



# Increasing Hospitalizations for DKA: A Need for Prevention Programs

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Diabetic ketoacidosis (DKA) is a diabetes emergency associated with high morbidity in patients with diabetes (1). In patients with type 1 diabetes, DKA can occur at new onset of diabetes but can also recur due to lack of insulin use and precipitating causes such as infection. DKA is a hallmark of type 1 diabetes; however, DKA is increasingly recognized in patients with type 2 diabetes (2). In contrast to patients with type 1 diabetes who require life-long insulin therapy, most patients with type 2 diabetes who present with DKA can recover insulin secretion and maintain glycemic control with oral antidiabetes medications (3). While inpatient mortality rates for DKA are generally very low, <1% in the U.K. (4) and in the U.S. (5), DKA is the leading cause of mortality among children and young adults with type 1 diabetes, accounting for ~50% of all deaths in this population (1). In addition, rates vary substantially based on health care setting; a recent analysis conducted in India reported that up to 30% of hospitalized DKA cases result in inpatient death (6).

The article by Zhong et al. (7) in this issue of *Diabetes Care* examines temporal trends of DKA according to the diagnosis of type 1 and type 2 diabetes between the years 1998 and 2013 in the U.K. This report used the Clinical Practice Research Datalink and the Hospital Episode Statistics databases. Overall, the

authors found that hospitalizations for DKA increased in the U.K. for patients with both type 1 and type 2 diabetes. Most cases of DKA were associated with type 1 diabetes, but one in five cases of DKA were associated with a patient history of type 2 diabetes. For patients with type 1 diabetes, DKA admissions increased from 1998 to 2007 and then the rate stabilized from 2007 to 2013. The incidence in 2013 was 1.5 times higher (1.53) than in 1998 and higher than that for patients with type 2 diabetes. The incidence was highest for patients between the ages of 18 and 24 years with short duration of diabetes (<1 year). Incidence of DKA increased in men, patients with diabetes duration of <1 year or >20 years, and patients >35 years of age. Length of stay decreased over time without a change in 30-day readmission. In patients with type 2 diabetes, the incidence of hospitalization was lower than that in patients with type 1 diabetes but with an annual increase of 4.2% between 1998 and 2013. The incidence was highest in patients using insulin with <1 year or ≥10 years of diabetes and in young adults. Despite the increased hospitalizations, there were no changes in mortality or differences in mortality between patients with type 1 diabetes and those with type 2 diabetes.

The rise in hospitalization for DKA in the U.K. is similar to the trends observed in the U.S. and other countries. The

Centers for Disease Control and Prevention reported that age-adjusted hospitalizations for DKA decreased 1.1% per year from 2000 to 2009 but increased 6.3% per year from 2009 to 2014 (8). A long-term observational cohort study in patients with type 1 diabetes in the U.S. (T1D Exchange) reported an incidence rate of DKA of ~20 cases/1,000 patient-years at the 12-year follow-up (9). Several epidemiological studies have reported that hospitalizations for DKA have increased worldwide (10,11) (Table 1). A recent systematic review (12) reported worldwide incidence rates in patients with type 1 diabetes ranging between 8 and 51.3 cases/1,000 patient-years. In a Chinese study (13), a much higher incidence rate was reported (263/1,000 patient-years), which the investigators attributed, at least in part, to differences in national health care systems with limited access to routine health care for patients with type 1 diabetes as well as infrequent self-monitoring of blood glucose by patients (12). In some countries, such as Taiwan and Italy, hospitalization for DKA has been decreasing (10,14).

The reasons for increasing hospitalizations for DKA are unknown. This finding may in part be explained by the number of adults and children presenting with DKA at initial diagnosis of diabetes. Worldwide, 12.8–80% of patients present with DKA as the initial presentation

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See accompanying article, p. 1870.

**Table 1—Trends for hospitalizations for DKA**

Study	Country	Years examined	Total (n)	Diabetes type	Trend/incidence	Readmission	Mortality
Abdulrahman et al. (27)	Wales	1999–2010	8,543 adults/children	85% T1D, 15% T2D	Increased 4.2% AAPC	NR	NR
Lombardo et al. (14)	Italy	2001–2010	251,528 adults/children	NR	Decreased incidence rate 5.7%	12.1%	7.6%
Liu et al. (10)	Taiwan	1997–2005	31,842 adults/children	NR	Decreased incidence rate from 6/1,000 to 5/1,000 person-years	11.5–13.4%	1.1–2.0%
Venkatesh et al. (11)*	Australia and New Zealand	2000–2013	8,553 adults/children	63% insulin-requiring, 27% noninsulin-requiring	Increased from 0.97 to 5.3/100,000 patient-years	NR	1.4%
Henriksen et al. (28)	Denmark	1996–2002	4,807 adults/children	78% T1D, 12% T2D	Increased annual incidence 12.9/100,000 patient-years	NR	4%
Li et al. (13)	China	2010–2012	611	100% T1D	26.4/100 patient-years	NR	NR
Centers for Disease Control and Prevention (8)	U.S.	2000–2014	~30 million	NR	Increased 6.3% per year	NR	Declined from 1.1% to 0.4%
Zhong et al. (7)	U.K.	1998–2013	264,687 adults	9% T1D, 91% T2D	Increased 35.84/1,000 patient-years for T1D and 0.85/1,000 patient-years for T2D	12.67% T1D, 6.18% T2D	No difference in mortality between T1D and T2D; no change over time

