Preventing Diabetic Ketoacidosis

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KEYWORDS

• Type 1 diabetes mellitus • Diabetic ketoacidosis • Prevention • Education • Recurrent • Noncompliance • Girls

KEY POINTS

- Diabetic ketoacidosis (DKA) is a complication of severe insulin deficiency leading to hyperglycemia, with its attendant glycosuria, dehydration, and ketogenesis, leading to acidosis.
- DKA is associated with significant morbidity, non-negligible mortality, and excessive health care expenditures.
- DKA is largely an avoidable and preventable complication of type 1 diabetes mellitus (T1DM).
- Risk factors associated with DKA at diagnosis of T1DM include age less than 5 years old, lack of private health insurance, lower socioeconomic status (SES), misdiagnosis, delayed diagnosis, and living in regions with a low background incidence of T1DM.
- Factors associated with increased DKA risk in children with established T1DM include age greater than 13 years, female gender, low SES, lack of private health insurance, poor family functioning, psychiatric disorders, higher reported insulin dose, and poor glycemic control.

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INTRODUCTION

T1DM is one of the most common chronic diseases of childhood with significant morbidity and non-negligible mortality.[1,2] The global incidence of T1DM is increasing by 3% per year in children and adolescents and by 5% per year in preschoolers.[3,4] Acute complications, such as DKA, are potentially avoidable causes of hospitalizations and mortality in children and adolescents with T1DM. DKA occurs in the presence of severe insulinopenia and is characterized by hyperglycemia, acidosis, and ketosis.

The early development of T1DM involves progressive insulin deficiency, leading to weeks of symptomatic hyperglycemia with polyuria, polydipsia, and weight loss.[5,6] If left untreated, the combination of insulin deficiency and stress (mediated through increased circulating levels of counter-regulatory hormones, including cortisol, catecholamines, growth hormone, and glucagon) leads to lipolysis. Hepatic metabolism of free fatty acids as an alternative energy source (ie, ketogenesis) results in accumulation of acidic intermediate and end metabolites (ie, ketones and ketoacids). The predominant ketones in the body are β-hydroxybutyrate, acetate, and acetoacetate.[5,6] In DKA, the ratio of β-hydroxybutyrate to acetoacetate increases from equimolar amounts (1:1) up to 1.3:1 to 5.5:1.[7] Accumulation of ketoacids is due to their rate-limiting metabolism. Diagnosis of DKA has been traditionally made with a combination of hyperglycemia (blood glucose >11 mmol/L or 200 mg/dL), venous pH less than 7.3 and bicarbonate levels less than 15 mmol/L.[8]

DKA at initial presentation is common, but rates vary strikingly between countries, ranging from approximately 13% to 80%.[9–11] The highest rates are typically seen in the developing world, not surprisingly given the resource constraints.[11] DKA in children previously diagnosed with T1DM is also unfortunately common, with highly variable rates between centers and countries.[11,12] DKA remains the most common cause of mortality in T1DM. The most devastating consequence of DKA is cerebral edema with an incidence of 0.5% to 0.9%.[13,14] The mortality rate from cerebral edema is 21% to 24%, and morbidity from serious neurologic sequelae occurs in 15% to 35% of cases.[11,12] Furthermore, DKA has a long-term impact on cognitive function, including a fall in IQ and persistent loss of short-term memory. The health care expenditures associated with 1 episode of DKA are substantial, estimated at more than $3500.[15]

EPIDEMIOLOGY AND CAUSES OF DIABETIC KETOACIDOSIS

DKA occurs generally under 2 circumstances and in a limited number of situations:

1. At diagnosis
2. In those with established diabetes
   a. As a result of accidental or deliberate insulin omission or
   b. Inappropriate management of intercurrent illness

Most, if not all, episodes of DKA can be prevented. These episodes generally represent a failure of timely diagnosis and/or management of T1DM. Understanding the epidemiology and factors associated with the onset of DKA is essential in developing measures to prevent these episodes.

