Received: 20 October 2020 | Revised: 7 January 2021 | Accepted: 13 January 2021

DOI: 10.1111/pedi.13185

CLINICAL CARE AND TECHNOLOGY

ISPAD WILEY

Previous diabetic ketoacidosis as a risk factor for recurrence in a large prospective contemporary pediatric cohort: Results from the DPV initiative

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Funding information
German Center for Diabetes Research (DZD), Grant/Award Number: 82DZD14A02; German Diabetes Association; German Robert-Koch-Institute

Abstract

Objective: To assess the role of previous episodes of diabetic ketoacidosis (DKA) and their time-lag as risk factors for recurring DKA in youth with type 1 diabetes (T1D).

Research Design and Methods: In a population-based analysis, data from 29,325 children and adolescents with T1D and at least 5 years of continuous follow-up were retrieved from the "Diabetes Prospective Follow-up" (DPV) multi-center registry in March 2020. Statistical analyses included unadjusted comparisons, logistic and negative binomial regression models.

Results: Among 29,325 patients with T1D, 86.0% (n = 25,219) reported no DKA, 9.7% (n = 2,833) one, and 4.3% (n = 1,273) more than one episode, corresponding to a DKA rate of 4.4 [95% CI: 4.3–4.6] per 100 patient-years. Female sex, migratory background, higher HbA1c values, higher daily insulin doses, a lower glucose monitoring frequency, and less CGM usage were associated with DKA. In patients with a previous episode, the DKA rate in the most recent year was significantly higher than in patients with no DKA (17.6 [15.9–19.5] vs. 2.8 [2.7–3.1] per 100 patient-years; $p < 0.001$). Multiple DKAs further increased the recurrence rate. The risk for DKA in

Abbreviations: CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; DKA, diabetic ketoacidosis; DPV initiative, diabetes prospective follow-up initiative; T1D, type 1 diabetes.

Prior presentation of study data as an abstract or poster: Parts of the data have been included in an abstract and e-poster presented at the 46th annual ISPAD conference in October 2020.

the most recent year was higher in patients with an episode in the preceding year than in patients with no previous DKA (OR: 10.0 [95% CI: 8.6–11.8]), and remained significantly elevated 4 years after an episode (OR: 2.3 [1.6–3.1]; $p < 0.001$).

Conclusions: Each episode of DKA is an independent risk factor for recurrence, even 4 years after an event, underlining the importance of a close follow-up after each episode.

1 | INTRODUCTION

Diabetic ketoacidosis (DKA), a potentially life-threatening acute complication of type 1 diabetes (T1D), is the leading cause of death in childhood-onset diabetes.[1-3] Mortality of a DKA episode ranges between 0.15% and 0.3%[4]; most deaths are related to cerebral edema.[5] Even if an episode of DKA is not immediately life-threatening, it may lead to acute kidney injury[6] or may negatively impact cognitive development of children and adolescents.[7,8] DKA frequently occurs at the time of T1D diagnosis,[9-11] but also during follow-up at a rate of 1–10 events per 100 patient-years,[4,12-15] which does not only account for considerable morbidity and mortality, but also for substantial health care costs.[16-18] Whereas the incidence of severe hypoglycemia in T1D has declined over the last years, the rate of DKA in established patients remains stable.[10,12,13,19] Female sex, adolescence, ethnic minority status, low socioeconomic status, an HbA1c level above the target range, and DKA at T1D manifestation are associated with an increased DKA frequency.[10,13,20,21] Relapsing DKA is not rare in pediatric patients with T1D: readmission for DKA within one year after an episode may account for up to 20% of all DKA admissions.[18] In a different pediatric cohort, more than half of all reported DKA events could be attributed to only 5% of all patients.[15] Since DKA mortality is higher in patients with several episodes,[22] patients with relapsing DKA require special awareness. Growing up in a deprived area especially predisposes pediatric T1D patients to repetitive DKA[23]; moreover, females, adolescents, and patients with psychiatric comorbidity are more likely to be readmitted for DKA within 30 days after discharge.[24] The role of previous episodes as an independent risk factor for acute T1D complications is increasingly understood: an episode of severe hypoglycemia increased the recurrence rate in pediatric patients with T1D even years later.[25] Similarly, in adults with T1D, a previous episode of an acute hyperglycemic event was identified as independent risk factor for recurrence.[26]

Strategies to find individuals at risk for recurrent DKA and to reduce the frequency of relapsing DKA in patients with established T1D are still needed. The aim of this study was to assess the role of previous episodes of DKA and the time-lag between episodes as risk factors for recurring DKA in a large population-based cohort of pediatric patients with T1D by analyzing data from the Diabetes Prospective Follow-up (DPV) register.

