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Current Concepts and Controversies in Prevention and Treatment of Diabetic Ketoacidosis in Children

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Abstract Diabetic ketoacidosis (DKA) is caused by absolute or relative lack of insulin. Lack of insulin leads to hyperglycemia, ketonemia, and acidosis. Prevalence of DKA at diagnosis of type 1 diabetes (T1D) varies around the world from 18 % to 84 %. Incidence of recurrent DKA is higher among females, insulin pump users, those with a history of psychiatric or eating disorder, and suboptimal socioeconomic circumstances. DKA is the most common cause of death in children with T1D. Children with DKA should be treated in experienced centers. Initial bolus of 10–20 mL/kg 0.9 % saline is followed by 0.45 %-0.9 % saline infusion. Fluid infusion should precede insulin administration (0.1 U/kg/h) by 1–2 hours. The prevention of DKA at diagnosis of diabetes can be achieved by an intensive community intervention and education of health care providers to raise awareness. Prevention of recurrent DKA requires continuous patient education and access to diabetes programs and telephone services.

Keywords Diabetic ketoacidosis · Epidemiology · Prevention · Treatment of DKA · Cerebral edema

Introduction

Pathophysiology

Diabetic ketoacidosis (DKA) is caused by progressive beta-cell failure in previously undiagnosed patients or omission of insulin, pump failure or inadequate insulin dosing during infection, surgery, trauma, and stress in established patients. Lack of insulin leads to development of hyperglycemia due to impaired glucose utilization and increased glucose production by the liver and kidneys due to excess of counterregulatory hormones. An increase in glucagon, catecholamines, cortisol, and growth hormone leads to catabolism of fat and protein. Lipolysis results in increased production of ketones, especially β-hydroxybutyrate (ß -OHB) with the ratio between acetoacetate and ß -OHB increased from 1:1 to about 1:10, ketonemia and metabolic acidosis (Fig. 1).

Definition

A consensus of the American Diabetes Association (ADA) [1, 2], the European Society for Paediatric Endocrinology (ESPE), and the Lawson Wilkins Pediatric Endocrine Society (LWPES) [3] defines DKA in children as the presence of hyperglycemia with plasma glucose higher than 250 mg/dl or ~14 mmol/l, venous pH <7.3 and/or bicarbonate <15 mmol/L, and elevated ketone levels in urine or blood. DKA is categorized by the severity of acidosis into mild, moderate and severe form:

Mild: venous pH >7.2 and <7.3, bicarbonate <15 mmol/L
Moderate: venous pH >7.1 and <7.2, bicarbonate <10 mmol/L
Severe: venous pH <7.1, bicarbonate <5 mmol/L.

Prevalence and Risk Factors of DKA at the Diagnosis

The prevalence of DKA at the diagnosis of type 1 diabetes (T1D) varies around the world. The most recent, population-based study from the USA, reported 29 % of patients with T1D younger than 20 years at diagnosis presenting in DKA [4]. A lower rate of 18.6 % has been reported from Canada [5]. In

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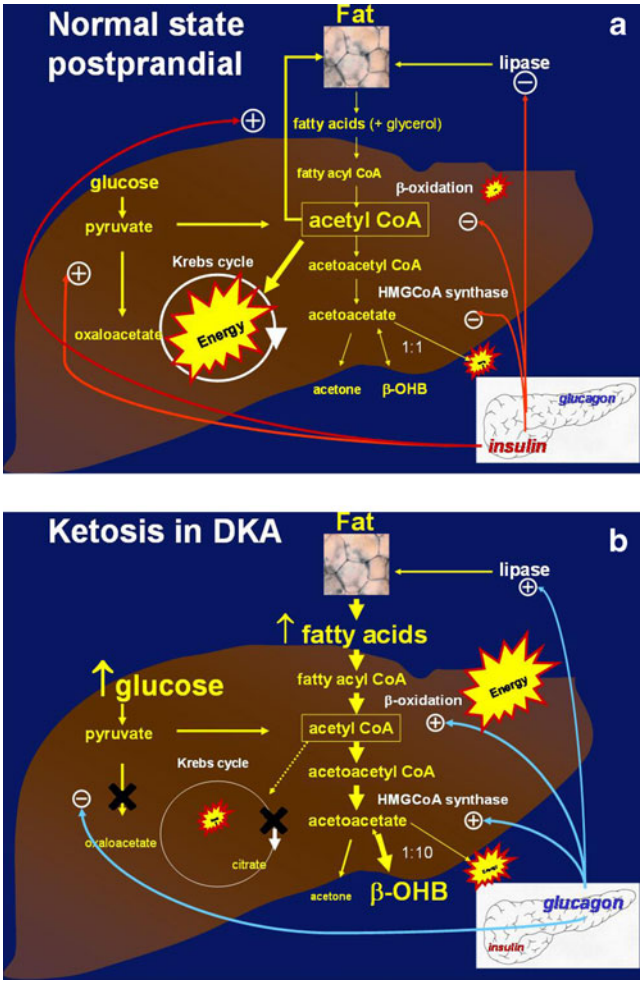