DIABETIC KETOACIDOSIS AT DIAGNOSIS

Symptoms of new-onset T1DM typically develop over a few days to weeks before presentation, whereas DKA rapidly evolves once ketones accumulate[16]: 75% of patients with new cases of T1DM in the EURODIAB (the Epidemiology and Prevention of

Diabetes) project had symptoms for more than 2 weeks before diagnosis.[17] Thus, DKA at diagnosis of new T1DM ultimately reflects lack of awareness by parents and primary care physicians of the evolving symptoms of T1DM.[17]

A systematic review in 2011 identified 46 studies, including more than 24,000 children with T1DM from 31 countries[18]: the frequency of DKA at diagnosis varied 6-fold, from 12.8% to 80% (**Table 1**).[16] Rates were lowest in Sweden, and Canada and highest in the United Arab Emirates, Saudi Arabia, and Romania. There was an inverse correlation between DKA frequency at diagnosis and the regional background incidence of T1DM, findings that are consistent with previous studies from Europe. This may be explained by an overall increased awareness of T1DM and its presenting symptoms, leading to earlier recognition and diagnosis. DKA frequencies were also found to be lower in countries further from the equator and with a higher gross domestic product (GDP).[12] There are several explanations for this association. Latitude may represent a group of characteristics, including economy, health care provision, and disease burden.[12] Usher-Smith and colleagues[12] found a colinearity between latitude and a country's GDP, suggesting that the variation in latitude may be explained more by a country's economy and health care provision than distance from the equator. In addition, in a recent report analyzing data from countries identified as "wealthy" by the Organisation for Economic Co-operation and Development, a close correlation was found between DKA risk at disease onset and income inequality, defined as the difference in average incomes between a nation's highest and lowest income earners.[19] Among the countries included in the analysis, the frequency of DKA at diagnosis ranged from 16% to 54%, with countries with the lowest income inequality having lower DKA frequencies.

Table 1
Frequency of diabetic ketoacidosis at disease onset of type 1 diabetes mellitus

Country	Diabetic Ketoacidosis (%)
United Arab Emirates	80
Romania	67
Saudi Arabia	40–77
France	54
Kuwait	38–49
Poland	33–54
China	42
Oman	42
Lithuania	35
Austria	37
Italy	32–41
Bulgaria	35
Germany	26–53
United States	27–44
Turkey	29
United Kingdom	25–38
Ireland	25
Finland	19–22
Canada	18.6
Sweden	13–14

The key individual factors associated with greater risk of DKA were being less than 2 years old at presentation, being incorrectly diagnosed or having treatment delayed, belonging to an ethnic minority, lower SES, lack of health insurance in the United States, lower parental education, lower body mass index, and preceding infection.[20] Conversely, having a first-degree relative with T1DM was protective (odds ratio [OR] 0.33).

A small qualitative study (16 children) within the East of England found that the families were aware of symptoms for several weeks before a trigger, such as weight loss, led them to seek medical advice.[21] At the time of presentation, many families suspected the diagnosis. A strong protective effect of a family history of T1DM has been noted in several studies.[21–23] This relationship is unlikely to be genetic, because although high-risk genotypes are associated with DKA risk, having even 1 first-degree family member with T1DM is associated with dramatically reduced risk of DKA.[24] Furthermore, participating in a long-term follow-up study, The Environmental Determinants of Diabetes in the Young, was associated with reduced risk of DKA.[25] Thus, this protective relationship is almost certainly due to greater family awareness of the symptoms of diabetes.

Supporting this proposal, studies have found an overall fall in the risk of DKA over a 20-year interval in northern Finland,[26] consistent with the overall increase in incidence of T1DM over this period. There are some contradictory findings, however. In some countries, the rate of new-onset DKA has not fallen over time despite a temporal increase in incidence, even where there are highly organized and easily accessible health care systems. In Austria for example, the risk of DKA on a prospectively recorded country-wide register remained similar between 2005 to 2009 and 2010 to 2011.[27] A single-center study from Australia found no change in the risk of DKA in 1073 children and adolescents ages up to 18 years with newly diagnosed T1DM from 1998 to 2010.[28] Similarly, in Auckland, the largest city in New Zealand, the incidence and severity of new-onset DKA remained stable at approximately 27% over the past 15 years[29] and are similar to the previous review in 1995 to 1996.[10] These findings suggest that health care providers and families are failing to recognize the early symptoms of T1DM.