AAPC, annual percentage change; NR, not reported; type 1 diabetes, T1D; type 2 diabetes, T2D. \*Intensive care unit only.

of diabetes (15). Although the exact number of patients with type 2 diabetes who present with DKA is unknown, it is possible that the number of patients with ketosis-prone diabetes has increased. Ethnic minorities usually present with ketosis-prone diabetes, and the incidence of diabetes has been rising in these populations. Although the report by Zhong et al. (7) did not specify which of the hospitalizations were DKA at diagnosis of diabetes, the rates of DKA increased even when data were analyzed only including the first DKA hospitalization. Further, hospitalizations for DKA have increased mostly in younger patients with a short duration of diabetes for both type 1 and type 2 diabetes, suggesting that more patients are presenting with DKA at the time of diagnosis. It is also possible that DKA is underrecognized in adults. According to the T1D Exchange registry, 78% of patients presenting with type 1 diabetes at age >18 years have a detectable C-peptide level (16). This can possibly lead to misdiagnosis of type 1 diabetes and lack of awareness

of DKA symptoms until presentation with DKA.

In the report by Zhong et al. (7), recurrent DKA accounted for a significant portion of the hospitalizations; 65.72% for type 1 diabetes and 35.28% for type 2 diabetes. Recurrent DKA is associated with increased mortality in both the U.S. and the U.K. (4,17). A possible explanation for this increase could be admissions for mild DKA. In 2001, the American Diabetes Association expanded the definition of DKA to include mild DKA (18). The rise in DKA hospitalizations was observed starting in 2004. Although there is no biochemical data in the study by Zhong et al., it is possible that the rise in DKA could be due to presentation with mild DKA, especially since the length of stay has decreased without change in mortality. An important component in prevention of readmissions is appropriate education after the initial hospital discharge. A survey of U.K. hospitals in 2014 performed after the institution of new guidelines for treatment of DKA noted a shortage of staff needed for patient education (19).

This could lead to improper insulin administration and poor recognition of symptoms of DKA with an increase in recurrent episodes.

The study by Zhong et al. (7) and previous reports (Table 1) highlight the need to have targeted programs to prevent DKA at new onset of diabetes and recurrent episodes of DKA in adults. Strategies such as early screening, close follow-up of high-risk children, and education of parents and communities have been successful in prevention of DKA at onset of diabetes. In The Environmental Determinants of Diabetes in the Young (TEDDY) study, there was a lower incidence of DKA at diagnosis when parents were made aware of the high risk of diabetes in their children (20). Similarly, in the Diabetes Autoimmunity Study in the Young (DAISY), close follow-up of high-risk children in the prediabetes stage reduced hospitalizations for DKA at diagnosis (21). In Italy, a prevention program aimed at education of parents, pediatricians, and personnel at primary and secondary schools to recognize symptoms of DKA

significantly decreased the number of children presenting with DKA at initial diagnosis of diabetes (22).

Strategies for prevention of recurrent episodes of DKA include more intensive care coordination with patient and family engagement. The Novel Interventions in Children's Healthcare is a comprehensive program that includes care coordination with family while incorporating telemedicine to engage youth with multiple hospitalizations for DKA (23). This program showed that daily communication through text messages and other forms of telecommunication decreased DKA readmissions in adolescents (23). Similar programs targeted toward adults need to be instituted to prevent recurrent episodes. Incorporating new technology such as real-time continuous glucose monitoring and insulin pumps could be useful for prevention of recurrent DKA episodes. Recent studies showed that use of real-time continuous glucose monitoring decreased DKA incidence in both children and adults (24–26). Further, newer insulin analogs with long half-life such as insulin degludec or glargine U300, which facilitate management by allowing for variable timing of insulin dose, are currently being investigated for prevention of recurrent DKA in patients with type 1 diabetes (NCT03001323, ClinicalTrials.gov). Future studies should adapt successful strategies in the pediatric population to the adult population to prevent both DKA at diagnosis and recurrent episodes and to reduce the increasing rate of DKA hospitalizations.

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