Received: 8 March 2022 | Revised: 13 May 2022 | Accepted: 7 June 2022

DOI: 10.1111/pedi.13379

ORIGINAL ARTICLE

Diabetic ketoacidosis incidence among children with new-onset type 1 diabetes in Poland and its association with COVID-19 outbreak—Two-year cross-sectional national observation by PolPeDiab Study Group

Iwona Pietrzak[1] | Arkadiusz Michalak[1,2] | Sebastian Seget[3] | Maria Bednarska[4] | Iwona Beń-Skowronek[5] | Artur Bossowski[6] | Agata Chobot[4,7] | Katarzyna Dżygało[8] | Barbara Głowińska-Olszewska[6] | Martyna Górnicka[9] | Anita Horodnicka-Józwa[10] | Katarzyna Jakubek-Kipa[11] | Przemysława Jarosz-Chobot[3] | Katarzyna Marcinkiewicz[10] | Artur Mazur[11] | Małgorzata Myśliwiec[12] | Joanna Nazim[13] | Elżbieta Niechciał[14] | Anna Noczyńska[15] | Ewa Rusak[3] | Monika Seifert[15] | Elżbieta Skotarczyk-Kowalska[16] | Anna Skowronek[5] | Agnieszka Szypowska[8] | Paulina Wais[14] | Mieczysław Walczak[10] | Anna Wołoszyn-Durkiewicz[12] | Marta Wysocka-Mincewicz[9] | Agnieszka Zubkiewicz-Kucharska[15] | Agnieszka Szadkowska[1]

[1]Department of Pediatrics, Diabetology, Endocrinology and Nephrology, Medical University of Lodz, Lodz, Poland

[2]Department of Biostatistics and Translational Medicine, Medical University of Lodz, Lodz, Poland

[3]Department of Children's Diabetology, Medical University of Silesia, Katowice, Poland

[4]Department of Pediatrics, University Clinical Hospital in Opole, Opole, Poland

[5]Department of Pediatric Endocrinology and Diabetology, Medical University in Lublin, Lublin, Poland

[6]Department of Pediatrics, Endocrinology and Diabetology with Cardiology Unit, Medical University of Bialystok, Białystok, Poland

[7]Department of Pediatrics, Institute of Medical Sciences, University of Opole, Opole, Poland

[8]Department of Paediatrics, Medical University of Warsaw, Warsaw, Poland

[9]Department of Endocrinology and Diabetology, Children's Memorial Health Institute, Warsaw, Poland

[10]Department of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology of the Developmental Age, Pomeranian Medical University in Szczecin, Szczecin, Poland

[11]Department of Pediatrics, Pediatric Endocrinology and Diabetes, Medical College University of Rzeszów, Rzeszów, Poland

[12]Department of Pediatrics, Diabetology and Endocrinology, Medical University of Gdansk, Gdańsk, Poland

[13]Department of Pediatric Endocrinology, Jagiellonian University Medical College, Faculty of Medicine, Institute of Pediatrics, Kraków, Poland

[14]Department of Pediatric Diabetes, Auxology and Obesity, Poznan University of Medical Sciences, Poznan, Poland

[15]Department of Pediatric Endocrinology and Diabetology, Wroclaw Medical University, Wroclaw, Poland

[16]Department of Children Endocrinology and Diabetology, Regional Polyclinical Hospital, Kielce, Poland

Iwona Pietrzak and Arkadiusz Michalak are co-first authors.

Correspondence
Arkadiusz Michalak, Department of Pediatrics, Diabetology, Endocrinology and Nephrology – Medical University of Lodz, Sporna 36/50, 91-738 Lodz, Poland.
Email: arkadiusz.michalak@umed.lodz.pl

Abstract

Background: There are several observations that the onset of coronavirus 19 (COVID-19) pandemic was associated with an increase in the incidence of diabetic ketoacidosis (DKA). However, due to heterogeneity in study designs and country-specific healthcare policies, more national-level evidence is needed to provide generalizable conclusions.

Objective: To compare the rate of DKA in Polish children diagnosed with type 1 diabetes (T1D) between the first year of COVID-19 pandemic (15 March 2020 to 15 March 2021) and the preceding year (15 March 2019 to 15 March 2020).