Age

Several studies have consistently demonstrated that younger age at diagnosis of T1DM is a significant risk factor in the development of DKA. Usher-Smith and colleagues[18] conducted a meta-analysis consisting of 32 studies and found that children ages less than 2 years old had 3 times the risk of presenting with DKA as children ages greater than 2 years old (OR 3.41; 95% CI, 2.54–4.59). This increased risk continued up to age 5 years (OR 1.59; 95% CI, 1.38–1.84). In general, studies have demonstrated that the frequency of DKA at diagnosis decreases significantly with age from 37% to 40% (95% CI, 32.9%–41.8%) in children ages 0 to 4 years old to 14.7% to 23.6% (95% CI, 11.7%–17.7%) in children ages 15 to 19 years old.[23,30] The higher rates of DKA in the younger age groups may be related to several factors, including (1) the classic symptoms of T1DM may not be obvious and easily distinguishable from other common acute illnesses, resulting in a delay in diagnosis; (2) clinicians may have a lower index of suspicion for T1DM among younger children, particularly in the under 2-year age group;[3,25] (3) younger children have a less developed mechanism of metabolic compensation resulting in faster development of acidosis and dehydration;[23,31] and (4) β-cell destruction[4] may be more aggressive in younger children because serum levels of C-peptide are lowest in the under 2-year age group at diagnosis of T1DM compared with older age groups.[32]

Ethnic Minority

Studies in both the United States and United Kingdom have demonstrated an increased risk of DKA among ethnic minorities. A recent multicenter US study found that nonwhite youth were more at risk of presenting with DKA at diagnosis compared with non-Hispanic white youth, independent of SES and age (OR 1.21; 95% CI, 1.03–1.43).[20] A study in the United Kingdom reported a higher frequency of DKA at diagnosis among ethnic minorities (41.3%) compared with non-Hispanic white patients (21.4%) ($P = .03$).[33] In addition, a study in New Zealand showed that non-Europeans were more likely to present in DKA than those of European ethnicity (OR 1.52; $P = .048$).[29] These disparities may be due to cultural or language barriers, lack of access to health care services, or lack of awareness of T1DM in ethnic minorities.

Lower Socioeconomic Status

Lower SES as measured by family income or neighborhood income is associated with an increased risk of DKA at diagnosis.[34] One US study found that the frequency of DKA was 70% to 80% higher in patients with a family income below $50,000 compared with those with a family income greater than $50,000 (higher income).[20] In Canada, where patients enjoy universal access to health care, patients with low SES, as measured by neighborhood income quintiles, were more likely to present with DKA at diagnosis compared with the highest income quintiles (OR 1.39; 95% CI, 1.17-1.63).[34]

Lack of Private Health Insurance

In countries without universal health coverage, lack of private health insurance has been consistently found to be a significant risk factor for DKA at diagnosis.[35,36] For instance, study in the United States found that patients with private health insurance were least likely to present with DKA.[35] Patients with no health insurance were 60% more likely to present with DKA compared with those with health insurance coverage. Furthermore, when uninsured patients presented with DKA, they were more likely to present with severe DKA.[37] The odds of uninsured patients presenting with severe DKA (ie, venous pH <7.10; serum bicarbonate <5 mmol/L) were 6 times (OR 6.09; 95% CI, 3.21–11.56) the odds for insured patients.[36] These findings suggest that patients without health insurance may delay seeking timely medical care and thus present with severe DKA.

Delayed Diagnosis

A delay of more than 24 hours between the initial presentation to a primary or secondary care provider and referral to a multidisciplinary diabetes team in the United Kingdom has been reported associated with an increased risk of presenting with DKA (52.3% vs 20.5%, $P<.05$).[33] The most common reason cited for the delayed diagnosis was arrangement for a fasting blood sugar prior to referral to a multidisciplinary team.

Diagnostic Error

Several retrospective cohort studies have reported an increased risk of DKA in children not diagnosed with T1DM at first presentation to the health care system due to either a misdiagnosis or lack of recognition of the symptoms of T1DM.[33,34] In Ontario, Canada, the authors previously reported that children with DKA at diabetes diagnosis were more likely to have seen a health care professional on 1 or more occasions in the weeks prior, at which time the diagnosis of T1DM was missed.[34] Diagnostic error at first presentation to the health care system has been associated with a 3-fold increased risk of presenting with DKA (OR 3.35; 95% CI, 2.35-5.79), independent of the presence of a

preceding infectious illness.[1] Misdiagnosis was more likely to occur among younger children. In 1 study, patients with DKA in whom the diagnosis of diabetes was missed at initial presentation tended to be younger (mean age 5.4 ± 4.4 years old) compared with those in whom the diagnosis was not missed (mean age 8.8 ± 4.0 years old) ($P<.001$). Younger children tended to be misdiagnosed with urinary tract infection, upper respiratory tract infection, gastroenteritis, or otitis media.[34]

Preceding Infectious Illness

The presence of a concomitant infection may mask the early symptoms of diabetes or delaying the diagnosis resulting in an increased risk of DKA.[20] Furthermore, an infectious or febrile illness generally increases the counter-regulatory response, resulting in insulin resistance and metabolic decompensation.

