Chapter 5

Diabetic Ketoacidosis in the Pediatric Population with Type 1 Diabetes

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Additional information is available at the end of the chapter

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Abstract

Diabetic ketoacidosis (DKA) is a leading cause of morbidity and mortality in patients with type 1 diabetes (T1DM). Individuals familiar with this complication of diabetes should be able to identify the earliest signs and symptoms and act promptly to prevent further deterioration. However, even in patients with established diabetes, the rates of DKA are considerable. This chapter discusses in detail the various aspects of DKA in the pediatric population with T1DM. The prevalence and regional effects on the prevalence of DKA as well as the specific risk factors, whether disease, patient, or physician related, are reviewed. Patients with DKA experience a condition of starvation despite the abundance of metabolic substrate (i.e., glucose); the pathophysiological mechanisms responsible for the development of DKA are outlined. Next, a detailed discussion of the clinical aspects of DKA is provided. This includes the clinical findings at presentation, the approach to treatment, and potential complications. Prevention is the best method for reducing rates of DKA. Somewhat different factors apply in patients with new-onset diabetes when compared with those with established diabetes and these are reviewed.

Keywords: Diabetic ketoacidosis, pediatrics, type 1 diabetes, epidemiology, treatment

1. Introduction

Diabetic ketoacidosis (DKA) is an acute life-threatening complication of type 1 diabetes (T1DM). Despite our detailed knowledge of this condition, rates of occurrence both in new-onset diabetes and in established diabetes are significant. This chapter will discuss various aspects of DKA in the pediatric population with T1DM, ranging from epidemiology and pathophysiology through the spectrum of clinical considerations, including the clinical

presentation, diagnosis, treatment, and complications, and will end with a discussion of the importance and means for prevention of DKA.

Chapter outline:

- Epidemiology of DKA in the pediatric population
- Pathophysiology of DKA
- Clinical presentation and diagnosis of DKA
- DKA Treatment in children
- Complications of pediatric DKA
- Prevention of pediatric DKA
- Conclusion

2. Epidemiology of DKA in the pediatric population

Despite our thorough understanding of the pathophysiology of this potentially life-threatening complication of T1DM, DKA remains a relatively common occurrence in childhood diabetes.

2.1. DKA at diagnosis of T1DM

2.1.1. DKA prevalence

The prevalence of DKA at T1DM diagnosis varies greatly worldwide and ranges between 13% and 80% in different countries [1-11]. A large systematic review of 65 studies including over 29,000 children worldwide found that the lowest prevalences were reported in Sweden, Canada, the Slovak Republic, and Finland and the highest prevalences in the United Arab Emirates, Saudi Arabia, and Romania [1]. Latitude and the regional background incidence of T1DM were negatively associated with the prevalence of DKA [1, 10, 12]. Increased incidence of T1DM has previously been associated with more northern latitudes, although it is unclear whether this represents a true environmental effect or rather reflects ethnic and racial variations between populations [13, 14]. Taken together, these associations suggest that decreased awareness to T1DM and related complications may be a risk factor for DKA at diabetes diagnosis. To further support this, lack of a family history of diabetes was shown to increase the risk of presenting with DKA at diabetes diagnosis [7, 15]. However, despite the increasing incidence of T1DM around the world in recent decades [16], and therefore potentially increased awareness, the prevalence of DKA at diagnosis appears to remain stable [5, 6, 9, 17]. Data from the Search for Diabetes in Youth study (SEARCH), a multicenter US study, found that rates remained stable during 8 years of follow-up for the whole pediatric group as well as when assessing separately the younger children (<4 years of age) and the older children and [9]. They also did not detect any significant gender or ethnicity-specific changes over time.