2 | METHODS

2.1 | Data source

Data originate from the DPV Initiative database, in which participating German, Austrian, Swiss, and Luxembourgian diabetes treatment centers document data from diabetes-related clinical visits for quality improvement and scientific research purposes using the freely available DPV software. Twice a year, anonymized data are transferred to a centralized data management unit at the Institute of Epidemiology and Medical Biometry at Ulm University, where data are validated and aggregated into an anonymous cumulative register. The DPV initiative as well as the analyses of anonymized data have been approved by the ethics committee at the University of Ulm. Participating centers obtained local ethics/data protection approval for participation in the DPV project.

For this report, data were retrieved from the DPV database in March 2020 and included datasets from visits between January 1, 2006 and December 31, 2019. 273 German, 26 Austrian, 1 Swiss, and 1 Luxembourgian diabetes centers contributed to the analysis.

2.2 | Study population

Patients with T1D aged at least 6 months at onset of the disease and less than 20 years throughout the 5 years of observation were included in the study if diabetes duration was longer than 10 days (to exclude possible DKA at manifestation), and if there were at least 5 years of continuous follow-up with at least one visit per year. For each patient, the most recent 5 years were used for analyses.

The final study population consisted of 29,325 patients (Figure S1).

For a sensitivity analysis, patients considered to have psychiatric comorbidities were excluded from the study population if they had a diagnosis of or if they had received treatment for depression, attention deficit hyperactivity disorder, schizophrenia, an anxiety disorder (including needle phobia and mutism), or if a diagnosis of autism or eating disorder had been made. When excluding patients with psychiatric comorbidity (n = 3012), the cohort comprised 26,313 patients.

2.3 | Variables

Patient characteristics included sex, age in the most recent year and at onset of diabetes. A migratory background was assigned if the

patient or at least one parent was born outside of Germany, Austria, Switzerland, and Luxembourg.

Variables documented at each visit and considered in this study were duration of diabetes, daily insulin dose (in units per kg body weight), frequency of daily self-monitoring of blood glucose (SMBG), use of continuous glucose monitoring systems (rtCGM or iscCGM), and mode of insulin administration: conventional therapy (CT) if there were 1–3 daily insulin injection time-points, intensified CT (ICT) if there were 4–8 daily insulin injection time-points, and continuous subcutaneous insulin infusion (CSII) The most intensive treatment documented in the respective patient year was considered for analyses. In order to correct for different laboratory methods, HbA1c values were mathematically standardized to the reference range of 4.05%–6.05% (IFCC 20.8–42.6 mmol/L) of the Diabetes Control and Complications Trial applying the multiple of the mean method.[12,27]

DKA was defined as presence of metabolic acidosis with a pH below 7.3 and/or bicarbonate levels below 15 mmoL/L and/or hospital admission due to DKA.

2.4 | Statistical analyses

For each patient, multiple data entries per year were aggregated; the median was used for continuous variables, sums were used for the time between visits or the number of DKAs. Wilcoxon's rank sum test and Chi-squared test were used for unadjusted comparisons between groups. *p*-values were adjusted for multiple testing using the Bonferroni stepdown method. DKA rates were estimated based on negative binomial regression using individual time under risk as offset. This model was additionally stratified by age groups (patients aged <12 years, 12 to <18 years, and ≥18 years in the most recent year), treatment modality (multiple daily injections only, CSII only, or a combination of both in the 5 years of observation), and the patients' sex. The effect size of the association between DKA events in the most recent year and DKA events in previous years was determined by calculating Cramer's V.

Logistic regression models based on maximum likelihood estimation were used to determine the probability of developing a DKA in the most recent year; they were adjusted for the covariates age (in groups as described above), diabetes duration (in groups of patients with a duration of T1D of <6 years, 6–10 years, or >10 years), treatment modality, sex, and time lag to preceding DKA events in years. *p*-values of regression models were adjusted using the Tukey–Kramer correction if more than two groups were compared.

