

REVIEW

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# Morbidity and Mortality of Diabetic Ketoacidosis With and Without Insulin Pump Care

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## Abstract

Diabetic ketoacidosis (DKA) is one of the most common, costly, and dangerous acute complications in people with type 1 diabetes (T1D). Although DKA has been reported to occur with less frequency than severe hypoglycemia, it is associated with a higher mortality rate and is the leading cause of diabetes-related deaths in children and adolescents. The most common risk factor for DKA is lack of adherence to insulin treatment. Other factors include underinsurance, psychiatric disorders, occlusion of insulin pump infusion sets, and illness. It has been suggested that use of continuous subcutaneous insulin infusion therapy may increase the risk for DKA, although clinical trials have not supported this claim. Expert care within a T1D specialty clinic may help reduce the risk of DKA mortality. Further advances are needed in developing new technologies and methods to improve glycemic control in intensively treated patients without increasing the risk of acute complications. The purpose of this review is to discuss DKA morbidity and mortality in youth with T1D, particularly in relation to insulin pump use.

## Introduction

**D**IABETIC KETOACIDOSIS (DKA) and severe hypoglycemia (SH) are the two most common emergencies associated with type 1 diabetes (T1D).<sup>1</sup> Although SH can also result in a hospital visit, DKA results in a significant increase in medical costs. It was estimated from a review of insurance claims from 2007 of 7,556 youth with T1D that annual medical expenditures increased from \$8,398 (USD) to \$14,236 if there was an episode of DKA.<sup>2</sup> An analysis<sup>3-5</sup> of the 2004 National Hospital Discharge Survey and the Health Care Cost and Utilization Project National Inpatient Survey showed that uncontrolled diabetes was responsible for more than 196,000 hospital admissions per year in the United States, with an estimated direct and indirect cost of 2.8 billion USD. Over 62% (119,000) of these admissions were associated with a diagnosis of DKA, costing over 1.8 billion USD.

Many care providers are not aware that, although SH is more common than DKA for people with T1D, DKA is associated with a higher risk of mortality. Factors associated with the morbidity and mortality of DKA will be reviewed. Data will be presented to suggest morbidity and mortality may be reduced for young people cared for in a T1D specialty clinic. In addition, insulin pump use will be reviewed in relation to the morbidity and mortality of DKA.

## DKA: Morbidity and Associated Risk Factors

Many studies have evaluated the risk factors associated with DKA in T1D. The frequency of DKA in one pediatric T1D clinic was found to be 8/100 patient-years, whereas the frequency of SH was 19/100 patient-years.<sup>1</sup> DKA was defined as an episode of hyperglycemia or ketoacidosis leading to an emergency department visit and/or hospital admission. SH was defined as a hypoglycemic episode leading to loss of consciousness, seizure or resulting in an emergency department visit or hospital admission. Eighty percent of all DKA episodes occurred in the 20% of the population who experienced recurrent episodes. DKA occurred more frequently with increasing age (in females only), higher glycosylated hemoglobin levels, higher reported insulin dose, underinsurance, and the presence of psychiatric disorders. The European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society joint consensus statement concluded "75% of episodes of DKA beyond diagnosis probably are associated with insulin omission or treatment error. The remainder are due to inadequate insulin therapy during intercurrent illness."<sup>6</sup> Similarly, an American Diabetes Association consensus statement relating to children and adolescents with established T1D stated, "Insulin omission, either inadvertently or deliberately, is the cause of DKA in

most cases.<sup>7</sup> They also noted intercurrent infection rarely contributed to episodes of DKA if the family was properly educated and received regular follow-up care by a diabetes care team with a 24-h telephone helpline. DKA as a result of poor adherence to insulin therapy has also been reported in the adult population. Randall et al.<sup>8</sup> found that among inner-city adults, 68% of patients who experienced DKA had discontinued their insulin.

