The significant CE is believed to be the result of a vasogenic and cellular process working together. Not only can DKA contribute to CE, but it also seems that CE is frequently exacerbated by incorrect and occasionally aggressive therapy. Patients who come at younger ages and have symptoms that last longer have higher levels of acidosis, dehydration, and hyperglycemia and may have an increased likelihood of developing CE. (Table 1) However, the exact mechanism of CE is still unknown [7, 8]. Treatment strategies involving adequate fluid administration, insulin and bicarbonate seem to be considered in the prevention of the development of CE [9, 10].

Table 1

Cerebral Edema Risk Factors	
Uncontrollable	**Controllable**
• Younger age (< 5 years) • New onset diabetes • Longer duration of symptoms • Severe hypocapnia (more than expected for acidosis) • Increased serum urea nitrogen • Severe acidosis	• IV Bicarbonate treatment for correction of acidosis • Administration of insulin in the first hour of fluid treatment (bolus or infusion) • Greater volumes of fluid given in the first 4h • A marked early decrease in effective serum osmolality (> 5 mOsm/hr)* • Serum sodium (corrected)** dropping or not rising with treatment

Some neuroimaging studies showed narrowing of the lateral ventricles in more than 50% of children with DKA during treatment despite slight changes in those children's mental states which indicates that children with DKA have a far greater prevalence of subclinical cerebral edema than what was previously believed. This demonstrates the need for more studies on the long-term effects of DKA on brain cells [11].

In the long run, DKA is linked with decreased cognitive outcomes. After having a DKA episode, parents and medical professionals noticed significant learning and emotional deficits as well as poor attention in diabetic children compared to their classmates. Evidence also shows that persistent declines in memory function occur years after the onset of DKA in school-aged children (ages 7 to 16). The results of (Tandy Aye) imply that having a previous history of DKA episodes and the episode severity should be considered in future investigations and research on juvenile type 1 diabetes effects on brain and cognitive function. However, currently, there is no evidence that DKA has an adverse effect on a child's brain development. The incidence of complications was greater in those who developed DKA at or soon after diagnosis [11, 12].

There are various potential mechanisms through which fluctuations in blood glucose levels can damage the neurons and axons. Exposure to acute or chronic hyperglycemia and glycemic extremes harm the neurons more than other cells of the body. Glucose interacts with reactive oxygen species creating a state of oxidative stress under which cellular and extracellular macromolecules alter their functions and ultimately result in cellular damage and mitochondrial malfunctioning [5, 6].

Coagulopathy

Children with T1D and DKA have demonstrated a number of transient changes in the coagulation system, which include alteration in coagulation factors, greater activation of platelets and endothelial cells and increased fibrinolytic activity. A prospective study found that children with DKA had low levels of free protein S and protein C which made them unable to function as inhibitors of the von Willebrand factor. As a result, the von Willebrand factor has increased activity. Those effects were transient and resolved after treatment of DKA. Additionally, an inflammatory state ensues during DKA due to an increased number of inflammatory markers like CRP, cytokines (IL6, IL1 beta, and TNF alpha) and activation of the complement system. As a result, patients become at increased risk of developing thrombosis or stroke.

Children who are severely ill and require insertion of the central venous catheter, a foreign material, that results in harm to the endothelium and impedes blood flow appear to be at increased risk of developing DVT. Another risk factor for thrombosis is shock which is exacerbated by DKA, given that severe dehydration sets off the coagulation cascade and causes venous stasis as well as the fact that DKA per se confers a hypercoagulable state.

Both ischemic and hemorrhagic strokes, involving single or multiple infarctions or thrombi over unilateral or bilateral brain lobes, were reported in children and adolescents with DKA. It is still not known whether a diabetic child with acute cerebral infarction linked to DKA would have different pathological tissue results from a non-diabetic child with a stroke [5, 6].

However, the connection between DKA and venous thromboembolism is not as established. However, there are many cases have been reported and demonstrate the relation between diabetic ketoacidosis and pulmonary thromboembolism, with no any other known risk factors. For instance, obesity should be considered as a contributing factor but not always the primary cause if the patient has new-onset diabetic ketoacidosis, is still somewhat ambulatory, and also has pulmonary thromboembolism [13].