Methods: Reference centers in 13 regions (covering ~88% of Polish children) retrospectively reported all new-onset T1D cases in children from assessed periods, including DKA status at admission, administered procedures and outcomes. Secondly, we collected regions' demographic characteristics and the daily-reported number of COVID-19-related deaths in each region.

Results: We recorded 3062 cases of new-onset T1D (53.3% boys, mean age 9.5 ± 4.3 years old) of which 1347 (44%) had DKA. Comparing pre- and post-COVID-19 period, we observed a significant increase in the rate of DKA (37.5%–49.4%, $p < .0001$). The fraction of moderate (+5.4%) and severe (+3.4%) DKA cases increased significantly ($p = .0089$), and more episodes required assisted ventilation (+2.1%, $p = .0337$). Two episodes of DKA during 2020/2021 period were fatal. By region, change in DKA frequency correlated with initial COVID-19 death toll (March/April 2020) ($R = .6$, $p = .0287$) and change in T1D incidence ($R = .7$, $p = .0080$).

Conclusions: The clinical picture of new-onset children T1D in Poland deteriorated over a 2-year period. The observed increase in the frequency of DKA and its severity were significantly associated with the overlapping timing of the COVID-19 epidemic.

KEYWORDS
children, COVID-19, diabetic ketoacidosis, new-onset diabetes, Poland, type 1 diabetes

1 | INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) forced stricter sanitary regimes around the world. Around March 2020 many countries imposed severe restrictions on social communication, out-of-home activities, travel and working conditions, resulting in national lockdowns. In Poland, official restrictions were introduced on 15 March 2020. The pro-isolation policies were coupled with a change in patients' behavior toward avoidance of medical facilities and contact with doctors, as well as abrupt changes in health care organization (reassignment of hospital wards for COVID-19 patients, switch from face-to-face to online consultation). Consequently, access to health care decreased. These negative changes were also observed in pediatric care. In children, delayed contact with medical professional or consultation without a physical examination might have impeded diagnosis of many pediatric conditions and possibly aggravated their outcomes. One of such "neglected" disorders might have been type 1 diabetes (T1D). Its initial symptoms might be difficult for parents to recognize or properly communicate and could be overlooked during teleconsultation if they are not the primary concern. Delayed diagnosis of type 1 diabetes puts a child at risk of developing diabetic ketoacidosis (DKA), which is an acute, life-threatening complication that requires urgent care. Moreover, DKA not only poses a threat of complications and death[1] but also prolongs time of hospitalization, decreases the chance of entering partial clinical remission and is ultimately associated with impaired future metabolic control of T1D and increased risk of its long-term complications.[2–5]

Before COVID-19 pandemic, the rate of DKA among new-onset T1D patients was already relatively high in Poland.[6–9] It is therefore a concern that lockdown-related environment might have further aggravated DKA incidence and possibly affected its

course. Unfortunately, current reports on the association between COVID-19 pandemic and DKA incidence change remain inconclusive, with most studies focusing on the period of first wave (3–4 months) or presenting perspective of single centers and few multicenter analyses.[10] Moreover, there are important differences between the reporting countries in terms of health care system structure, as well as COVID-19 incidence and mortality. Therefore, we decided to conduct a national, multicenter study to collect data representative for Polish pediatric population and add to the collective body of evidence in this area.

1.1 | Aim

The aim of this study was to compare the rates of DKA in new-onset children with T1D in Poland during 1 year preceding the COVID-19-related lockdown and 1 year following its introduction.

2 | METHODS

In Poland, diabetes care for children and adolescents is provided within public health care and aggregated in specialized centers, mostly medical university-affiliated ones. These units provide both outpatient and inpatient care for children and adolescents with diabetes, and treat all new-onset cases referred there directly or from other, non-referral hospitals as quickly as possible.[11,12]

The study design was a retrospective chart review. As such, it was the exempt from Bioethical Committee review. Nevertheless, we followed the principles of the Declaration of Helsinki and protected patients' confidentiality. All regional pediatric diabetes care centers affiliated with medical universities received an invitation to participate in this study. Each participating center received a uniform electronic spreadsheet to be filled with data on each new-onset T1D case hospitalized in that unit.