### DKA Mortality

Although there are many reports related to mortality in youth previously diagnosed with T1D, the studies summarized below and in Table 1 are three of the most comprehensive. It is important to differentiate between all causes of death and diabetes-related causes of death. The diabetes-related causes of death include acute metabolic problems, such as DKA and SH, and comprise approximately 50% of all deaths in patients under age 30 years.<sup>9-11</sup> In contrast, cardiovascular disease is the leading cause of death (approximately two-thirds of the total) in adults over 30 years of age with T1D.<sup>9</sup> New-onset deaths are not included in the percentages in Table 1, as these increase DKA-related deaths disproportionately. Mortality for people with diabetes is described to be two to six times higher compared with age-matched individuals without diabetes; however, there is considerable variability depending in part on the specific population being studied.<sup>9-12</sup> Likewise, recent data from the United States showed improved overall (not cause-specific) survival for people diagnosed when <18 years old, although the mortality rate was still 5.5 times higher than for the general population.<sup>12</sup>

A British study followed 23,752 youth with insulin-treated diabetes diagnosed under the age of 30 years (Table 1).<sup>9</sup> In this cohort, 759 deaths were reported in subjects under the age of 60 years between 1972 and 1997. Acute metabolic complications of DKA and SH were the leading cause of death in

subjects under 20 years of age. Deaths due to all causes were reported in 12% and 18% of males and females, respectively. Likewise, all-cause mortality related to hypoglycemia was reported in 4% and 1% of males and females in this study, respectively. Diabetes-related deaths were attributed to DKA in 54% and 76% of males and females, respectively, whereas hypoglycemia was the etiology of diabetes-related mortality in 18% and 6% of males and females, respectively.

A national study of 10,200 youth diagnosed prior to age 14 years in Sweden (Table 1) reported 78 deaths between 1977 and 2000.<sup>10</sup> Of the 23 deaths clearly related to diabetes, 14 were due to DKA, and one was due to hypoglycemia. An additional 17 subjects were found "deceased in bed at home, without any cause of death found at thorough forensic autopsy."

The EURODIAB study in 12 countries (Table 1) evaluated 141 deaths over 219,061 person-years of follow-up.<sup>11</sup> Of the 47 deaths directly related to T1D, 27 were attributed to DKA, five were due to hypoglycemia, and another seven were classified as "dead in bed."

In summation, mortality due to DKA has been described to be at least threefold greater than for SH. A limitation to these reports relates to the undiagnosed causes of death in subjects designated as "dead in bed." Dahlquist and Kallen<sup>10</sup> stated that when autopsies were consistently done, normal glucose levels were found. These deaths may have been related to autonomic dysfunction or to other causes.<sup>13</sup>

### Morbidity: Insulin Pump Therapy and DKA

A consensus statement on insulin pump therapy and DKA concluded that individuals using continuous subcutaneous insulin infusion (CSII) were "potentially at increased risk of developing DKA," with DKA rates varying from 2.7 to nine episodes per 100 patient-years.<sup>14</sup> They recommended "randomized clinical trials are needed to evaluate whether young

TABLE 1. MORTALITY IN YOUTH DIAGNOSED WITH TYPE 1 DIABETES

Study or country (reference)	Period of study	Cohort	Person-years of exposure	DRD	
				Mortality	Causes of DRD
British Diabetes Association Cohort Study (Laing et al. <sup>9</sup> )	1972-1997	23,752 youth <30 yo at dx	317,522	<60 yo 759 total deaths 170 (22%) DRD Based on death certificates	Onset deaths excluded Male deaths=54% DKA; 18% SH Female deaths=76% DKA; 6% SH All causes=15% DKA; 3% SH
Sweden (Dahlquist and Kallen <sup>10</sup> )	1977-2000	10,200 youth <14 yo at dx	81,600	<37 yo 78 deaths 23 (29%) DRD Based on death certificates	6 new-onset T1D (DKA) 1 SH (alcohol) 14 DKA (60%) (18% of all deaths) 17 "dead in bed" (no cause on autopsy including normal glucose levels) 2 myocardial infarction
EURODIAB (12 countries) (Patterson et al. <sup>11</sup> )	1989-2005	28,887 youth <15 yo at dx	219,061	<30 yo 141 deaths 41 (35%) DRD Based on death certificates and information from centers	Onset deaths excluded 27 DKA (66%) (19% of all deaths) 5 SH (12%) (4% of all deaths) 7 "dead in bed" (no cause; ± autopsy)