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2.1.2. Risk factors for DKA

The majority of data points to similar rates of DKA at diabetes diagnosis in boys and girls worldwide [7, 9, 11, 12, 15] (Table 1). However, one study based in Germany did suggest a slightly increased prevalence in girls [4] and another suggested increased prevalence in girls when assessing the very young age-group, under 2 years of age [3]. A younger age at diabetes diagnosis is consistently identified as an important risk factor related to DKA at presentation [2, 3, 6, 7, 9, 15, 18]. In a systematic review of 46 studies involving 24,000 children worldwide, younger age was found to be the most common factor associated with increased risk for DKA at diabetes diagnosis [12]. Different age cutoffs between 2 and 5 years of age were used in studies to describe this association. Odds ratios higher than 4 were found for Finnish children under 2 years of age when compared to those 2 years or older [19, 20]. In the SEARCH study increased prevalence of DKA at presentation was detected in children less than 4 years of age, particularly when compared to youth 15–19 years of age [7]. The causes for this increased prevalence in younger children are likely multiple. Younger children are more prone to misdiagnosis when initially presenting with T1DM [21]. This can reflect a lower index of suspicion on the physician's side combined with the difficulty of identifying the classic symptoms in a toddler; infants and young children might not be able to describe symptoms, and findings may be similar to those of other acute illnesses. However, toddlers may actually suffer a more aggressive progression of metabolic decompensation. There is evidence that younger children have a shorter prodromal period [22] as well as a more rapid decline in beta cell reserve after diabetes diagnosis [19, 23]. A lower BMI or weight loss have also been associated with increased risk for DKA at diagnosis in a number of small studies [15, 24]. Children from ethnic minorities are at increased risk for DKA at T1DM onset [12]. In the United States, higher rates of DKA at diagnosis have been recorded in Hispanic and African American youth when compared with non-Hispanic white North-American youth [9]. In the UK, children from an Asian background were at increased risk of presenting with DKA, particularly if under 5 years of age[11]. Another study from the UK demonstrated that children from non-white ethnicity were at higher risk of a delayed T1DM diagnosis and that a delayed diagnosis was associated with increased risk of DKA at presentation [25]. In the Israeli Negev, the prevalence of DKA at diabetes diagnosis was significantly higher in the Bedouin minority when compared to either the general population or the Jewish population [26]. In another study from Israel, children from an Ethiopian origin had an increased prevalence of DKA at presentation [15]. However, this is not supported by all studies, and others did not find a predilection to minority groups [7, 27]. Another predictor of DKA is a lower socioeconomic status [28]. Several components of the socioeconomic status have been identified as significant. Lower household income was found in US and Canadian studies to be a risk factor [2, 7, 9]; however, European studies did not necessarily support this [29]. In the United States, lack of private health insurance was also identified [7, 9, 30]. More years of parental education as well as academic education of the parents were found protective [7, 31, 32]. However, even in the more privileged populations, the rate of DKA at diagnosis of diabetes is substantial and recorded to occur in over 20% of patients [7]. "Physician-dependent" factors may also increase the risk for DKA at diabetes diagnosis. Such factors include delayed diagnosis of diabetes or a missed diagnosis [25, 21], delayed presentation to secondary care, or delayed treatment after T1DM diagnosis [10, 17].

Risk factors for diabetic ketoacidosis at diabetes diagnosis	
Patient specific	Younger age
	Ethnic minority
	Lower socioeconomic status
Physician related	Delayed diabetes diagnosis
	Delayed initiation of treatment
Epidemiological	Lower regional background prevalence of T1DM
	Residence in a less northern latitude
Risk factors for recurrent diabetic ketoacidosis	
	Insulin omission and poor adherence to treatment
	Poor metabolic control
	Previous episodes of DKA
	Behavioral and psychiatric disorders
	Higher levels of family conflict
	Lower socioeconomic status
	Limited access to outpatient diabetes care

Table 1. Risk factors for diabetic ketoacidosis in the pediatric population

2.2. DKA in patients with established T1DM

Recurrent DKA is by large a preventable complication in patients with established T1DM. In a large cohort of 1243 children with T1DM, the incidence of DKA in patients with established T1DM was 8/100 person-years [33]. Another study assessing a large database of children with established T1DM from Germany and Austria evaluated the incidence of DKA in the most recent year of follow-up [34]. They found that 6% of children suffered from DKA, 5% had a single episode, and 1% had two or more episodes. Two smaller studies followed children with T1DM for about 8 years and found 20–28% to experience at least one episode of DKA [26, 35]. As reflected in these data, it is estimated that it is the same small proportion of patients (around 20%) that account for the majority of admissions for DKA [33, 36]. Insulin omission and poor adherence to treatment are major risk factors [37] (Table 1). Poorer diabetes control, higher hemoglobin A1c, higher insulin doses, and previous episodes of DKA are also important risk factors [33, 34, 38]. Recurrent DKA episodes peak in teenage years, particularly in females [33, 34]. Moreover, the incidence of DKA was found to increase with age in females, yet remained stable in males. A study evaluating the role of patient and family psychosocial functioning as predictors of recurrent acute diabetic complications [35] found girls with recurrent DKA to demonstrate lower social competence and higher rates of behavioral problems. The families exhibited higher levels of family conflict and decreased family cohesion and organization. Major psychiatric disorders have also been implicated in recurrent DKA [39]. As is the case in DKA at T1DM diagnosis, lower socioeconomic status and limited access to outpatient diabetes care are also predictors of recurrent DKA [39].