For a sensitivity analysis, logistic regression models were additionally adjusted for the German Index of Socioeconomic Deprivation of 2012 (GISD_2012) as described before.[28]

All analyses were performed using SAS version 9.4 on a windows server 2016 mainframe computer. A two-sided *p*-value <0.05 was considered significant.

3 | RESULTS

3.1 | Description of the study population

A total of 29,325 patients were included in the study, 52.6% of them were male, 21.2% had a migratory background. In the most recent year, the patients' median age was 17.1 [first and third quartile: 14.3; 18.0] years, the median duration of T1D was 7.8 [5.6; 10.8] years (Table 1). During the 5 years of observation, 40.5% of the patients (n = 11,889) continuously received insulin via CSII, 39.9% of the patients (n = 11,707) always administered insulin with injections, and 19.5% of the patients (n = 5,729) used both treatment modalities. In the most recent year, 13.5% of the patients (n = 3,969) were less than 12-years-old, 61.7% (n = 18,084) were aged 12 to less than 18 years, and 24.8% (n = 7,272) 18 years or older. Diabetes duration was <6 years, 6–10 years, and >10 years in 29.8%, 39.4%, and 30.8% of the patients, respectively. Almost half of the cohort (49.6%) reported 0 years of CGM usage during the observed period, 16.8% of the study population had one year with CGM usage in the 5-year period, and 1.5% 5 years with CGM usage. CGM application increased during the 5 years of observation; in the first year of the observational period, 4.2% of the patients applied CGM devices, in the most recent year, 42.3% of the patients used CGM.

3.2 | Frequency of DKA

A majority of the patients, 25,219, corresponding to 86%, did not experience a DKA during the 5 years of observation (Table 1). The remaining 4,106 patients experienced at least one DKA in the period of observation, 2,833 individuals (9.7% of all patients and 69.0% of those with at least one DKA episode) reported one DKA event, 743 patients had two DKA events, 273 had patients three events, and 257 patients had more than three events. With 1,244, 1,064, 1,108, 1072, and 954 individuals in year 0, −1, −2, −3, and −4, respectively, the number of persons experiencing at least one DKA in the particular year remained stable throughout the observation time (Table S1). The DKA rate in the 5-year-period was 4.4 [95% CI: 4.3–4.6] per 100 patient-years (Table 2).

3.3 | Risk factors for DKA episodes

In unadjusted comparisons, demographical characteristics, treatment modalities, and glycemic control of patients who experienced no, one or more than one DKA during the 5-year period were compared to identify predisposing conditions and risk factors for DKA. In the 5 years of observation, female individuals and those with a migratory background were significantly less often found among patients who experienced no DKA episode. A higher HbA1c value and a higher daily insulin dose were significantly associated with a risk of DKA (Table 1).

With a mean of 4.2, the number of daily SMBG events was highest in the group of patients with no DKA in the 5-year period,

TABLE 1 Patient characteristics in the most recent year (year 0)

Variable	Whole cohort	n	5-year period						*p*-value
			no DKA	n	1 DKA	n	>1 DKA	n	
Sex (% male)	52.6	29,325	53.3	25,219	49.0	2833	46.0	1273	0.000[a]
Age (years)	17.1 (14.3; 18.0)	29,325	17.2 (14.2; 18.1)	25,219	16.8 (14.4; 17.7)	2833	17.2 (15.3; 17.8)	1273	0.000[a]
Duration of T1D (years)	7.8 (5.6; 10.8)	29,325	7.8 (5.6; 10.9)	25,219	7.8 (5.7; 10.6)	2833	7.8 (5.7; 10.5)	1273	0.939
Migratory background (% yes)	21.2	29,325	20.4	25,219	26.7	2833	26.2	1273	0.000[a]
HbA1c (%)	7.9 (7.2; 8.8)	29,094	7.8 (7.1; 8.6)	25,026	8.6 (7.7; 9.8)	2810	9.6 (8.4; 11.0)	1258	0.000[a]
Daily insulin dose (U/kg)	0.9 (0.7; 1.1)	28,696	0.9 (0.7; 1.1)	24,685	1.0 (0.8; 1.2)	2770	1.0 (0.8; 1.3)	1241	0.000[a]
# SMBG/day	4.0 (3.0; 5.0)	25,845	4.0 (3.0; 5.0)	22,140	4.0 (2.0; 5.0)	2543	4.0 (2.0; 5.0)	1162	0.000[a]
CSII (%)	55.5	29,017	55.7	24,944	56.7	2806	48.7	1273	0.000[a]
CGM (%)	42.3	29,325	42.6	25,219	41.3	2833	37.2	958	0.002[a]

Note: Median, first and third quartiles are indicated for continuous variables and proportions for categorical variables.
[a]Significant differences.