Fig. 1 Metabolic changes in DKA. **a** In the normal postprandial state, glucose oxidation through the Krebs cycle is the main source of energy. Excess energy is stored in fat and lipolysis is suppressed. **b** In DKA, low levels of effective circulating insulin and a rise in glucagon suppress glucose oxidation and increase lipolysis. Lipolysis leads to increased production of ketones, especially ß-OHB. The ration between acetoacetate and ß-OHB increases from 1:1 to 1:10. While oxidation of fatty acyl-CoA and acetoacetate provides alternative source of energy, ensuing ketonemia contributes to metabolic acidosis

Europe, the prevalence varied from 18 %–67 % [3, 6–10]. The prevalence was higher in populations with lower incidence of T1D, most likely due to lower societal awareness of diabetes symptoms. In Australia, the overall prevalence was 26 % over a period of 15 years (1985–1999) with a slight downward trend in the prevalence over the study period [11], and higher prevalence from 42 % to 63 % in more recent years has been observed in New Zealand [12]. Data from Middle Eastern populations are sparse. In initial reports the prevalence of DKA at diagnosis was very high, reaching 85 % [13]. Over the last several years the prevalence of DKA at diagnosis decreased but it is still high [14, 15].

The prevalence of DKA at the diagnosis is higher among younger children [4, 16], reaching over 50 % in those aged less than 2 years [17]. Lower socioeconomic status is a significant risk factor [4, 18]. In addition, treatment with high dose glucocorticoids, atypical antipsychotic agents, diazoxide, and immunosuppressive drugs have been reported to precipitate DKA in individuals not previously diagnosed with diabetes.

Incidence and Risk Factors of DKA in Established T1D

The overall incidence of DKA in patients with established T1D varies from 1 to 12/100 person-years [19, 20]. The incidence of DKA increases significantly with age in females, but remains stable in males [19]. Most of the episodes of DKA beyond diagnosis are associated with insulin omission or treatment error, (eg, inadequate adjustment of insulin therapy during intercurrent illness or accidental interruption of insulin infusion). Patients with a previous episode of DKA are at higher risk for recurrent DKA [19].

The risk of recurrent DKA is higher in patients with poor metabolic control [19, 21]. Lower socioeconomic status and insufficient access to outpatient diabetes care are often the primary mechanism. Patients with recurrent ketoacidosis have been shown to exhibit more family conflict, and major psychiatric disorders (depression, bipolar disorder, schizophrenia) also play a role [19]. Patients treated with insulin pumps are at a higher risk for DKA than their classical risk-factor profile would suggest. Undetected interruption of insulin delivery for 4–6 hours may be enough for DKA to ensue.

Complications of DKA

In developed countries, as many as 0.3 %–1 % of children die at the diagnosis of diabetes [22]. At this rate, there are 65-210 potentially preventable deaths among an estimated 21 000 children and adolescents diagnosed in the U.S. annually. DKA is the most common cause of death in children with T1D [23]. Reported case fatality rate was 0.18 %–0.51 % among hospitalized children who presented in DKA in Canada [24, 25]. Brain edema accounts for nearly all deaths at diagnosis of T1D in children [26, 27], while it is rare in adults. Cerebral edema occurs in 0.3 %–3.0 % of childhood DKA cases and can be a fatal complication [26, 27]. Non-fatal cerebral edema quite often leads to permanent neurological deficits. Risk factors include receiving more than 50 ml/kg of fluid in the first 4 hours of treatment [28], younger age, low pCO_2 and high BUN at presentation and bicarbonate treatment [27], as well as a failure of sodium levels to rise as glucose levels decrease.