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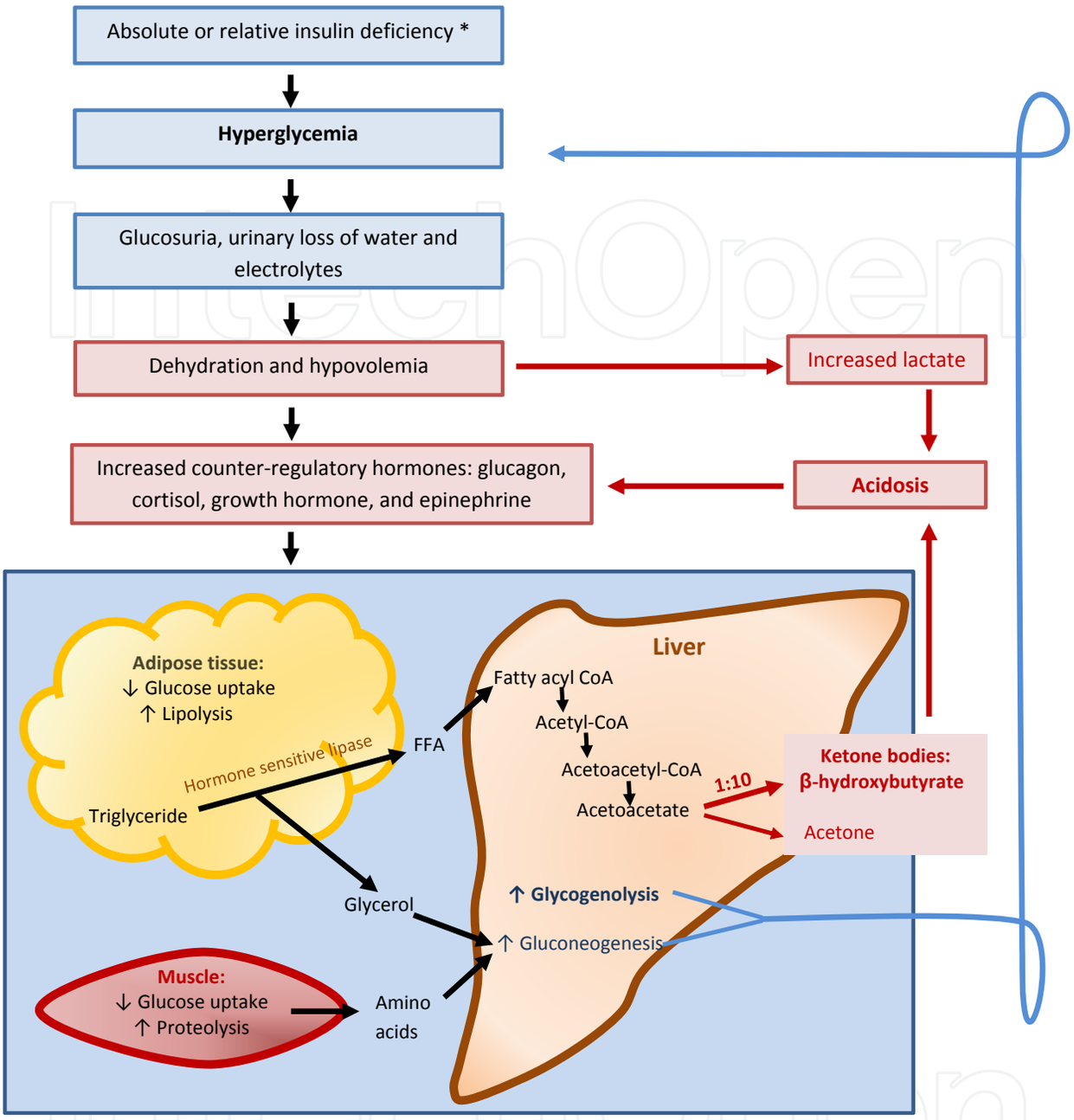
3. Pathophysiology of DKA in children

By definition, hyperglycemia and ketoacidosis are the major components of DKA [40]. The initial impairment leading to DKA is an absolute or relative insulin deficiency. The sequence of events that follows leads to a patient that suffers hyperglycemia, dehydration, acidosis, electrolyte deficiencies, and variable degrees of cerebral dysfunction [41] (Figure 1). In a patient with new-onset diabetes, the cause for the insulin deficiency is the progressive deterioration in beta cell reserve and function [42]. In patients with established diabetes, insulin omission (intentional, as a result of insulin pump failure or other technical problems, or related to lack of access to medical care) is a major cause. Acute stress, commonly induced by an intercurrent illness, might precipitate DKA. During stress, counterregulatory hormone (glucagon, cortisol, growth hormone, and epinephrine) levels increase, causing hyperglycemia and an increased requirement for insulin. If this increased need for insulin is not met, DKA may ensue. Furthermore, an acute illness may impair the child's ability to replace fluid losses.

Insulin deficiency leads to hyperglycemia as a result of decreased utilization of glucose at the same time of increased hepatic and renal glucose production. Hyperglycemia increases serum osmolality, and in response, thirst is induced and osmotic diuresis occurs. The increased fluid loss further promotes polydipsia. Because of the unavailability of glucose to tissues, compensatory mechanisms are activated. Counterregulatory hormones are secreted, leading to increased glucose production by gluconeogenesis and glycogenolysis [43]. Insulin resistance increases and lipolysis is promoted, resulting in production of free fatty acids (FFAs). FFAs are metabolized into ketone bodies, particularly β-hydroxybutyrate, by the liver as an alternative energy source. The accumulation of ketones leads to metabolic acidosis. Another result of the decreased insulin and elevated counterregulatory hormone levels is proteolysis and reduced production of proteins. By this mechanism, substrates for gluconeogenesis are added, further contributing to the hyperglycemia. Initially, plasma ketone body levels rise, causing ketonemia and a base deficit; compensating mechanisms are activated and might lead to measurement of a normal pH. As the condition progresses, ketones further accumulate, ketonuria occurs, and eventually the metabolic acidosis becomes evident. The ketoacidosis causes decreased bowel motility, particularly of the small bowl, accompanied by nausea and vomiting. At this stage, the patient may be unable to compensate for the urinary fluid losses. In a vicious cycle, dehydration impairs the renal ability to clear glucose and ketoacids, thus further worsening the hyperglycemia and acidosis. The increasing osmolality, dehydration, and acidosis decrease cerebral function. This might be manifested as lethargy, or even an altered level of consciousness, further impairing the patient's ability to rehydrate. At presentation, the degree of dehydration ranges from mild to severe, with the majority of children presenting with moderate degrees of dehydration [44]. To compensate for the acidosis, respiratory mechanisms are activated, causing the labored, rapid, deep breathing typically described in patients with DKA (i.e., Kussmaul respirations). The acetone released in the breath results in a characteristic fruity odor.