TABLE 2 Unadjusted DKA rates in the most recent year of observation (year 0) based on previous history of DKA

Group	Number of patients	Fraction (%)	DKA rate in most recent year, per 100 patient-years (95% CI)	*p*-values
No DKA events in years −4 to −1	25,974	88.6	2.8 (2.7–3.1)	0 vs.1 DKA: <0.001
1 DKA event in years −4 to −1	2428	8.3	11.9 (10.5–13.6)	1 vs. >1 DKA: <0.001
>1 DKA events in years −4 to −1	923	3.2	32.6 (27.8–38.2)	0 vs. > 1 DKA: <0.001
Whole cohort	29,325	100	4.5 (4.3–4.8)	

Note: DKA rate per 100 patient-years in 5-year period, (95% CI): 4.4 (4.3–4.6).

whereas patients with one or more than one DKA event in the observational period reported 3.8 and 3.6 daily SMBG events, respectively. In parallel to this, CGM use was most common in those patients with no DKA, and was significantly less often reported in patients with one or more than one DKA episode. Thus, frequency of SMBG events and CGM usage differed significantly between the groups of patients who experienced one, more than one, or no DKA.

Treatment modality in the DKA groups was compared. CSII use was lowest in the group of patients who reported more than one DKA, and highest in patients with one DKA (Table 1).

Whereas diabetes duration did not differ significantly between the groups of patients who experienced no, one, more than one DKA, the patients' age varied between the DKA groups: individuals with one reported DKA were younger than the other groups (Table 1). Patients with a history of more than one DKA had a mean age of 16.4 years and were thus older than those with one or no DKA, whose mean age was 15.9 years.

The impact of a previous episode as a risk factor for DKA was analyzed by calculating unadjusted DKA rates for the most recent year. In the group of 3,351 patients who had a history of DKA in years −4 to −1, the DKA rate in year 0 was significantly higher than in those 25,974 patients who had not experience DKA during the preceding 4 years (17.6 [95% CI: 15.9–19.5] vs. 2.8 [2.7–3.1] per 100 patient-years; $p < 0.001$). With an unadjusted DKA rate of 32.6 [27.8–38.2] per 100 patient-years in the most recent year, the frequency of DKA was highest in the group of 923 patients with a history of several episodes in the past 4 years (Table 2). Thus, a previous episode is a significant risk factor for occurrence of DKA, and several DKAs further increase the recurrence rate.

3.4 | Time lag of recurrent DKA episodes

To determine if the time lag of previous episodes had an impact on recurrence of DKA, the proportion of patients who experienced an episode in the most recent year was analyzed. While 24.3% of the patients with a preceding DKA in year −1 experienced an episode in the most recent year, this proportion of patients decreased continuously with an increasing time lag: only 6.4% of the patients who had experienced an episode of DKA 4 years earlier reported a recurring episode in year 0, which was still a higher fraction of patients than in those individuals who had no history of DKA – only 2.9% of these patients reported a DKA in the most recent year (Figure 1).

The odds for occurrence of a DKA in the most recent year in patients with a preceding episode in each of the years −1 to −4 were estimated in logistic regression analyses and compared to patients with no history of DKA. In accordance with the previous results, the odds ratio for occurrence of a DKA in the most recent year was highest in patients with an episode in the year before (10.0 [95% CI: 8.6–11.8]), decreased with each year, but still remained significantly elevated when the previous episode had occurred 4 years earlier (2.3 [1.6–3.1]; $p < 0.001$) (Figure 2). This analysis was adjusted for the