The etiology of cerebral edema is still unclear. A recent body of evidence suggests that DKA-related cerebral edema may be caused by cerebral injury hypoperfusion induced by

dehydration and hypocapnia and followed by reperfusion during treatment, which leads to vasogenic edema [29••]. Brain hypoperfusion can also trigger an exaggerated cytokine expression, especially IL-1, leading to brain ischemia and edema [29••, 30, 31].

Less frequent causes of mortality include hypokalemia, hyperkalemia, thrombosis, neurological complications, shock, sepsis, pancreatitis, aspiration pneumonia, and pulmonary edema.

Diagnosis of DKA

Clinical Presentation

The clinical picture of DKA includes polyuria, polydipsia, and dehydration. Weight loss is invariably present, but polyphagia is unusual. Abdominal pain, nausea, and vomiting and rapid, deep breathing are common, as are symptoms of infection that sometimes delay proper diagnosis.

Clinical Monitoring

Careful and continuous monitoring of patients in DKA is critical, as the clinical condition and laboratory values change quickly and require immediate therapeutic response.

1. A flow sheet for fluids, insulin, vital signs, lab values, etc.
2. Fluid intake and output record.
3. Patient should be placed on cardio-respiratory monitor; if potassium level is abnormal, obtain ECG.
4. Two large bore IV catheters for therapy and frequent blood draws.
5. Neurological check (pupils, neurological exam, Glasgow Coma Scale) hourly for signs of cerebral edema.

Initial laboratory tests include:

1. Blood glucose and blood or urine ketones.
2. Electrolytes: sodium, potassium, chloride, calcium, phosphorus, bicarbonate and blood urea nitrogen. Sodium levels are spuriously low in the setting of hyperglycemia and should be expressed as corrected Na = measured Na + (plasma glucose-100)(1.6)/100.
3. Blood gases including venous pH and pCO_2. There is growing evidence that some of the currently recommended tests are repetitive. A retrospective review has shown that serum bicarbonate accurately predicts abnormal venous pH in children with DKA. Venous pH determination may not be necessary for all patients being evaluated for DKA [32].
4. Serum osmolality can be measured directly or calculated as 2(Na + K) + glucose/18 + BUN/2.8 (mOsm/L).
5. Appropriate cultures (blood, urine, throat, skin) if infection is suspected.
6. If chest film is indicated, it should be delayed until hydration is normalized.
7. CT or MRI of the head is not routinely indicated.

Follow-Up Laboratory Tests

1. During the first four hours or until glucose and electrolytes are stable:

   Hourly blood/plasma glucose, electrolytes, venous pH and/or β-HOB

2. When glucose and electrolytes are stable and until pH >7.3 or bicarbonate >15 mEq/L:

   Every two hours blood/plasma glucose, electrolytes; venous pH and/or β –HOB.
   Other studies (osmolality, calcium, phosphorus, etc) as indicated.

Treatment of DKA in the Emergency Department/ Hospital Setting

Fluids

Initial Bolus

The main goal of fluid therapy is to restore extracellular and intracellular fluid volume and replace electrolytes, which have been depleted through osmotic diuresis and vomiting. The fluid loss is usually 5 %–10 %, but unfortunately it appears that the magnitude of dehydration in DKA is not reflected by either clinical or biochemical parameters [33••, 34]. The current recommendations for initial volume expansion is intravenous (IV) infusion of 10-20 ml/kg of normal saline (0.9 %) or Ringer's lactate over the first 1 to 2 hours [1]. The bolus of fluid may be repeated if the patient is in shock or severely dehydrated, and/or if urine output is massive. However, the initial bolus re-expansion should never exceed 40 ml/kg of total IV fluid in the initial four hours of treatment.

Replacement of Fluid Deficit Over the Next 24–48 Hours of Treatment

Subsequent fluid replacement should be done with ½ to NS normal saline (0.45 %– 0.9 %). Potassium can be added at this time (see below under potassium replacement). Fluid loss estimated on physical exam is recommended to be replaced evenly over the next 48 hours [1]. Significant additional fluid loss after initiation of treatment is rare,

though additional replacement may be required for vomiting or excessive urine output, which should resolve within the initial 2 to 4 hours of therapy as hyperglycemia subsides.

Bolus(es) given in the first hours of treatment should be subtracted from the 24 hour totals. In addition to replacement of estimated fluid loss, the patient requires maintenance fluids calculated as shown in (Table 1) or using 4:2:1 formula. In our institution we have been using the "2 bag system," which helps quickly react to any changes in glucose levels [35].