Protective Factors

The protective factors associated with a decreased risk of DKA at disease onset include first-degree relative with T1DM and higher parental education. Having a higher awareness and better recognition of the signs and symptoms of hyperglycemia likely explain the decreased risk of DKA among families with a first-degree relative with diabetes.[1,30,32] Children from families in which parents had greater than a postsecondary education or had at least 1 parent with an academic degree are at a decreased risk of DKA at diagnosis.[18,30,32]

Can Diabetic Ketoacidosis Be Prevented at Diagnosis?

In light of the existing evidence, it is highly plausible that improving community and medical awareness of the presenting features of T1DM in children may help prevent DKA. There have been few studies, however, on community education with indirect and unmonitored methods used, which have led to inconclusive results.

A small study from Parma, Italy,[38] involved providing a poster to primary and secondary public schools and providing local pediatricians with equipment for measuring urine and blood glucose and patient cards. Over the subsequent 8 years, the rate of DKA in children ages 6 to 14 years was 12.5% (3/24) in Parma compared with 83% (25/30) in nearby areas, where children did not receive the information. Furthermore, the duration of symptoms was much shorter in the Parma area (mean 5 vs 28 days), and the length of hospitalization was also shortened. Despite its encouraging results, this study was limited by its small size and the high baseline rate of DKA compared with typical European rates.

Another small prospective study also suggested significant benefit from an educational campaign in Australia. In this study, a 2-year control period was followed by a 2-year intervention[37] in 1 region (Gosford) but not in 2 others (Newcastle and Sydney). Posters were provided to childcare centers, schools, and doctors' offices, with doctors also given glucose and ketone testing equipment. The proportion of children with DKA decreased in the intervention region from 38% (15/40) to 14% (4/29), whereas there was no change in DKA rates in the control regions (37% [46/123] and 39% [49/127]). Unexpectedly, the incidence of T1DM in Gosford also fell by 28%, raising the possibility that the reduction in new-onset DKA might have partly reflected redirection of patients to other larger, children's hospitals in the region.

In contrast, a national study in Wales found no benefit.[39] Posters were sent to every pharmacy, school, and general practitioner surgery across Wales, and the campaign publicized with radio interviews. Before the campaign, the risk of DKA was approximately 25% from 1991 to 2009, with no temporal change. After the campaign, from 2008 to 2009, 26% of children diagnosed with T1DM had DKA. Questionnaires

suggested that few families were aware of the campaign. Thus, it seems that the format of the campaign without more direct engagement with the community may not be effective.

Furthermore, another nationwide prospective study in Austria involving 4038 children with new-onset T1DM also found no effect of community education.[27] This study attempted greater penetration than other studies, and posters were given to all kindergartens, schools, pharmacies, pediatricians, and general practitioners in 2009. In addition, medical officers in schools received education twice a year, and there was national media publicity. Before the campaign (2005–2009), 26% of children had mild DKA and 12% had severe DKA compared with 27% mild and 9.5% severe cases afterward (2010–2011). Although DKA was more common in younger children, there was no effect of stratification by age. This study suggests that a primarily poster-based education campaign is insufficient, possibly because of greater competition for parent's attention. Regional differences cannot be excluded, however, and it is also possible that simply displaying posters was the wrong media tool for the modern generation.

Thus, there is at best limited evidence that community-based mass campaigns improve the risk of DKA in new-onset T1DM. Critical to any mass educational program is a clear simple message. It is worth reflecting that in the Parma study, approximately 90% of children had bed wetting at diagnosis.[38] Similarly, in Auckland, a local audit from 2000 to 2009 suggests that more than 95% of children newly diagnosed with T1DM had bed wetting or increased night-time urination (Starship Children's Hospital, unpublished data). The authors speculate that a focus on such a simplified message may be more effective for community education and should be tested.