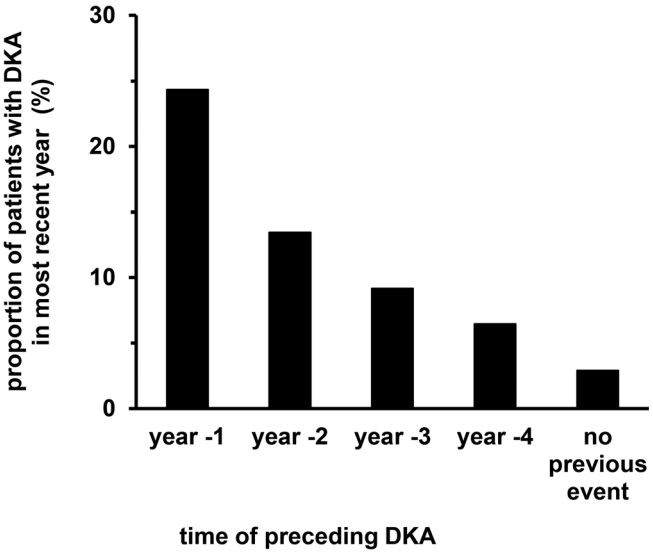

FIGURE 1 The proportion of patients with at least one episode of DKA in the most recent year depending on the time lag to the previous episode is indicated

covariates age group, duration of diabetes group, sex, and therapy. Stratification of this model by age groups, treatment modality, and patient sex gave similar results, but with a less strong influence of a four-year time lag in children aged <12 years, in females, and in patients using CSII only (Figure 2).

3.5 | Sensitivity analyses

In a sensitivity analysis, all statistical tests and models were applied to the cohort of patients that excluded individuals with psychiatric comorbidities. In these 26,313 patients, the mean DKA rate in the 5-year-period was 3.8 [3.7–4.0] per 100 patient-years. Risk factors for DKA and the influence of previous episode and their time lag on recurrence risk were similar.

In a second sensitivity analysis for the cohort of patients without psychiatric comorbidities, all regression analyses were additionally adjusted for social deprivation according to the GISD_2012. For 2,205 patients, this information was missing, the remaining 24,108 patients were divided into quintiles according to their social deprivation index, with 21.5%, 18.3%, 19.8%, 19.8%, and 20.6% of the patients being in the least deprived first, second, third, fourth, and most deprived fifth quintile, respectively.

The results of the logistic regression models in the sensitivity analyses were similar, but with a less strong influence of a previous episode on recurrence risk after a four-year time lag in females, patients aged less than 12 or ≥18 years, and for patients using always CSII and both CSII and injections during the 5 year-period (Figure S2). For the whole cohort of patients as well as for all other subgroups in the stratified models, the risk for DKA in the most recent year was higher in patients with an episode in the preceding year than in patients with