Serum hyperglycemia and hyperosmolarity together with the acidosis and osmotic diuresis lead to significant electrolyte deficiencies and imbalances [40, 45, 46].



* May be induced by stress, infection, or inadequate insulin dosing in a patient with diabetes. FFA = free fatty acids.

Figure 1. Pathophysiology of diabetic ketoacidosis.

3.1. Potassium depletion

Total body stores of potassium are depleted in basically every patient with DKA, and the average potassium loss is 5 mmol/kg body weight. However, the serum potassium levels may not reflect these losses, and the actual level may be low, normal, or even elevated, particularly if renal function is impaired. The entry of hydrogen ions, accumulated extracellularly due to the acidosis, into cells drives out the intracellular potassium. The osmotic diuresis together with the high levels of aldosterone secreted as a result of the dehydration cause significant

urinary loss of potassium. Emesis might cause further loss of potassium through the gastrointestinal tract. However, an exception is patients with severe volume depletion, in whom renal insufficiency may lead to hyperkalemia. During treatment of DKA, both the insulin itself and the reversal of acidosis generate a net shift of potassium back into cells. Moreover, there is some evidence suggesting a kaliuretic effect of insulin [47]. Altogether, these may result in severe hypokalemia. Patients with hypokalemia at presentation likely suffer more severe total body potassium depletion and are at particular risk of severe hypokalemia and cardiac instability as treatment is provided.

3.2. Sodium and chloride depletion

The osmotic diuresis in DKA results in urinary loss of sodium, and the hyperosmolar state drives water out of cells into the extracellular space, leading to dilutional hyponatremia. The average sodium loss is 6 mmol/kg body weight. Chloride is secreted in the urine with sodium, and the loss is on average 4 mmol/kg body weight. It should be kept in mind that the administration of chloride during the treatment of DKA may lead to hyperchloremic metabolic acidosis, thus interfering with the correction of acidosis.

3.3. Phosphate depletion

Phosphate shifted extracellularly by the acidosis is then lost in the urine. Phosphate losses can be substantial and are estimated to be about 0.5–2.5 mmol/kg body weight. Significant hypophosphatemia has the potential to impair oxygen delivery to tissues and cause muscle weakness. However, despite very low serum levels of phosphate in some patients, such complications are rare, and studies did not demonstrate a benefit for phosphorous replacement [48, 49].

Beyond the electrolyte deficiencies described, in recent years, several studies have pointed out that a deficiency of thiamine (vitamin B1), a water-soluble vitamin of the B complex, may be clinically significant in patients with DKA. Thiamine deficiency was found to be common in children with DKA and may worsen with treatment [50]. The role of this deficiency in the clinical presentation of DKA is yet to be revealed.

4. Clinical presentation and diagnosis of DKA

Metabolic decompensation in DKA usually develops over a period of hours to a few days. Progression can be particularly rapid in patients with established diabetes. Misdiagnosis of a patient with new-onset diabetes may lead to deterioration of the metabolic status. Particularly in young children, misdiagnosis may be a result of the nonspecific symptoms and signs often described in DKA. The earliest clinical manifestations of DKA are related to hyperglycemia and may differ according to age, length of prodromal period, degree of acidosis, and volume depletion [51, 52]. Symptoms and signs in DKA are most often related to the hyperglycemia, dehydration, and acidosis [4, 53-55].

4.1. Symptoms

- Polydipsia, polyuria, and/or nocturia are almost always present, although often not reported.
- Nocturnal or daytime secondary enuresis is often described; polyphagia and weight loss may occur.
- As a result of the acidosis, patients may suffer nausea, vomiting, abdominal pain, shortness of breath, lethargy, or fatigue.

4.2. Physical signs

- Dehydration: Children with DKA often present with 5–10% fluid deficit [51, 56]. They may lack the classical signs of hypovolemia and dehydration because of the acute and chronic losses of both extracellular and intracellular water [57]. Findings depend on the degree of dehydration and may include dry oral mucosa and decreased skin turgor, tachycardia, a sunken fontanelle, and/or sunken eyes. Most patients are normotensive, although postural hypotension can occur.
- Tachypnea or Kussmaul (deep, sighing, and labored) respiration with a fruity acetone odor.
- Signs of decreased tissue perfusion such as a slow capillary refill.
- Neurologic findings [58]: from confusion and drowsiness to decreased consciousness and coma. Neurologic findings should raise the suspicion of cerebral edema.

