Diabetic Ketoacidosis and Mortality in People With Type 1 Diabetes and Eating Disorders

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OBJECTIVE

To determine the risk of diabetic ketoacidosis (DKA) and all-cause mortality among adolescents and young adults with type 1 diabetes with and without an eating disorder.

RESEARCH DESIGN AND METHODS

With use of population-level health care administrative data covering the entire population of Ontario, Canada, all people with type 1 diabetes aged 10–39 years as of January 2014 were identified. Individuals with a history of eating disorders were age- and sex-matched 10:1 with individuals without eating disorders. All individuals were followed for 6 years for hospitalization/emergency department visits for DKA and for all-cause mortality.

RESULTS

We studied 168 people with eating disorders and 1,680 age- and sex-matched people without eating disorders. Among adolescents and young adults with type 1 diabetes, 168 (0.8%) had a history of eating disorders. The crude incidence of DKA was 112.5 per 1,000 patient-years in people with eating disorders vs. 30.8 in people without eating disorders. After adjustment for baseline differences, the subdistribution hazard ratio for comparison of people with and without eating disorders was 3.30 (95% CI 2.58–4.23; $P < 0.0001$). All-cause mortality was 16.0 per 1,000 person-years for people with eating disorders vs. 2.5 for people without eating disorders. The adjusted hazard ratio was 5.80 (95% CI 3.04–11.08; $P < 0.0001$).

CONCLUSIONS

Adolescents and young adults with type 1 diabetes and eating disorders have more than triple the risk of DKA and nearly sixfold increased risk of death compared with their peers without eating disorders.

Eating disorders are complex mental health conditions characterized by abnormal eating behaviors and disrupted body image. They include anorexia nervosa, bulimia nervosa, binge eating disorder, and other specified feeding and eating disorders (1). Eating disorders are more common in adolescents and young adults with type 1 diabetes than in peers without diabetes (2–4). This association is likely multifactorial, but a focus on meal planning as part of diabetes management, along with continuous attention to numeric parameters (carbohydrate counting, glucose monitoring, and weight management), may contribute to this risk (5). In addition,

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people with type 1 diabetes may engage in insulin underdosing and omission, a dangerous behavior often used to promote weight loss or compensate for overeating. This behavior is strongly associated with risk of engaging in other disordered eating behavior and increases the likelihood of adverse medical events (6). Established risk factors for disordered eating behavior in people with type 1 diabetes include age, female sex, weight dissatisfaction, and BMI (7–11).

Having both an eating disorder and type 1 diabetes is associated with poorer glycemic control, as represented by higher hemoglobin A_{1c} (2,3,8,12–14). Eating disorders have also been shown to contribute to worse clinical diabetes outcomes including retinopathy, nephropathy, neuropathy, severe hypoglycemia, and diabetic ketoacidosis (DKA) (12–17). Rates of hospitalization and length of hospital stay have been found to be higher in patients with type 1 diabetes with an eating disorder than in those without (13). In addition, individuals with type 1 diabetes are more likely than those without diabetes to drop out of eating disorder treatment or to have a poor treatment response (18). Increased mortality, although expected based on increased rates and severity of diabetes complications, has not been widely reported, presumably because mortality studies require large, population-based sample sizes and a long outcome observation period (19). The objective of this study was to examine the association of eating disorders with DKA and all-cause mortality among adolescents and young adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Study Design and Data Sources

A population-based cohort study was conducted with use of real-world data for Ontario, the most populous province of Canada. Under the single-payer universal health care system, these databases cover all health care delivery to all residents of Ontario, with no loss to follow-up or missing data. The databases used included demographic data for all residents, records from all admissions to acute care and mental health hospitals, records of all emergency department visits, and all service claims from physicians for inpatient or ambulatory visits or procedures. These data sets were linked with use of unique encoded identifiers and analyzed at ICES (formerly the Institute for Clinical Evaluative Sciences).

Study Population

The study population included adolescents and young adults aged 10–39 years on 1 January 2014 from the Ontario Diabetes Database, a population-based disease registry derived using these health care administrative data, which has been validated in both adults and children (20,21). We selected those with type 1 diabetes using an algorithm validated to have specificity of 99.5% and positive predictive value of 79.4% (22). We selected this age range both because of improved detection of type 1 diabetes using our algorithm and because eating disorders are more prevalent compared with older adults.

The cohort was divided into two groups based on diagnosis of an eating disorder (anorexia nervosa, bulimia nervosa, or eating disorder not otherwise specified) prior to the index date. Diagnosis of an eating disorder was defined by an acute care or psychiatric hospitalization or an emergency department visit coded with an eating disorder as the primary or a secondary diagnosis (23). These were identified with ICD-9 codes 307.1, 307.50, and 307.51 and ICD-10 codes F50.0, F50.1, F50.2, F50.3, F50.8, and F50.9.