DIABETIC KETOACIDOSIS IN ESTABLISHED TYPE 1 DIABETES MELLITUS

Diabetes mellitus management in children is complex and requires intense resources as well as regular access to timely and effective health care services to prevent complications. T1DM is an ambulatory-care sensitive condition, defined as a group of medical conditions typically managed in an ambulatory setting, whereby an admission to hospital indicates a potentially avoidable complication and is an indirect indicator of access and overall quality of outpatient care.[40,41] DKA is generally avoidable and its occurrence in children and adolescence with established T1DM may indicate poor outpatient diabetes mellitus care and could be prevented with comprehensive multidisciplinary outpatient care and improved adherence to diabetes management. **Table 2** outlines the risk factors for DKA among youth with established T1DM.

Epidemiology

Globally, reported rates of DKA in children with established T1DM range between 1 per 100 patient-years in a Swedish cohort[35] to 12 episodes per 100 patient-years in US cohort.[36,42] A retrospective cohort study conducted in the United States by Rewers and colleagues[36] determined that the incidence of DKA was 8 per 100 patient-years in 1243 children from 1996 to 2000. This incidence increased in age among girls (4 per 100 patient-years in <7 year olds; 8 in 7–12 year olds; and 12 in $\geq$13 year olds) but not boys. In addition, approximately 60% of the DKA episodes occurred in 5% of children with recurrent events (>2 episodes). In a more recent retrospective cohort study from Europe (1995–2008), the incidence of DKA among 28,770 patients with T1DM was 6.3 per 100 patient-years and remained relatively unchanged over the study period, with recurrent episodes seen in 1% of patients.[43] The overall incidence of DKA was slightly higher in girls (7% vs 5.8%) and in immigrants, but there

Table 2
Risk factors associated with new-onset diabetic ketoacidosis versus recurrent diabetic ketoacidosis

New-onset Diabetic Ketoacidosis	Recurrent Diabetic Ketoacidosis
Young age (especially <2 y)	Older age (especially adolescents)
Lack of access to medical care	Lack of access to medical care
Lack of awareness of diabetes	Psychiatric disorders
Lack of family history of T1DM	Low SES
Delayed medical diagnosis of T1DM	Low family cohesion
Low parental education	Higher HbA_{1c}
Recent infection	Low income
Minority ethnic groups	Minority ethnic groups
—	High insulin doses and noncompliance with insulin therapy

was no effect of treatment type or duration of diabetes. Recurrent DKA was associated with older age (in particular the early teenage years), higher hemoglobin A_{1c} (HbA_{1c}) levels, and higher insulin doses.

In the United States, in the T1D Exchange Clinic Registry of 13,487 children and young adults (<26 years of age) with T1DM for at least 2 years,[35] DKA was most frequent in adolescents and associated with higher HbA_{1c}, nonwhite race, lack of private health insurance, and lower household income. A small Swedish study identified 142 episodes of DKA in 1990 to 2000; subjects were aged 14.6 years on average with a mean T1DM duration of 6.6 years.[44] The reported triggers of DKA included missed insulin doses (48.6%), gastroenteritis (14.1%), technical pump problems (12.7%), infections (13.4%), and social problems (1.4%). Pump users had approximately double the rate of DKA compared with patients using intermittent injections. This finding is not universal, however, and may reflect an improved understanding of insulin pumping and early testing for blood ketones.[44] Although the risk of DKA increases with duration of diabetes, there is an appreciable rate in the first year after diagnosis. In a population-based study in Germany, 373 subjects with newly diagnosed T1DM aged less than 15 years who were followed for a mean of 1 year had 4.7 times higher risk of hospitalization.[45]

Risk Factors in Children with Established Type 1 Diabetes Mellitus

In a prospective cohort study of 1243 children and youth with T1DM, the risk of DKA increased with higher HbA_{1c} and higher reported insulin doses among children ages less than 13 years old (see **Table 2**).[45,46] Among older children (>13 years old), the risk of DKA increased with higher HbA_{1c} (relative risk [RR] 1.43 per 1% increase; 95% CI, 1.3–1.6), higher reported insulin dose, underinsurance, and the presence of psychiatric disorders, including major depression, bipolar or anxiety disorder, and/or use of psychotropic medications. These factors were also found to confer an increased risk of recurrent DKA. Other studies have also found similar risk factors for DKA.[35,42,45]