In infants, especially those who are not toilet trained, the diagnosis may be delayed. Weight loss, irritability, and decreased activity are common at presentation. Dehydration and severe diaper rash may be the only physical signs. Older children and adolescents can manifest profound wasting, cachexia, and prostration on DKA presentation, especially with a prolonged course of uncontrolled/misdiagnosed diabetes.

4.3. Laboratory findings

4.3.1. Diagnostic criteria

Biochemical criteria for the diagnosis of DKA are defined as follows [40, 51, 56, 59]:

- Hyperglycemia: blood glucose (BG) >200 mg/dl (11 mmol/L)
- Metabolic acidosis: venous pH <7.3 and/or bicarbonate <15 mmol/L
- Ketonemia and ketonuria: serum beta hydroxybutyrate ≥3 mmol/L

On certain occasions, patients may present with "euglycemic ketoacidosis" where glucose levels are near normal [54, 59]. This may develop in young children who consumed small amounts of carbohydrates or are partially treated or in children with emesis.

The severity of DKA is established by the degree of acidosis: mild DKA, pH 7.2–7.3 or bicarbonate <15 mmol/L; moderate DKA, pH 7.1–7.2 or bicarbonate 5–10 mmol/L; and severe

DKA, pH <7.1 or bicarbonate <5 mmol/L [51, 56, 58]. The duration of symptoms, volume deficit, degree of ketosis, and neurologic status further determine the severity of illness in a child with DKA.

4.3.2. Acid–base balance

Acidosis is caused by the production and accumulation of ketones in the serum [49]. Three ketones are produced in DKA: two ketoacids (beta-hydroxybutyrate and acetoacetate) and the neutral ketone, acetone. In DKA, beta-hydroxybutyrate constitutes 75% of the circulating ketones. During recovery, it is converted to acetoacetate and acetone, which persists for a longer period. Therefore, measuring serum beta-hydroxybutyrate is the most useful for diagnosis. The severity of the metabolic acidosis is dependent on the compensatory respiratory alkalosis, the acid excretion in the urine [60], and the duration and rate of increased ketoacid production. The serum anion gap (AG) is an index of unmeasured anions in the blood (normal in children is 12 ± 2 mEq/L). Most patients with DKA present with a high AG (≥20 mEq/L) due to high serum levels of ketoacids. The resolution of ketoacidosis is followed by a normal AG.

4.3.3. Electrolyte imbalances

Laboratory tests that should be routinely monitored in the setting of DKA include serum glucose, electrolytes, creatinine and BUN, blood gases, pH, bicarbonate, and a complete blood count. Changes over time in electrolytes and renal function tests must be followed.

Serum potassium: As mentioned earlier, potassium loss can be a result of increased ketoacid excretion, osmotic diuresis, vomiting, or diarrhea. The serum potassium concentration may be normal, increased, or decreased at diagnosis of DKA. However, monitoring of potassium levels is crucial because hypokalemia may eventually develop.

Serum sodium: Low serum sodium in DKA may occur due to hyperglycemia and its effect on plasma osmolarity. Polydipsia and excessive consumption of water can also contribute to lowering sodium concentration. Osmotic dieresis and water loss in excess of sodium and potassium will tend to raise the serum sodium concentration. Hyperlipidemia can cause pseudohyponatremia [61].

Serum phosphate: Decreased phosphate intake and phosphaturia may result in a negative phosphate balance. At presentation of DKA, serum phosphate is usually normal or high due to the combined effect of metabolic acidosis and insulin deficiency. The degree of phosphate loss in DKA is apparent after insulin treatment [62].

4.4. Differential diagnosis of DKA

DKA should be differentiated from other causes of acidosis and/or hyperglycemia, such as acute gastroenteritis with metabolic acidosis, uremia, salicylate intoxication, starvation ketosis and lactic acidosis. When the presenting symptom is altered consciousness or coma, encephalitis and other CNS pathologies must be ruled out. Diabetic ketoacidosis should also be

distinguished from the hyperosmolar hyperglycemic state, which is infrequent in children [51, 57, 63]. The main differences between these conditions are the degree of acidosis and insulinopenia.

5. DKA treatment in children

Successful treatment of DKA requires correction of dehydration, acid–base and electrolyte imbalances, insulin administration, and identification of comorbid and precipitating conditions. This treatment may be associated with inherent risks of inducing hypoglycemia, hypokalemia, and cerebral edema. Therefore, any protocol must be used with caution, and close monitoring of patients is crucial. Children with severe DKA, an altered level of consciousness, or those who are at increased risk for complications should be considered for treatment in an intensive care setting. In this chapter, we will focus on the general principals and considerations in DKA management as well as controversies regarding DKA treatment.

5.1. Standard protocols for DKA management

There is some variability in protocols for DKA management, but the basic principles are similar in the various protocols available in the literature [40, 51, 64, 65]. Protocols enabling standardization of treatment are of great value to the treating team involved; however, clinical judgment should always be practiced. Frequent monitoring of the patient is a very important aspect of the treatment and should include meticulous documentation of clinical observations, fluid balance, laboratory results, and medications administered. A neurological follow-up for warning signs and symptoms of cerebral edema is also essential.