Outcomes

Two primary outcomes were ascertained between 1 January 2014 and 1 January 2020: all-cause mortality and DKA, defined as any emergency department visit or hospitalization with an ICD-10 revision code of E10.1.

Statistical Analysis

Baseline characteristics as of index date included age, sex, income (based on median household income from census data at the level of the census dissemination area and then divided into province-wide quintiles), rurality, and diabetes duration. Each person with an eating disorder was matched to 10 without on age (within 1 year) and sex. Remaining baseline characteristics were compared between patients with a diagnosed eating disorder and those without an eating disorder using standardized differences, which describe differences between group means relative to the pooled SD; differences >10% reflect potentially meaningful imbalance (24,25). The crude incidence of each outcome was determined for people with and without eating disorders. To determine the independent effect of eating disorders, we used Cox proportional hazards regression for all-cause mortality and a Fine-Gray model for DKA, where mortality was treated as a competing risk. Models were stratified on matched sets. The DKA model was adjusted for income, rurality, and diabetes duration. For avoidance of overfitting with a low number of events, the mortality model was adjusted for diabetes duration only. Sex-specific models were also examined. We explored whether income or rurality were modifiers of the effect of an eating disorder on DKA by repeating the original model with additional interaction terms.

For comparison purposes, we repeated the mortality analysis among people who did not have type 1 diabetes. Finally, we conducted a sensitivity analysis that restricted the look-back period for prior hospitalization or emergency department visit coded with an eating disorder diagnosis to 5 years.

The use of data in this study was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board.

RESULTS

There were 20,035 adolescents and young adults with type 1 diabetes who were included in the study. Of those, 168 (0.8%) had a diagnosis of an eating disorder. The baseline characteristics of the overall population are shown in Supplementary Table 1. Those with eating disorders were overwhelmingly female. Patients with eating disorders were older and had a longer duration since diabetes diagnosis than those with no eating disorder. After matching on age and sex, there remained a meaningful imbalance (standardized difference >10%) for rural residency and diabetes duration between 5 and 10 years (Table 1).

The crude incidence of DKA was 112.5 per 1,000 patient-years in people with eating disorders vs. 30.8 per 1,000 person-years in people without eating disorders (Fig. 1). After adjustment for

Table 1—Baseline characteristics of adolescents and young adults with type 1 diabetes with and without eating disorders, matched on age and sex

	With eating disorder	Without eating disorder	Standardized difference
N	168	1,680	
Age, years	27.1 ± 6.8	27.1 ± 6.8	0
Sex			
Female	156 (92.9)	1,560 (92.9)	0
Male	12 (7.1)	120 (7.1)	0
Income quintile			
Lowest	44 (26.2)	385 (22.9)	7.6
2nd	29 (17.3)	337 (20.1)	7.2
3rd	34 (20.2)	333 (19.8)	1.0
4th	29 (17.3)	327 (19.5)	5.7
Highest	32 (19.0)	298 (17.7)	3.4
Rurality			
Urban	120 (71.4)	1,130 (67.3)	9.0
Semiurban	36 (21.4)	370 (22.0)	1.4
Rural	12 (7.1)	180 (10.7)	12.5
Diabetes duration, years			
<5	21 (12.5)	191 (11.4)	3.5
5 to <10	23 (13.7)	352 (21.0)	19.3
10 to <15	42 (25.0)	384 (22.9)	5.0
≥15	82 (48.8)	753 (44.8)	8.0

Data are *n* (%) or means ± SD unless otherwise indicated.

baseline differences, the subdistribution hazard ratio for comparison of people with and without eating disorders was 3.30 (95% CI 2.58–4.23; $P < 0.0001$). Female patients with eating disorders had a slightly higher risk for DKA compared with male patients (Table 2). All-cause mortality was 16.0 per 1,000 person-years in people with eating disorders vs. 2.5 per 1,000 person-years in people without eating disorders (Fig. 2). The adjusted hazard ratio was 5.80 (95% CI 3.04–11.08; $P < 0.0001$). Males with eating disorders had an increased risk for mortality compared with females (Table 2). In comparison, among adolescents and young adults without type 1 diabetes, the prevalence of eating disorders was 0.2%. All-cause mortality was 2.5 per 1,000 person-years in those with eating disorders vs. 0.4 per 1,000 person-years in those without, with adjusted hazard ratio 5.83 (95% CI 4.71–7.22; $P < 0.0001$).