The higher risk of DKA among adolescent girls may be related to body image issues, whereby 10% of adolescent girls with T1DM meet *Diagnostic and Statistical Manual of Mental Disorders*[47] criteria for eating disorders compared with 4% of their age-matched controls without diabetes.[48] One aspect of T1DM that contributes to the development of an eating disorder is that adolescent girls may deliberately omit insulin

as a unique and readily available way to control weight through induced hyperglycemia and glycosuria, increasing the risk of DKA.[49–51]

Higher reported insulin dose may represent either lower endogenous insulin secretion with longer duration of T1DM or insulin resistance related to puberty or obesity.[45] Alternatively, in patients who omit insulin, a higher prescribed insulin dose may not be the actual dose taken.

Psychiatric conditions are a significant risk factor for DKA, particularly among adolescent girls (RR 3.22; 95% CI, 2.25–4.61).[8,52] This association may be due to nonadherence to diabetes self-management and to insulin omission.[53]

Lower SES as measured by lack of private health insurance, head-of-household unemployment, or low household income has consistently been found associated with an increased risk of DKA.[36] This association maybe driven by factors, such as compliance with medical care, including decreased blood glucose monitoring, access to transportation, and irregular physician visits.

Additional risk factors include longer diabetes duration,[54] family functioning, the transition to adult care,[55] and insulin pump therapy.[46] Several studies suggest that family functioning is associated with DKA risk. In 1 study, children who had an episode of DKA were more likely to perceive their parents as less warm and caring toward their diabetes management (measure of diabetes-specific family support) and had caregivers who rated themselves as less supportive of their child's diabetes care (measure of parental negativity) compared with children who did not have a DKA episode.[55]

The transition to adult care occurs during a critical and vulnerable period for those with T1DM. The authors' data from the province of Ontario, Canada, identified a small but significant increase in DKA rates as youth with T1DM transitioned from a pediatric to adult health care team. Furthermore, the authors found that girls and lower SES, as measured by neighborhood level income, decreased local medical resources, and previous hospitalizations for DKA, were significant predictors of post-transition DKA episodes.[55]

In summary, DKA in children and adolescents with established T1DM is an avoidable complication that can be prevented through appropriate education and psychosocial support, consistent self-monitoring of blood glucose and ketones, and improved adherence to diabetes self-management.

Poor glycemic control

Poor glycemic control is a major risk factor for recurrent DKA in teenagers.[49] In turn, poor glycemic control is directly related to poor adherence with insulin treatment. For example, in Scotland, in a cohort of 89 patients at a mean age 16 years, there was a significant inverse association between HbA_{1c} and adherence ($r^2 = 0.39$).[40] Not surprisingly, poor adherence was associated with more admissions for DKA and the secular trend for deterioration in glycemic control from 10 to 20 years.

Small studies in which children were studied in more detail have highlighted a clear role for underlying behavioral and psychological stresses in association with recurrent DKA. In a sample of 92 school-age children followed for an average of 9 years from diagnosis, 28% had 3 or more admissions for DKA. Recurrent DKA was associated with higher HbA_{1c} levels, more behavioral problems, younger age at diagnosis, and lower SES.[54] Similarly, in a cohort of 61 children and adolescents followed for 8 years after diagnosis, 28% had 1 or more episode of DKA.[56,57] DKA was more common in girls and was associated with more behavior problems and lower social competence, higher levels of reported family conflict, and lower levels of family cohesion, expressiveness, and organization in year 1.

These studies indicated that a mixture of poor background glycemic control, disadvantaged groups, and (particularly in the United States) lack of medical insurance as key risk factors for recurrent DKA. Nonetheless, even countries with comprehensive medical systems have found little change in the rate of DKA over time. For example, in Ontario, Canada, there were 5008 hospital admissions for DKA in children younger than 19 years from 1991 to 1999, with no change in the admission rate or the case fatality rate of 0.18% over this time.[57]

Prevention of recurrent diabetic ketoacidosis

The existing evidence suggests that there are 2 broad targets for preventing recurrent DKA: improving access to medical care and improving management of individual patient approach to diabetes. The impact of social and access issues in deprived populations is substantial. For example, among adult urban African Americans who developed DKA, more than two-thirds of cases occurred due to cessation of insulin therapy because of lack of money for insulin or transportation to the hospital as well as limited self-care skills.[38] A recent study in the same setting again highlighted the strong link between DKA and lack of adherence to insulin treatment in adult inner-city minority patients in the United States.[58] Once more, two-thirds of cases of DKA were due to cessation of insulin therapy and were linked to depression, alcohol and drug abuse, and homelessness (but not psychiatric illnesses). Such high-risk populations would benefit from practical, targeted assistance.