Pulmonary

When pulmonary edema develops with DKA, it can be difficult to treat since it typically necessities fluid restriction while DKA necessitates substantial fluid supply to make up for total body water losses. In general, pulmonary edema rarely develops with juvenile DKA and overall outcomes are poorly described. All of the children with DKA in case reports recovered without suffering any severe pulmonary adverse effects [6, 14].

Gastrointestinal

Upper GIT bleeding

Upper gastrointestinal bleeding (GI) is not commonly reported in children, it usually affects the adults. Affected individuals report coffee ground emesis as the most common symptom that might cause stress ulcers, and some report hematemesis and melena [5].

Acute Pancreatitis

It might be difficult to diagnose an illness with concurrent DKA since stomach discomfort is a frequent symptom and non-specific increases of both lipase and amylase are reported with DKA. Because T1D and DKA prevalence is increasing among young patients, they will require more medical attention [5].

In children with DKA, clinically evident pancreatitis is rare; however, increases in blood pancreatic enzyme concentrations are frequent, do not cause stomach discomfort, and usually revert to baseline following DKA therapy. In order to prevent incorrectly diagnosing acute pancreatitis in children with DKA who have stomach discomfort and high pancreatic enzymes, doctors should be aware of this phenomenon. BUN elevation and hypophosphatemia are two factors that are independently linked to an increase in pancreatic enzymes.

The relationships between these variables and pancreatic enzyme rise may imply that splanchnic ischemia or inadequate perfusion during DKA, as well as reperfusion of previously ischemic tissue, may result in mild pancreatic damage [15].

Cardiac Arrhythmia

The most prevalent pediatric arrhythmia is SVT, which has an incidence of 35 per 100000 person-years in the general population and a prevalence of 0.1%–0.4% in children. Without underlying cardiac disease, diabetic ketoacidosis can result in supraventricular tachycardia (SVT), and the risk is enhanced by changes in electrolyte, acid-base, and fluid balance [16].

Infections

Children with T1D and DKA may develop life-threatening infections that warrant early detection and treatment. One study reported a 16-year-old with DKA developed rhino cerebral mucormycosis, a severe fungal infection, which occluded the internal carotid artery and spread to multiple areas of the brain resulting in multiple cerebral infarcts. The clinical presentation included multifactorial shock, hypothermia, altered mental status, and cerebral edema [17].

Another study reported a 13-year-old with a new diagnosis of T1D and DKA and synchronous COVID infection presented with altered mental status and was suspected of cerebral edema. The patient did not improve despite trials of correction of metabolic derangements. Thus, after serial investigations, it appeared the patient had rhinocerebral mucormycosis.

Rhinocerebral mucormycosis is a serious infection that requires a high index of suspicious and early detection in children with T1D and DKA [18].

Acute Kidney Injury (AKI)

Acute kidney injury, which is defined by raised creatinine level, is common among DKA children, and mostly they were developing stage 2 (2-fold) or stage 3 (3-fold increase in creatinine levels) AKI. Studies showed association in DKA children between those who develop AKI and cerebral injury. Children with AKI reported low concentration and IQ levels during and after the DKA episode. Hypotheses included hypoperfusion to brain and kidney or development of multiorgan injury during the episode of DKA [19].

DKA children who developed AKI were usually those of older age, had higher levels of hyperglycemia and acidosis, had higher heart rates, and more volume depletion [20].

With repeated DKA episodes, development of AKI, and poor glycemic control, T1D children become at higher risk of developing diabetic kidney disease [21].

Conclusion

As type I diabetes and DKA are becoming more prevalent among children, more caution should be warranted regarding their short- and long-term complications that affect different body systems. They include neurological, coagulopathy, pulmonary, gastrointestinal, infectious, and renal manifestations. These findings are unusual and raise serious clinical concerns, but early detection and treatment might mitigate long-term damage. Public and professional efforts should be directed to raise the awareness of DKA clinical picture and complications to prevent both acute and chronic harmful effects. Manifestation, management, and consequences of DKA complications in children require further research.

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Author contribution

Both authors wrote initial and final draft of article and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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