5.2. Fluid replacement

Fluid replacement in children with DKA remains a controversial topic with regard to the amount of intravenous fluid, rate of delivery, and fluid composition. Current recommendations are based on expert consensus statements and accumulated clinical experience, as evidence from large randomized clinical trials is lacking.

5.2.1. First hour fluid resuscitation

The goals of initial volume expansion are to restore the effective circulating volume and the glomerular filtration rate. Intravenous fluid administration bares the risk of inducing an elevation in the intracranial pressure (ICP), potentially resulting in cerebral edema, and thus should be done carefully [66, 67]. In a rabbit model of DKA, the use of hypotonic fluids, compared with isotonic, was associated with greater rises in ICP [66]. Some studies suggest that rapid fluid replacement may increase the risk of cerebral edema [68, 69], although other studies did not support this finding [70, 71]. Studies in both adults and children demonstrated a more rapid correction of acidosis when a slower rate of fluid administration with isotonic or near-isotonic solutions was used [72, 73]. Hyperchloremic metabolic acidosis is another often

overlooked risk resulting from the use of large volumes of normal saline (NS) (0.9%) [73, 74]. At present, there is no data that support the use of colloid in preference to crystalloid in the treatment of DKA. Based on these data, most protocols recommend an initial IV infusion of 10–20 ml/kg of normal saline (NS) (0.9%) or Ringer's lactate over the first 1 to 2 h of treatment. Fluid boluses may be repeated according to the patient's hemodynamic status. However, total IV fluids should not exceed 40 ml/kg in the initial 4 h of treatment due to the aforementioned risks.

5.2.2. Fluid replacement over the next 24–48 h of treatment

Once the child is hemodynamically stable, subsequent volume expansion should be given more gradually, with a goal of replacing the remaining fluid deficit over the next 24 to 72 h. Significant additional fluid loss after initiation of treatment is rare because vomiting and excessive urine output usually resolve within the first hours of treatment. Half NS or NS (0.45–0.9%) solutions are appropriate for replacement. The rate of fluid administration is guided by the estimated degree of dehydration and fluid deficit. Calculating the effective osmolality is also of use, and most often, replacement is in the range of 1.5–2 times the usual maintenance requirement based on age and weight. Unless a contraindication exists, potassium must be added at this time (see below). To prevent a rapid decrease in plasma glucose concentration and hypoglycemia, 5% glucose should be added to the IV fluid when the plasma glucose falls to approximately 250–300 mg/dl (14–17 mmol/L), or sooner if rapidly decreasing. Fluids that were given in another facility before assessment should be factored into calculation of deficit and be subtracted from the 24-h totals.

5.3. Insulin administration

5.3.1. Intravenous insulin administration

Insulin therapy is essential to suppress lipolysis and ketogenesis and to correct acidosis. Insulin infusion is recommended 1–2 h after starting fluid replacement therapy and initial volume expansion. An initial IV bolus of insulin is unnecessary, it was not shown to affect the duration of time to attaining a serum glucose level of less than 250 mg/dl, yet it may increase the risk of cerebral edema [69, 75, 76]. A slow infusion of a low dose of 0.1 U/kg/h IV insulin is considered the standard of care in pediatric DKA [77, 78]. The dose of insulin should remain 0.1 U/kg/h at least until the resolution of DKA (pH >7.30; bicarbonate >15 mmol/L and/or closure of the anion gap). It is possible that even a lower dose of insulin is sufficient for DKA treatment. A recent randomized control trial compared a very low dose IV insulin infusion (0.05 U/kg/hr) to the standard dose. Similar results were achieved in terms of the rate of blood glucose decrease and the resolution of acidosis, suggesting that a dose lower than the current standard dose can be used [78].

5.3.2. Subcutaneous insulin regimens

Few studies, mostly in adults, demonstrated subcutaneous rapid acting insulin injected every 1–2 h to be a valid alternative for the standard intravenous insulin treatment of mild-to-moderate uncomplicated DKA [79, 80]. In our practice, we administer subcutaneous regular

insulin (SCRI) every 4 h for treating children with DKA and pH ≥7.00 and K >2.5 mEq/L. Insulin therapy is initiated during the second hour of treatment and administered every 4 h until resolution of DKA. The insulin dose is calculated as 0.8–1 IU/kg/day divided by 6. This treatment was found to be a simple, effective, and safe alternative to the standard DKA protocol. Such treatment has the potential to simplify insulin administration and reduce both patient inconvenience and admission costs. Subcutaneous insulin should not be used in subjects whose peripheral circulation is impaired.