The more common background for recurrent DKA, however, is teenage patients from nondisadvantaged populations. A systematic review in 2000 identified 24 randomized controlled trials of behavioral interventions for adolescents with T1DM.[53] The effect on DKA rates was rarely examined in the individual studies; therefore, DKA was not a focus of the review. The effect on glycemic control was small and notably heterogeneous, equivalent to a reduction in HbA_{1c} of 0.3%. Furthermore, the studies were small, there were few common outcomes to allow direct comparison of interventions, and there was no long-term follow-up. Moreover, the most effective interventions seem to involve such high institutional and patient commitments that it is questionable whether they could be translated to routine care.

Subsequently, there have been several small studies with similar limitations. For example, a small study in which 17 children received ten 90-minute sessions of in-home behavioral family systems therapy had no effect on glycemic control.[59,60] A modified version of this program in 104 families (involving either educational support for multiple families or 12 sessions over 6 months) was associated with improved glycemic control up to 18 months from the start of the program, but its cost-effectiveness and effect on DKA risk are still unclear. Scheduled bimonthly telephone calls over 17 months from a pediatric diabetes educator did not improve glycemic control or reduce rates of hospital admission in 123 patients at a mean age of 12 years.[61] A more ambitious program consisted of a 6-month home-based intervention for 37 adolescents with poorly controlled T1DM (HbA_{1c} >9.0%), involving monthly home visits and weekly phone contact.[62] In comparison to 32 adolescents in routine care only, there was a modest improvement in HbA_{1c}, from 11.1% to 9.7% at 6 months, that was not maintained at 12 and 18 months. It is unknown whether continuing treatment would have been more effective.

In contrast, recent larger studies of behavioral interventions have yielded encouraging results. In a randomized controlled trial in 127 adolescents with poorly controlled T1DM, intensive home-based psychotherapy over 2 years was associated with sustained reduction in hospital admissions compared with baseline or to controls over the full period.[41] This intensive intervention was expensive ($6934 per patient), but

this cost was offset by reduced admissions for DKA. A subsequent trial in 146 adolescents with T1DM or type 2 diabetes mellitus showed that this approach was superior to telephone support in improving glycemic control over 12 months.[63] Another study involved more general training in adolescents before 20 years of age, based on 6 small group sessions and monthly follow-up, including social problem solving, cognitive behavior modification, and conflict resolution.[64] There was an associated improvement in glycemic control, and the impact of diabetes on their quality of life was lessened compared with intensive diabetes management alone. This intervention, however, did not reduce the rate of DKA.

On the other hand, in patients with recurrent DKA, Golden and colleagues[65] demonstrated a significant decrease in DKA episodes among patients who were given their insulin injections by a responsible adult. Similarly, Nguyen and colleagues[66] demonstrated a significant improvement in HbA_{1c} levels when teens with persistently poor metabolic control received a dose of long-acting insulin analog at lunchtime by a school nurse.

SUMMARY

The factors associated with DKA at presentation and recurrent DKA after diagnosis are different. Broadly, DKA at presentation seems to be a problem of lack of awareness of the symptoms of T1DM, whereas recurrent DKA in patient with established diabetes seems primarily related to omission of insulin, augmented by social issues. In cases of DKA at presentation, despite promising results from 2 community education projects, nationwide educational campaigns have been ineffective. The authors speculate that simplified messages and better ways of increasing awareness are needed.

In contrast, recurrent DKA is a problem of a minority, in particular girls in early adolescence with related family and behavioral issues, often from disadvantaged backgrounds. The key to reducing recurrent DKA is likely to be achieved by providing targeted intervention for high-risk patients. There is increasing evidence that several forms of support can modestly reduce DKA, but the most promising interventions involve a substantial and expensive commitment and have not been validated in large trials. The challenge for future research is to find programs that are not only efficacious but also readily applicable in routine clinical practice.

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