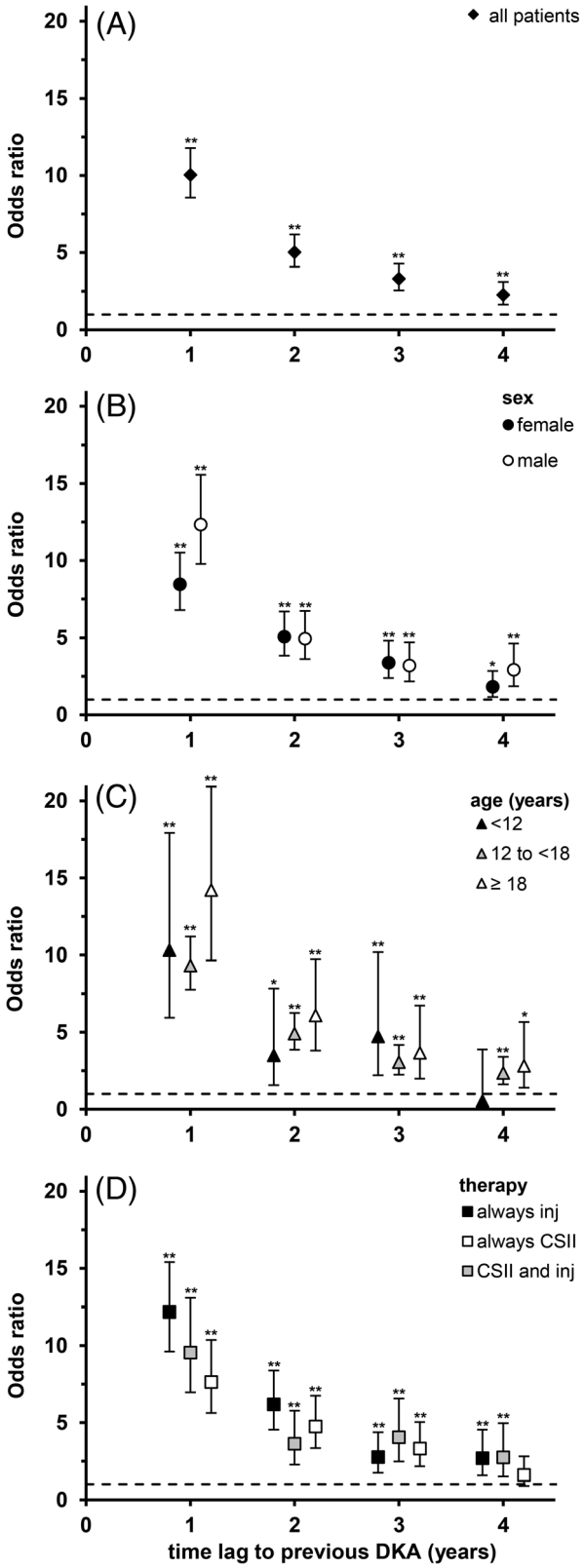

FIGURE 2 Odds ratios (OR) for occurrence of DKA in the most recent year depending on time lag to the last preceding episode in the whole cohort (A), and stratified by sex (B), age groups (C), and treatment modality (D). OR = 1 is indicated with a dashed line in each graph and refers to individuals with no past history of DKA in the previous 4 years. *p*-values <0.001 are marked with two asterisks, those <0.05 with one asterisk

no previous DKA, and remained significantly elevated 4 years after an episode.

4 | DISCUSSION

This study of a population-based cohort of 29,325 pediatric patients with T1D clearly identifies each episode of DKA as a risk factor for recurrence: more patients experienced a DKA in the most recent year if they had previously undergone such an episode, and the proportion of individuals with an episode in the most recent year depended on the time lag between the current and the previous episode, with a higher recurrence rate in patients with a more recent DKA. The effect is long-lasting: DKA frequency remained higher than in subjects with no previous episode even 4 years after an event. DKA is a considerable concern in pediatric patients with T1D—with more than four events per 100 patient-years, the DKA rate in our cohort corresponded to the DKA frequency observed in other cohorts of patients with established T1D.[4,15,29]

Whereas the outcome of DKA has improved tremendously over the last decades,[4,30] the incidence remained stable, and recurring events or readmission to a hospital are frequent concerns.[15,18,22-24,31] Previous studies of repetitive DKA events were designed as case–control-studies,[30] analyzed only a group of patients with DKA-related hospital admissions, covered a shorter period of time[18,19,24] or a smaller group of patients. To our knowledge, this is the first population-based study of a large pediatric cohort over a long period of time that emphasizes the role of previous episodes and their time-lag as independent risk factor for DKA, which acts independently of the patients' age, sex, and treatment modality.

Patient characteristics associated with an increased DKA frequency in our cohort - female sex, migratory background, a higher HbA1c value, a higher daily insulin dose, a lower frequency of daily SMBG measurements and less common CGM usage—have been previously identified as risk factors for DKA.[10,13,20,21]

Special attention should be paid to patients with recurring DKA episodes. Adolescents and females were at higher risk of recurring DKA in our cohort and in previous studies.[4,20] Besides metabolic differences during puberty, behavioral aspects may influence DKA recurrence: struggle for autonomy, escaping parental control, metabolic differences during puberty or insulin purging for weight loss may be more common among adolescents and females. In the United States, readmission for DKA is higher in patients with public insurance[20] – thus, socioeconomic status may also determine DKA recurrence. Technological devices, insulin pumps and CGM devices, were less frequently used in patients who experienced repetitive DKA episodes, corresponding to results from recent studies showing a reduction of DKA frequency after implementation of CGM[32] or in patients using insulin pumps.[33] In our cohort, CSII was most frequently used in the group of patients who experienced one DKA, which is somewhat surprising, but may be related to the younger age of this group. In summary, usage of emerging technologies—CSII and CGM—may be beneficial in prevention of repetitive DKA events, which may help to reduce the recurrence rate in the future, if these devices become even more accessible. New treatment modalities have contributed to an improvement of metabolic control in pediatric patients with T1D in the past[12] and may continue to a better achievement of treatment goals. Situations in which insulin is omitted deliberately to lose weight or to escape abusive or otherwise unbearable familial circumstances may put patients at a high risk of recurrent DKA,[4] underlining the importance of a multidisciplinary specialist team in the care of patients with recurring DKA.