DKA, diabetic ketoacidosis; DRD, diabetes-related death; dx, diagnosis; SH, severe hypoglycemia; T1D, type 1 diabetes; yo, years old.

patients treated with CSII are more vulnerable to metabolic deterioration." Additionally, they suggested, "DKA should be preventable in CSII using published DKA prevention guidelines."

Hanas et al.<sup>15</sup> found the most common causes of DKA in patients using CSII were missed insulin doses (48.6%), gastroenteritis (14.1%), and technical pump problems (12.7%). Tamborlane and Sikes<sup>16</sup> noted insulin delivery interruptions "were most commonly caused by a problem with the infusion set or a partial disconnection or kinking of the subcutaneous catheter."

Several studies have suggested CSII therapy does not result in an increase in DKA episodes in comparison with multiple daily injection (MDI) therapy. A meta-analysis of 1,547 patients from 52 studies prior to 2003 concluded that there was no increase in DKA as a result of pump usage.<sup>17</sup> It is important to examine "real life" data, as subjects entering most clinical research studies are highly selected and supervised. A report of 104 preschoolers who began insulin pump therapy within 4 weeks of diagnosis at 63 centers in Germany found no episodes of DKA in the pump users.<sup>18</sup> The success of the preschool age group may be attributed to the fact that the parents are very involved in the diabetes management in this young population.

Scrimgeour et al.<sup>19</sup> evaluated episodes of DKA in 291 youth who were treated with CSII for a mean duration of  $3.7 \pm 1.9$  years (range, 1–9 years). The rate of occurrence of DKA was 4.0 episodes/100 patient-years during CSII therapy compared with 1.4 episodes/100 patient-years in the year prior to initiating CSII. In spite of this increase, all subjects in the same clinic (using CSII or MDI) had a rate of DKA of eight episodes per 100 patient-years.<sup>1</sup> This was likely higher because subjects at high risk for DKA were less apt to transition from MDI to CSII therapy.

Real-life data on DKA from 18,109 people participating in the U.S. T1D Exchange Registry<sup>20</sup> showed an incidence of DKA for users of insulin pumps of approximately 10 episodes/100 patient-years for subjects who were <15 years old or >25 years old. The highest incidence of DKA (18–20 episodes/100 patient-years) was in people 15–25 years of age. However, for all age groups, the incidence of DKA was lower ( $P < 0.001$ ) for pump users than for patients using MDI. The incidence of DKA in people using pumps was higher in minority subjects, in subjects from lower-income families, in females, and in subjects with higher glycosylated hemoglobin levels, as previously described.<sup>1</sup> The incidence was significantly lower for all age groups for subjects who used a continuous glucose monitor (CGM) with or without an insulin pump. This may have been a reflection of warnings given for high glucose levels or due to the closer attention paid to dia-

betes care by CGM users. The nationwide T1D Exchange Registry reported a higher frequency of DKA compared with data published from a T1D pediatric specialty clinic.<sup>1</sup>

A major question has been whether suspension of an insulin pump to prevent SH will increase the risk of DKA. There have been several comprehensive studies addressing this issue. An early study from Yale<sup>21</sup> compared suspension of insulin pumps in nine subjects using either insulin lispro or human regular insulin. The suspension began at 0300 h and lasted for up to 8 h or until the blood glucose level was  $>350$  mg/dL ( $>19.4$  mmol/L) or until moderate ketonuria had developed. Eight of the nine subjects using lispro discontinued the suspension early ( $337 \pm 25$  min) compared with six of nine using regular insulin ( $400 \pm 26$  min). Serum  $\beta$ -hydroxybutyrate levels exceeded the normal levels of  $>0.6$  mmol/L in approximately 4 h for both groups.