Fluid replacement in children with DKA has not been studied in detail, and remains a controversial issue with regard to the amount of intravenous fluid, rate of delivery, and type of fluid. Current recommendations regarding fluid replacement rates and types are based on expert consensus and accumulated clinical experience, as evidence from a large randomized clinical trials is lacking. However some studies have suggested that a less rapid fluid deficit correction with isotonic or near-isotonic solutions results in earlier reversal of acidosis [36, 37]. A small double blind randomized controlled trial compared Ringer's lactate to 0.9 % sodium chloride solution for resolution of acidosis during treatment of DKA. This study demonstrated no difference between the 2 solutions in the time to resolution of DKA [38]. In another small study, after initial rehydration with NS, patients were given 5 % dextrose solution with a 1/2 NS or 2/3 NS. Changes in blood glucose, effective plasma osmolality, plasma sodium, pH, anion gap, pCO_2, and HCO did not showed a difference between groups [39].

Shock is rare in the course of DKA. Decreased vascular volume and impending circulatory collapse are features of severe DKA and must be addressed immediately in the first hour of therapy. Five percent albumin (10 ml/kg over 30 min) or other colloid should be given if there is still evidence of shock after receiving 3 boluses of NS. In patients with severe dehydration or in patients with severe mental status changes, intravascular pressure monitoring to follow hydration status is indicated despite the risk of thrombosis.

Insulin

Insulin treatment allows normal glucose utilization and stops ketogenesis. Normal glycogen and fat stores, and protein synthesis also need to be restored over time. The standard of care is "low dose" continuous IV insulin administration [40, 41], after initial fluid bolus has been completed and blood glucose level has been checked at the bedside with a glucose meter and a confirmation sample sent to laboratory. An initial intramuscular or IV insulin bolus should not be given to avoid rapid fall of glucose levels without sufficient time given to correct the acidosis [1].

Table 1 Calculations for fluid replacement

Body weight (kg)	24-hour fluid maintenance requirements
Up to 10	100 mL/kg
10 to 20	1000 mL+50 mL/kg over 10 kg
>20	1500 mL+20 mL/kg over 20 kg

A continuous insulin drip should be started after the initial rehydration bolus is completed to lower the risk of cerebral edema [42]. The serum glucose level falls rapidly during volume re-expansion with or without insulin.

Continuous IV regular insulin drip is recommended at a dose of 0.1 units/kg per hour. In established patients or those with mild to moderately severe DKA, this rate may need to be reduced. IV insulin drip provides a slow and steady decline in blood glucose levels with an aim to have blood glucose levels decrease by 50–100 mg %/hr. When blood glucose levels are about 250 mg%, 5 %–10 % dextrose should be added to the IV solution to keep blood glucose levels between 150 and 250 mg/dL. Unless a patient is truly hypoglycemic, the insulin drip should not be decreased to less than 0.05 units/kg/hr as this is likely to prolong the time needed to suppress ketogenesis. IV insulin should not be discontinued until the bicarbonate is >15 mEq/L or venous pH >7.30.

Given the concern that the rapid rate of insulin delivery can promote cerebral edema, a few new studies looked at the lower rates of insulin [43–45]. As most of those studies are small, retrospective or observational, the advantages of using lower rates are not very clear and should be approached with caution.

Rapid-acting insulin analogs hold no advantage over regular insulin in treatment of DKA despite several recent trials. Insulin binds to the walls of the IV tubing so the tubing should be first washed with 50 ml of the insulin solution.

Electrolytes

Potassium

Total body potassium is usually depleted about 3–6 mmol/kg, but serum levels may be normal or high [46]. Hyperkalemia may lead to cardiac arrest while hypokalemia may cause cardiac arrhythmias, ileus, and muscular weakness and cramps. ECG monitoring is strongly recommended. Potassium must not be given as a rapid IV bolus.

Once the serum potassium is known to be normal or low, and urine output is confirmed, all IV fluids following the initial bolus(es) should include 20–40 mEq/L of potassium. The replacement may be in the form of KCl, K acetate,

K_2HPO_4 or a combination of these supplements; no more than half of the potassium replacement should be given as K_2HPO_4.