5.4. Electrolyte replacements

5.4.1. Potassium replacement

Children with DKA suffer from total body potassium deficits of approximately 3–6 mmol/kg. Hypokalemia at presentation may be related to prolonged duration of disease, whereas hyperkalemia primarily results from reduced renal function [60]. Insulin administration and the correction of acidosis drive potassium back into the cells, which may cause hypokalemia and predispose the patient to cardiac arrhythmias. Replacement therapy is usually required regardless of the serum potassium concentration. In most protocols, potassium is not given during the first hour of fluid resuscitation unless the patient is hypokalemic, in which case some protocols recommend adding potassium to the initial volume expansion before starting insulin therapy. Potassium can be given as potassium phosphate or potassium chloride. The starting potassium concentration in the infusate should be 40 mmol/L. Subsequent potassium therapy should be based on serum potassium measurements.

5.4.2. Phosphate and calcium replacement

Prospective studies have not shown clinical benefit from phosphate replacement [48, 49, 81]. The deficit usually corrects spontaneously, although it should be kept in mind that it may persist for several days after the resolution of DKA [45]. Therefore, only severe and symptomatic hypophosphatemia accompanied by significant weakness should be treated with phosphate supplements. Potassium phosphate may be used safely in combination with potassium chloride or acetate to avoid hyperchloremia. Careful monitoring of serum calcium should be performed to avoid hypocalcemia. In a study on nine children with DKA, during phosphate infusion, transient hypocalcemia occurred in 67% and transient hypomagnesemia in 56%. One child developed carpopedal spasms refractory to intravenous infusion of calcium gluconate but responsive to intramuscular injection of magnesium sulfate. In 33%, parathyroid hormone was low at the time of hypocalcemia, an observation that suggests transient hypoparathyroidism [82].

5.4.3. Bicarbonate therapy

Acidosis is reversible by insulin replacement. Several clinical trials have shown no clinical benefit from bicarbonate administration in pediatric DKA [83-86]. Moreover, bicarbonate therapy may cause paradoxical CNS acidosis. Bicarbonate crosses the blood–brain barrier slowly, yet the CO_2 formed ($HCO_3 + H+ \rightarrow H_2O + CO_2$) crosses rapidly into the CNS forming

H_2CO_3, thus worsening the CNS acidosis [87, 88]. As a result of the sodium supplement included in the bicarbonate preparations, this therapy may be associated with hypokalemia and increasing osmolality. Bicarbonate administration was also reported as a risk factor for cerebral edema in several studies [51, 69, 89]. Despite all the risks mentioned, in must be kept in mind that patients with severe acidemia (arterial pH ≤6.9) in whom decreased cardiac contractility and peripheral vasodilatation can further impair tissue perfusion and patients with life-threatening hyperkalemia may benefit from cautious alkali therapy [84]. If bicarbonate is considered necessary, it should be cautiously administered at a dose of 1–2 mmol/kg over 60 min.

5.5. Introduction of oral fluids and transition to SC insulin injections

Upon resolution of DKA and when substantial clinical improvement has occurred, oral fluids can be introduced and a protocol of subcutaneous insulin can be initiated or restarted.

6. Complications of pediatric DKA

As mentioned in detail earlier, diabetic ketoacidosis (DKA) is treated with fluids, electrolytes, and insulin. With prompt treatment, complications of DKA are uncommon. However, when complications do occur, they are usually serious with significant mortality and long-term morbidity. Surprisingly, the most common complication of DKA (cerebral edema) may be related to this lifesaving treatment.

6.1. Cerebral edema

Cerebral edema is a devastating and unpredictable complication of DKA and its treatment. Epidemiological studies demonstrate that overall cerebral edema occurs in around 7/1000 episodes of DKA and is more common in children and newly diagnosed patients. Other studies found that clinically apparent cerebral edema develops in 1–2% of children with DKA [90]. The pathophysiology of cerebral edema is not well understood, and it is likely that several processes contribute to the development of this complication: ischemic, osmotic, and vasogenic.

Osmotic: ultimately, cerebral edema is due to excessive entry of water into the cells of the central nervous system due to the presence of intracellular idiogenic osmoles causing swelling of the brain as serum osmolality drops during treatment.

Vasogenic: studies using magnetic resonance diffusion weighted imaging demonstrate that the apparent diffusion coefficient of brain water is greater during treatment of DKA than during recovery, indicating increased extracellular fluid due to an increase in blood brain barrier permeability during the acute treatment phase of DKA [91-93]. These findings are consistent with the vasogenic cerebral edema, i.e., fluid surrounding the cells, rather than osmotic cell swelling that has previously been suggested. This vasogenic theory is also supported by the fact that the degrees of dehydration and hyperventilation at presentation, but not initial osmolality or osmotic changes during treatment, were correlated with degree of edema

formation [92]. This edema (within the enclosed space of the cranium) can cause transtentorial brain herniation through the foramen magnum, leading to unconsciousness and respiratory arrest.

6.1.1. Risk factors for cerebral edema

Several case–control studies have pointed out risk factors for the development of cerebral edema [69, 70, 94, 95]. These can be divided into two main groups.