In other studies, race other than non-hispanic white, lower income, and lack of private insurance were associated with a higher frequency of DKA.[14] In a sensitivity analysis performed by us, the GISD_2012 was used to adjust models for regional deprivation, with similar results: a previous episode of DKA remained a significant risk factor for recurrence, underlining that patients with previous episodes should be followed closely. Targeted patient education may also help to reduce recurrence risk: structured patient education or multidisciplinary support programs can improve glycemic control[34] and reduce hospital admissions for DKA.[22,35] A language barrier is associated with higher HbA1c levels[36] and may partly explain the higher risk for DKA in patients with a migratory background. In order to reach this vulnerable group, patient and family education programs should address cultural differences as well as language barriers. Patient education should cover important causes of DKA, and therefore address management of intercurrent illnesses and insulin pump failure,[4] and emphasize the importance of home-based ketone measurements. Early and reliable evaluation of the metabolic situation by appropriate self-measurement of ketones is essential in the prevention of DKA. Compared to measurement of urinary ketones, determination of blood ketones may even detect metabolic decompensation and its resolution earlier, so that this method is preferably recommended for patients with T1D and co-medication with SGLT2 inhibitors, which especially increases the risk for euglycemic DKA and requires strict self-control to avoid metabolic decompensation.[37]

During the first months of the Covid-19 pandemic, a time in which contacts to health-care providers may have been limited, the DKA rate in children with T1D manifestation was increased,[38] underlining the importance of presence and accessibility of healthcare providers in the care of pediatric patients with T1D.

Possible limitations of this study may result from the retrospective character of the analysis, so that associations rather than casual relationships are described. Moreover, only DKA events reported by diabetes care teams and transferred to the DPV registry were included, not hospital discharge data, which may possibly lead to an underestimation of the number of events. However, DKA events as defined here will likely be reported by patients and clinicians, even if they were managed in an ambulatory setting. The number of annual visits and diabetes management education may also have an influence on occurrence of DKA, but these factors were not included in our analysis due to heterogeneity of patient education between treatment centers, which may represent a possible limitation of the study.

Many studies have shown an association of DKA with psychiatric comorbidity and substance abuse in adults and children.[24,30,39-43] DKA frequency is significantly increased in girls with T1D and eating disorders.[44] In a sensitivity analysis with and without exclusion of patients with psychiatric comorbidity, the results did not differ. Nevertheless, undetected psychiatric comorbidity may account for some relapsing DKA events, which may represent a potential limitation of our study. Psychiatric disorders, depression or attention deficit hyperactivity disorder tend to be underdiagnosed in children.[45,46] Moreover, affected individuals may not be referred to adequate specialist treatment. In adults with T1D, cannabis use increases the risk for DKA,[47] underlining the importance of a comprehensive medical history, including substance abuse, at each visit to the diabetes clinic. Thorough evaluation, treatment and close follow-up by a multidisciplinary diabetes care team, including psychologists, should be considered after each episode of DKA.

To conclude, our study shows that an episode of DKA is a significant independent and long-lasting risk factor for recurrence of DKA in pediatric patients with T1D. Since acute complications, above all DKA, account for the majority of premature deaths in patients with T1D aged less than 30 years,[1] our findings are of great clinical relevance. Caregivers should continue to document each episode of DKA and offer close follow-up by a multidisciplinary specialist care team to prevent further episodes. Self-monitoring of ketones, a structured self-management plan for patients, and—in the future—more abundant use of CGM devices and assisted insulin pumps may help to decrease the rate of DKA.

ACKNOWLEDGMENTS

We wish to thank all centers participating in the DPV project. For a full list of participating DPV centers, see the supplement. Special thanks to A. Hungele and R. Ranz for support and the development of the DPV documentation software, K. Fink and E. Bollow for the DPV data management (all clinical data managers, Ulm University). We also thank S. Lanzinger for checking the statistical program.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13185.

DATA AVAILABILITY STATEMENT

To protect patient privacy, patient level data cannot be shared with outside investigators. However, upon request and after agreement from the DPV scientific board, joint research projects are possible.

ETHICS STATEMENT

The DPV Initiative as well as the analyses of anonymized data have been approved by the ethics committee at the University of Ulm. Participating centers obtained local ethics/data protection approval for participation in the DPV project.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Hammersen J, Tittel SR, Warncke K, et al. Previous diabetic ketoacidosis as a risk factor for recurrence in a large prospective contemporary pediatric cohort: Results from the DPV initiative. *Pediatr Diabetes*. 2021;22:455–462. https://doi.org/10.1111/pedi.13185