Bicarbonate

The cause of the acidosis is primarily ketogenesis from insulinopenia. Insulin replacement will reverse the acidosis. Bicarbonate therapy is not necessary even in severe DKA (pH <7.1) and bicarbonate treatment may be an independent risk factor for cerebral edema [27]. Most of the existing evidence points against using bicarbonate therapy. Glaser et al have shown that treatment with bicarbonate was associated with cerebral edema, after adjustment for other covariates. Use of bicarbonate will lead to a more rapid initial correction of acidosis with resultant intracellular movement of potassium and hypokalemia. Potassium replacement requirements are 2 to 3 times greater in patients treated with bicarbonate. Recent systematic review of existing studies including 3 adult randomized controlled trials comparing bicarbonate administration vs no bicarbonate did not provide evidence that bicarbonate administration is beneficial in treatment of DKA [47••].

Prevention/Treatment of Cerebral Edema

Cerebral edema can develop at any time point during treatment [48]. There have been reports of children presenting with cerebral edema even before the onset of treatment [49]. During the treatment, hours after therapy for DKA has begun, the patient may complain of headaches, have a change in mental status, incontinence, focal signs, pupillary changes, seizures, or disturbed temperature regulation [48]. A sudden "normalization" of heart rate in appropriately tachycardic dehydrated patient is an early sign, while bradycardia, hypertension, and irregular respiration (Cushing's triad) are signs of greatly increased intracranial pressure. Most often, the patient's laboratory values are improving as she/he appears to be worsening clinically.

Early intervention before respiratory arrest is essential. Treatment includes decreasing fluids (75 % maintenance fluids), giving IV mannitol (1 gm/kg over 30 minutes), and elevating the head of the bed to a 45-degree angle. 3 % saline is has also been recommended for treatment of cerebral edema in the course of DKA [50]. There is no data from randomized clinical trials that would compare mannitol vs 3 % saline, however 3 % saline have been successfully used in treatment of cerebral edema due to traumatic brain injury in children. Recently, somatostatin (octreotide) infusion have been reported to be associated with favorable outcome in patients with DKA-related cerebral edema [51•, 52]. The mechanism of therapeutic effect still remains unclear. Dexamethasone is not recommended in the course of DKA-related cerebral edema. The intubation and hyperventilation should be avoided unless pCO_2 is >30 mmHg or patient is in respiratory arrest. While hypocapnia causes cerebral vasoconstriction, the patient is usually ventilating at a maximum rate and intubation may be, at least temporarily, an additional setback [53, 54].

Treatment of overt cerebral edema is indicated immediately after making a diagnosis and should not be delayed until after the radiographic studies have been obtained. On the other hand subclinical cerebral edema is present in a significant proportion of children with DKA [55, 56].

Medications that may alter mental status should be avoided during treatment of DKA. Agitated patients may have impending circulatory collapse or central nervous system catastrophe, which may be precipitated or masked by medications that alter mental status.

Transition to Subcutaneous Insulin Regiment

When ketoacidosis is resolved (ß-OHB <1 mmol/L and pH >7.3 or bicarbonate >15 mEq/L), the patient is generally ready to eat. Subcutaneous insulin injections can be initiated or resumed based on appetite as well as ability to hold down food.

Fluids

While IV fluids can be continued, IV dextrose should stop when the insulin infusion is discontinued.

Diet

Meals following DKA according to the ADA guidelines, exclude usually simple carbohydrates. The dieticians should determine the carbohydrate content of each meal and to help develop insulin-to-carb ratio for bolus-basal insulin therapy.

Insulin

The insulin drip should continue until at least 30 min after SC insulin was given to allow sufficient time for absorption. Basal insulin (glargine, levemir, or NPH) usually cover about half of daily insulin requirements, with the remainder given as boluses of rapid-acting insulin analogues (lispro, aspart, glulisine, or regular). The total daily insulin dose varies from 0.5-1.5 u/kg/day, depending on factors such as age, body mass index, pubertal status.

An established patient must have an appointment to see their diabetes-care-provider in the week after treatment. A new patient has to immediately begin education in outpatient management of diabetes.

Prevention of DKA

Prevention of DKA in Patients With Established T1D

Several studies suggest that identification of at-risk patients may prevent most, if not all, episodes of DKA beyond the diagnosis of diabetes. Risk factors, reviewed above, allow for the identification of high-risk patients and targeted interventions.

Education

Insulin-treated patients and their caregivers must be aware of the importance of glucose and ketones monitoring.