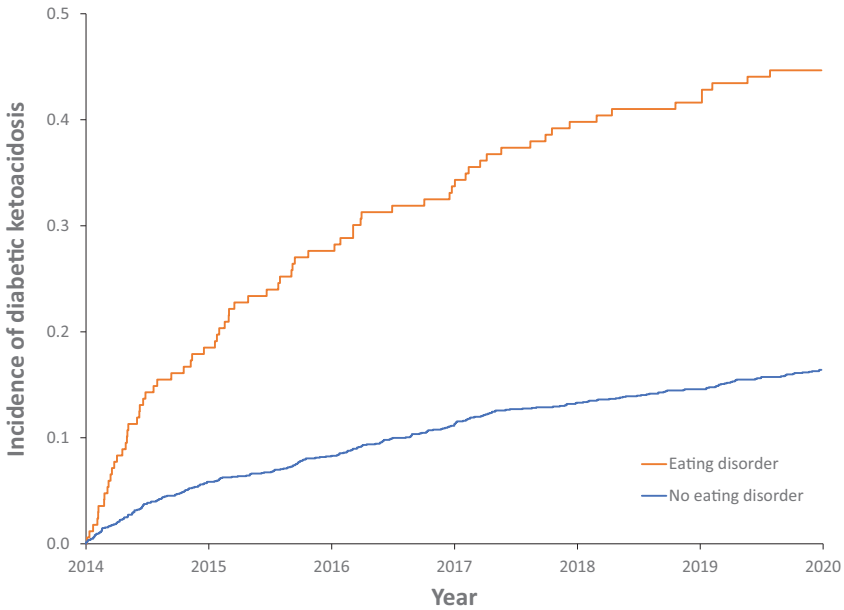

Figure 1—Cumulative incidence of DKA in adolescents and young adults with type 1 diabetes with and without an eating disorder.

Neither income nor rurality was an effect modifier of the relationship between eating disorder and DKA.

We also conducted a sensitivity analysis that restricted the look-back period for eating disorder diagnosis to 5 years. In this analysis, there were 73 people with eating disorders matched to 730 without. The incidence of DKA was, respectively, 117.3 per 1,000 person-years and 37.5 per 1,000 person-years, and the adjusted subdistribution hazard ratio was 4.37 (95% CI 4.23–4.51; $P < 0.0001$). All-cause mortality was 22.0 per 1,000 person-years in people with eating disorders vs. 2.8 per 1,000 person-years in people without, and the adjusted hazard ratio was 8.42 (95% CI 3.43–20.65; $P < 0.0001$).

CONCLUSIONS

Adolescents and young adults with type 1 diabetes had nearly five times the prevalence of eating disorders as adolescents and young adults without type 1 diabetes. Those with eating disorders have more than triple the risk of DKA hospitalizations compared with their peers without eating disorders. Strikingly, the all-cause mortality for young people with type 1 diabetes and eating disorders was 1.6% per year. Compared with those without eating disorders, female patients with eating disorders had a nearly 5.0-fold increased risk of death and male patients had >14-fold increased risk. Although the absolute mortality risk was much higher for people with type 1 diabetes compared with those without, the relative impact of eating disorders was essentially similar.

Many previous studies have shown that young people with type 1 diabetes are at increased risk of developing eating disorders compared with their peers without diabetes (2–4). However, few previous studies have examined the impact of eating disorders on the most serious adverse outcomes of type 1 diabetes, DKA, and mortality. A cohort of 91 young women with type 1 diabetes found that those with eating disorders had an increased risk of diabetic retinopathy after 4 years (12). Similarly, a small British cohort found a strong

Table 2—Hazard ratios for DKA and mortality for comparisons of adolescents and young adults with type 1 diabetes and eating disorders with those without eating disorders

	Overall		Females		Males	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
DKA*	3.30 (2.58–4.23)	<0.0001	3.41 (2.63–4.42)	<0.0001	2.47 (0.70–8.72)	0.16
All-cause mortality†	5.80 (3.04–11.08)	<0.0001	5.38 (2.70–10.71)	<0.0001	14.17 (1.26–159.06)	0.03

*Adjustment for income, rurality, and diabetes duration. †Adjustment for diabetes duration.

association between eating disorders and the development of microvascular complications (26). Severe hypoglycemia episodes have also been shown to be increased among people with eating disorders (14). Two large studies of European cohorts found that those with eating disorders had more than double the risk of DKA (13,14). A relatively large survey of Americans with type 1 diabetes found a similar result (27). Our study corroborates this finding, though the risk for DKA observed in our population was higher. Only one previous study has examined mortality in patients with type 1 diabetes and an eating disorder, which summarized data from various published registries in the 1970s and 1980s and found that standardized mortality ratio for women with type 1 diabetes and an eating disorder was 3.5 times that of women with type 1 diabetes without an eating disorder (19). Another small cohort of women with type 1 diabetes who restrict insulin had a threefold mortality rate compared with those who do not (28).