In another study, there was no evidence of DKA when insulin pumps were suspended for 90 min for predicted hypoglycemia in 40 subjects with T1D.<sup>22</sup> Four subjects developed blood ketone levels of 0.4–1.5 mmol/L. However, two of the four subjects had multiple suspensions, and the subject with the highest level had fasted for approximately 20 h. None of the subjects required extra insulin.

Other reports (Table 2) included a study of eight adults with pump suspension for 4 h<sup>23</sup> and a study of 18 adults with pump suspensions for 5 h.<sup>24</sup> Levels of  $\beta$ -hydroxybutyrate increased to 0.9 mmol/L and to 1.3 mmol/L in the two studies, respectively. There was no evidence of DKA in either study. The DirecNet study group<sup>25</sup> (Table 2) evaluated suspension for 2 h in subjects to prevent hypoglycemia induced by a 1-h session of moderate exercise. Levels of  $\beta$ -hydroxybutyrate did not increase above 0.4 mmol/L in this setting. Castillo et al.<sup>26</sup> evaluated pump suspension with high, normal, or low glucose levels. They found blood ketone levels rose more rapidly in association with higher glucose values.

Studies related to the low glucose suspend (LGS) feature in a sensor-augmented insulin pump (Table 3) have not reported any episodes of DKA. Danne et al.<sup>27</sup> and Choudhary et al.<sup>28</sup> evaluated 21 youth and 31 adults, respectively, in relation to use of the LGS feature. There were no episodes of deterioration of glucose control or of DKA in either study. Agrawal et al.<sup>29</sup> evaluated real-life data from 49,867 patient-days and reported elevated glucose levels more frequently when the LGS was off, compared with when it was being used.

In summary, current data do not show DKA to be more frequent with insulin pump use compared with MDI use. This is likely related to patient education and training now provided (for example, ketone checking, correction boluses by syringe, changing infusion sets, hydration, etc.). In addition, in the closely supervised research studies reviewed above,

TABLE 2. PUMP SUSPENSION AND LEVELS OF BLOOD GLUCOSE AND  $\beta$ -HYDROXYBUTYRATE

Reference	Duration of pump suspension	Initial		Final	
		BG (mg/dL)	$\beta$ -OH-B (mmol/L)	BG (mg/dL)	$\beta$ -OH-B (mmol/L)
Orsini-Federici et al. <sup>23</sup>	4 h (8 adults)	150 $\pm$ 54	0.1 $\pm$ 0.1	242 $\pm$ 42	1.0 $\pm$ 0.7
Guerci et al. <sup>24</sup>	5 h (18 adults)	149 $\pm$ 60	0.2 $\pm$ 0.2	285 $\pm$ 68	1.3 $\pm$ 0.5
DirecNet Study Group <sup>25</sup>	2 h with 1 h of exercise	161 $\pm$ 24	$\leq$ 0.4	44 $\pm$ 38 decrease	$\leq$ 0.4

BG, blood glucose;  $\beta$ -OH-B,  $\beta$ -hydroxybutyrate.

TABLE 3. USE OF LOW GLUCOSE SUSPEND FEATURE WITH A SENSOR-AUGMENTED INSULIN PUMP

Reference	Patients/methods	Results (SAP with LGS)
Danne et al. <sup>27</sup>	21 youth with T1D from 3 centers in Germany 2 weeks=SAP 4 weeks=SAP with LGS	No SH or DKA Decrease time spent (and decrease number of episodes) <70 mg/dL Positive device satisfaction
Choudhary et al. <sup>28</sup>	31 adults with T1D in the United Kingdom 2 weeks=SAP 3 weeks=SAP with LGS	No deterioration of glucose control Decrease time of nocturnal hypoglycemia in those with highest quartile of hypoglycemia at baseline All subjects found LGS "useful," and 93% said they were more secure at night.
Agrawal et al. <sup>29</sup>	935 patients 49,867 patient-days LGS feature in "real world"	Sensor glucose at 2 h = 150 ± 69 mg/dL More values >240 and >300 mg/dL when LGS "off" compared with when "on"

DKA, diabetic ketoacidosis; LGS, low glucose suspend; SAP, sensor-augmented insulin pump; SH, severe hypoglycemia; T1D, type 1 diabetes.