Risk factors related to disease severity at presentation:

a. Younger age

b. Newly diagnosed compared with established diabetes

c. More severe acidosis at presentation

d. Higher serum urea levels

e. Lower partial arterial CO_2 ($PaCO_2$) values

Risk factors related to therapy:

a. Larger volume of fluid given during the first 4 h of treatment

b. Administration of bicarbonate

c. Lower plasma sodium concentrations

d. Administration of insulin within the first hour of treatment

6.1.2. Symptoms and signs

These typically appear within 6–24 h after starting intravenous fluids and insulin treatment. Therefore, it is crucial to monitor and recognize the early warning signs of cerebral edema through careful monitoring of all DKA patients. These include signs and symptoms of increasing intracranial pressure, such as a decline in the level of consciousness, headaches, bradycardia, depressed respiration and apnea, papillary changes, papilledema, posturing, seizures, and coma.

6.1.3. Diagnosis

The diagnosis of cerebral edema is clinical. Recognition of the above-mentioned signs and symptoms should allow early intervention and hopefully prevention of morbidities associated with this condition. CT or MRI of the brain should be performed to rule out other diagnoses and potentially confirm the diagnosis of cerebral edema. However, it should be emphasized that radiographic imaging may be unhelpful in detecting cerebral edema if performed very early after the development of symptoms.

6.1.4. Treatment of cerebral edema

The patient should be treated and monitored in the intensive care unit; however, if located elsewhere, initial treatment must not be delayed until transitioned. Mannitol or hypertonic

saline should be readily available for use at the earliest signs and symptoms of cerebral edema. Other measures include a reduction in the rate of fluid administration and elevation of the head of the bed. Mannitol 1 g/kg (5 ml/kg of mannitol 20%) should be administered over 15 min; alternatively, hypertonic saline (3% NaCl) 5–10 ml/kg over 30 min can be administered. This treatment will reduce brain edema and blood viscosity and improve cerebral blood flow. Intubation and ventilation may be necessary to provide adequate ventilation and correct acidosis. Aggressive hyperventilation has been associated with poor neurological outcome and is not recommended [96].

6.2. Hypoglycemia and hypokalemia

These are additional potential complications of DKA treatment. Both are discussed earlier in the chapter.

6.3. Rare complications of DKA

6.3.1. Adult respiratory distress syndrome

This has been reported in patients with DKA, especially in patients younger than 50 years. Clinical features include dyspnea and tachypnea, with central cyanosis and nonspecific chest symptoms.

6.3.2. Acute renal failure

This can develop due to severe dehydration. Once fluid replacement is restored, kidney function should start to recover.

6.3.3. Thromboembolic complications

These may arise as a consequence of dehydration, increased blood viscosity, and coagulability. Rehydration and restoration of body fluids might help in preventing these complications [97]. Established thromboembolic complication should be treated promptly.

7. Prevention of pediatric DKA

The best approach for decreasing the burden of DKA is prevention. Preventive measures are based on the identified risk factors of T1DM and DKA and on their clinical presentation. Risk factors differ between DKA at the time of T1DM diagnosis and episodes occurring in patients with established diabetes. Identifying high-risk children, using both immunologic and genetic methods, can lead to earlier diagnosis of diabetes and decreased DKA incidence at disease onset [10, 33, 98, 99]. However, such screening raises obvious ethical questions, as the exact risk or timing of the development of diabetes in a child at risk are not known and no treatment has proved protective thus far. In families with T1DM, a special attention to early symptoms and signs is recommended to detect the onset of diabetes in other members and to prevent future DKA [51].

Greater public awareness to signs and symptoms of DKA has been related to decreased rates of DKA. This is further emphasized by the success of awareness campaigns in decreasing the rates of DKA. A campaign to increase awareness of physicians, schools, and parents was carried out in Parma, Italy [1991–1997] [100, 101]. The researchers displayed posters in pediatric centers, schools, and physician offices and demonstrated a significant reduction in the DKA rate from 78% to 12% in 6–14 years old children over an 8-year period. An Australian study demonstrated a reduction in DKA prevalence in new-onset diabetes from 38% to 14%, when repeating the Parma study diabetes awareness campaign [102]. However, it is important to mention that not all such programs have been successful [5], and complex risk factors might be involved.

The rates of DKA in patients with established diabetes can also be reduced. Identifying the specific causes for recurrent DKA in a child is important and may prevent future DKA events [40]. Detailed and intensive diabetes education programs, telephone help lines, and availability of skilled health care providers can reduce DKA occurrence [103-106]. Education programs lead to better understanding of the disease and might assist families in identifying times of increased risk (i.e., intercurrent illness or pump malfunction) as well as early signs of deterioration and of DKA. Such programs are important to the noncompliant children, especially those with recurrent episodes of DKA, and should be led by professional teams [17, 107]. Education and adult guidance were shown to decrease insulin omission in patients with recurrent DKA episodes [108]. Early identification of ketosis, using home measurement of beta-hydroxybutyrate, can prevent progression to DKA [109].

8. Conclusion

DKA is a serious complication of pediatric T1DM. The pathophysiology is complex, demonstrating reciprocal effects between the metabolic derangements involved. A "hunger" response takes place despite the abundance of metabolic substrate. Various risk factors have been identified, some are patient related yet others emphasize the important effects of both family and social circumstances. DKA is largely preventable, and efforts to further increase awareness to this complication of diabetes should be encouraged.

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