Appropriate Blood Glucose Monitoring

Patients should monitor blood glucose levels at home at least 4 times a day and those using insulin pumps 6-8 times a day. Additional frequent testing is recommended during 'sick days' - generally every 2 hours.

Monitoring of Urine or Blood Ketones Levels

Ketones can be measured in urine or blood.

- Home measurement of blood ß-hydroxybutyrate (ß -OHB) may help in the prevention of DKA in established patients. ß -OHB monitoring using hand-held devices has been shown to be as accurate as reference laboratory method, at least up to 3 mmol/L [57–59].
- Bedside measurement of ß -OHB in blood is more sensitive (80 %) in detecting ketosis than 'dip stick' methods (63 %) [60].
- Ketone strips have a short shelf life after opened.

Telephone Counseling Including Triage

Comprehensive diabetes programs and telephone services managed by a nurse diabetes educator have been shown to be effective in reducing the DKA rates from 15-60 to 5-6/100 patient-years, and significantly reduce hospital admissions [61–64].

Early Outpatient Treatment

Early detection of the mild ketosis (β-OHB >1.0 mmol/L) that often affects insulin-treated patients is a key to prevention of DKA. Children with mild ketosis who are not ill-appearing and not vomiting can be managed at home with telephone help from a diabetes provider. A recent clinical trial has found home β-OHB monitoring effective in the early detection of ketosis and prevention of DKA among patients with T1D aged 3–22 years [65].

Insulin

Blood glucose must be checked before any insulin injection. If blood glucose is above 250 mg/dL and β-OHB is in the 0.6-1.5 mmol/L range, we recommend corrective s.c. injection of a rapid acting insulin in the amount of 5 %–10 % of the total daily dose of all insulins. The dose should be 10 %–20 % of the total daily dose if β-OHB is 1.5-3.0 mmol/L.

Fluids

Oral fluid intake has to be increased in the presence of hyperglycemia and ketosis, to prevent dehydration. Water is the fluid of choice when blood glucose is above 250 mg/dl, while Gatorade, Pedialyte or Poweraid is recommended for blood glucose in the 150–250 range.

Prevention of DKA at Onset of T1D

The best strategy for prevention of DKA at the onset of diabetes is based on awareness of signs and symptoms of diabetes. The most widely reported symptoms are bedwetting (67 %), increased thirst, and nocturia. Knowledge of the classical triad of polydipsia, polyuria, and polyphagia with weight loss (present also in many cases of type 2 diabetes prior to diagnosis) is essential, as is awareness of the variably presenting symptoms, (eg, vomiting or rapid breathing in a young child). Most patients admitted with severe DKA have been seen hours or days earlier by health care providers who missed the diagnosis, particularly in children younger than 3 years of age [5]. Diabetes should always be considered in ill children - urine and/or blood check for glucose and ketones leads to early diagnosis. Although these strategies are intuitive, programs to decrease DKA at onset need to be designed and evaluated in diverse populations and age groups. These should include approaches that target both the public at large and health care providers.

The "Parma campaign", an intensive community intervention to raise awareness of the signs and symptoms of childhood diabetes among school teachers, parents and primary care providers in a region of Italy was found to reduce the prevalence of DKA at diagnosis of T1D from 83 % to 13 % [66]. A follow up study has shown that the campaign for DKA prevention is still effective in Parma's province 8 years later, but there is also an indication that the campaign should be periodically renewed [67].

Screening for Pre-Diabetes in High Risk Groups and in the General Population

A growing body of evidence suggests that primary prevention of DKA in newly diagnosed children is possible and should be a major goal of diabetes care systems. The Diabetes Autoimmunity Study in the Youth (DAISY) has demonstrated that DKA can be prevented by periodic testing for diabetes autoantibodies, glycated hemoglobin (HbA1c), and random blood glucose in children who are at high genetic risk for T1D [68]. In the Diabetes Prevention Trial (DPT-1), awareness of increased level of risk and close biochemical monitoring facilitated the early diagnosis and prevention of DKA [69]. The Environmental Determinants of Diabetes in the Young (TEDDY) study has also shown that knowledge of genetic risk and close follow-up results in lower prevalence of DKA at diabetes diagnosis in young children [70].

Conclusions

Diabetic ketoacidosis is the major life-threatening complications of diabetes. DKA can be prevented, but unfortunately, it still accounts for a large proportion of mortality, morbidity and hospitalizations in patients with diabetes, and contributes significantly to the high costs of diabetes care.

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