DKA secondary to pump suspensions for 2 h was not found. Similarly, in a real-life summary of the LGS data from 935 patients, there was not an increase in hyperglycemia or DKA.<sup>29</sup>

#### Mortality: Insulin Pump Therapy and DKA

Five deaths were reported to the Food and Drug Administration in 2005 regarding adolescent CSII users who "may have been negligent or noncompliant with the use of the device."<sup>30</sup> The Food and Drug Administration then evaluated all Manufactured and User Device Experience reported to the Food and Drug Administration between 1996 and 2005 in relation to insulin pumps: they found 13 deaths, three of which were due to DKA, over the 10-year period. The difference in mortality between 2005 and the previous decade may have been related to the increased use of insulin pumps during this interval or possibly because of the easing of restrictions for youth considered for pump therapy.

Prospective research trials have not found a high incidence of DKA or of deaths from use of insulin pumps. In the closely supervised Diabetes Control and Complications Trial, where two-thirds of subjects used an insulin pump at some time in the 7 years, the incidence of DKA was "lower than expected," with 1.8 and 2.0 episodes per 100 patient-years for control versus intensive treatment groups ( $P > 0.7$ ).<sup>31</sup> There was one death from DKA in a 38-year-old man receiving MDI and no deaths among subjects using CSII.<sup>32</sup> In the Juvenile Diabetes Research Foundation Study of patients receiving intensive insulin therapy with or without CGM use, there was only one episode of DKA, which occurred in the non-CGM group.<sup>33</sup> In the STAR 3 study of 485 patients there were three episodes of DKA in the sensor-augmented pump group and two episodes in the control group.<sup>34</sup> There were no deaths from DKA in either of these carefully supervised multicenter research studies. Despite encouraging results from carefully selected and supervised patients in randomized research trials, it is unknown whether these DKA-related morbidity and mortality data will translate to real-life insulin pump users.

Careful records of mortality in youth (<18 years old) have been kept at the Barbara Davis Center for Childhood Diabetes (Denver, CO) since January 1, 2000. Over 3,000 youth are followed in the T1D pediatric clinic on a regular basis, with

39% currently being treated with an insulin pump (approximately 1,200 youth). All subjects are accepted for care, with approximately 25% being under-insured as previously defined.<sup>1</sup> There have been no diabetes-related deaths for youth who had been seen at the Barbara Davis Center within 2 years during the 11-year period. One subject who was never treated with CSII (and who had not been seen at the Barbara Davis Center in >2 years after moving from the area) reportedly died of DKA. From these data, it is suggested that the incidence of diabetes-related deaths can be greatly reduced or even eliminated. Initial and continuing education has been emphasized.<sup>35</sup> The Center sees patients on a 3-month schedule, offering continuing education at each visit with the option of seeing a social worker to help with psychosocial issues. There is a 24-h help line staffed by a Certified Diabetes Educator for questions and diabetes emergencies. Further research is needed to determine the best resources and environments to prevent DKA-related morbidity and mortality in patients with known T1D.

#### Conclusions

Although studies have found SH to be more common than DKA, the risk of mortality has been greater with DKA. Furthermore, studies have not shown an increase in DKA as a result of insulin pump use. Advances in diabetes care and technology offer the possibility that mortality from DKA in youth with known T1D can be greatly reduced. The use of a CGM with alarms for hyperglycemia may reduce the time spent in hyperglycemia and subsequent episodes of DKA. Care in a specialty diabetes clinic offering proper education, follow-up care, and a 24-h helpline is important. As a result, the risk of death from DKA to a patient with known T1D should be greatly reduced or eliminated.

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