The strengths of this study include the use of large population-based health care administrative data, which allows sufficient power to study rare complications of relatively uncommon disorders. Ascertainment of diabetes status through a provincial population-based registry provides a more representative sample than most work to date, which has usually focused on individuals identified in specialized care settings. Because of the single-payer universal health care system in Ontario, these data include all residents of the province, with no loss to follow-up or missing data. There are several limitations to this study, however. We identified people with eating disorders based on a prior history of a hospital admission or emergency department visit coded for an eating disorder. This definition may have missed milder cases of an eating disorder, and the prevalence of eating disorders that we identified among people with type 1 diabetes is lower than what has previously been reported (3,4). Thus, the results of the study may not be generalizable to people with less severe eating disorders who have not required hospitalization or emergency department care. The eating disturbances identified in previous studies of type 1 diabetes tended to include a small number of individuals with anorexia nervosa and bulimia nervosa and a majority of individuals with other behavioral disturbances that may appear less severe but still conferred an elevated risk for metabolic complications due to high rates of insulin misuse and resulting compromised metabolic control. Additionally, we did not have access to clinical data such as glycemic control, weight, or BMI. However, these factors are likely part of the causal pathway linking eating disorders to both DKA and mortality, so their inclusion in the regression models would have been inappropriate. For the same reason, we chose not to measure or adjust for differences in comorbidities and complications. Finally, we were unable to explore the behavioral, psychological, and biological factors that may have contributed to the observed associations, as we were using population-level administrative data. Nevertheless, this study highlights the grave medical risks faced by individuals with eating disorders and diabetes presenting to acute care settings.

In summary, our study shows that adolescents and young adults with type 1 diabetes and concurrent eating disorders represent a high-risk group for both DKA and premature death as compared with peers without eating disorders. It is important to incorporate screening tools for disordered eating behavior into routine type 1 diabetes care to allow for timely identification of such patients and to consider eating disorders as a reason for poor glycemic control, potentially due to insulin withholding. In addition, regular screening for eating disorder symptoms in young individuals with type

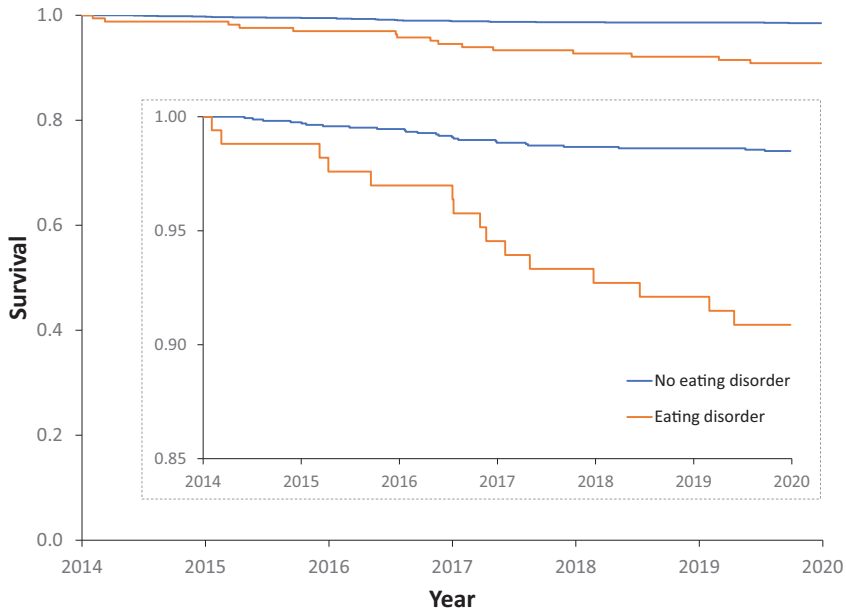

Figure 2—Survival of adolescents and young adults with type 1 diabetes with and without an eating disorder.

1 diabetes, early referral for mental health evaluation, and the development and evaluation of interventions to prevent these outcomes for these high-risk patients are all warranted, as a recent systematic review found that no interventions have been shown to be effective in this complex patient group (29). Health care providers involved in the dissemination of dietary and exercise education to adolescents and young adults with type 1 diabetes should carefully consider the impact these recommendations may have on eating behaviors.

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