The following data were collected from the medical records: age, sex, place of residence (urban vs. rural), name of region, body height and weight, family history of T1D in first-degree relatives (FDRs), laboratory tests at diagnosis (blood glucose, pH, HCO3, ketonuria or ketonemia, HbA1c) and assisted ventilation, treatment in intensive care unit (ICU), administration of mannitol or 3% NaCl, thrombosis, hospitalization duration, and outcomes (fatal or not).

T1D was diagnosed based on national guidelines[13] consistent with WHO, International Society for Pediatric and Adolescent Diabetes (ISPAD) and American Diabetes Association. The presence and severity of DKA was determined according to laboratory criteria by ISPAD.[14] In case those data were unavailable, DKA was ascertained based on the provider's documentation.

We collected demographic data from Poland's Central Statistical Office and government website for each region and downloaded publicly available data on COVID-19 dynamics in Poland between 15 March 2020 and 15 March 2021, focusing on the number of reported COVID-19-related deaths as the most reliable measure.

2.1 | Statistical analysis

To provide the most complete picture of new-onset T1D in Poland, all reported cases were included in the analysis. In case of missing specific data (laboratory results, body weight, or height), the number of patients available for each comparison was adjusted and shown.

All reported T1D cases were analyzed in two separate periods to reflect the research question: from 15 March 2019 to 14 March 2020 (abbreviated as 2019/2020) and from 15 March 2020 to 15 March 2021 (abbreviated as 2020/2021). The former was intended to represent the pre-COVID-19 period and be a reference for 2020/2021, which encompasses both first and second COVID-19 waves in Poland.

For each period and region, the total number of reported new-onset T1D cases was divided by the total number of children aged 0–18 years old to obtain T1D raw incidence. Importantly, T1D cases were assigned to each region based on the place of residence and not necessarily on the place of diagnosis. The rate of DKA in each region was calculated as the number of DKA cases divided by total number of new-onset T1D cases.

Body mass index (BMI) was calculated based on reported body weight and height. All those characteristics were transformed into z-scores and percentile values to comply with standard pediatric reporting.[15]

Quantitative group characteristics were presented as means and SDs. Given the high number of reported cases and high prevalence of normal distributions among variables, subsequent analyses were performed using parametric approach.

The main objective of the study was the change of DKA frequency in the analyzed population between 2019/2020 and 2020/2021 periods—these comparisons were performed using unpaired *t* tests. Similarly, the socio-demographic characteristics of children admitted with new-onset T1D in those period were compared in the same manner. Given that this study focuses on pediatric population, separate tests were performed in each of five age subgroups: 0–2 years old, 3–6 years old, 7–10 years old, 11–14 years old, 15–18 years old For these analyses, the alfa value for declaring statistical significance was adjusted according to Bonferroni rule to 0.01 (0.05/5 within-subgroup tests). The subgroups were also compared using analysis of variance (ANOVA) (with Bonferroni post-hoc tests) for the entire analyzed time (2019–2021)—global alfa significance for this test was upheld at 0.05. Such design was chosen for simplicity of result presentation and discussion. Alternatively, we performed ANOVA analysis with age subgroups and period defined as main effects and including their interaction—and obtained consistent results.

We also analyzed characteristics of children who did and did not present with DKA at T1D diagnosis. The DKA-positive and negative groups were compared for the entire assessed period (2019–2021), in addition the 2019/2020 and 2020/2021 periods were compared within each group—the alfa of these tests was adjusted to 0.017 respectively.

Nominal characteristics were presented as numbers and percentages. They were compared between the groups using a chi square test

TABLE 1 Group characteristics

Quantitative traits—Mean ± SD									
Characteristic	**Age group**	**Units**	**N**	**2019/2021**	**N**	**2019/2020**	**N**	**2020/2021**	***p* value**
HbA1c at T1D diagnosis	0–2	% mmol/mol	264	10.96 ± 2.1[*,†,‡] 96.3 ± 22.9	117	10.66 ± 2.28 93.0 ± 24.9	147	11.20 ± 1.91 98.9 ± 29.9	.0386
	3–6	% mmol/mol	632	11.41 ± 2.18[§,&,b] 101.2 ± 23.8	275	11.09 ± 2.07 97.7 ± 22.6	357	11.65 ± 2.23 103.9 ± 24.3	**.0012**
	7–10	% mmol/mol	920	12.3 ± 2.5[*,§,a] 111.1 ± 27.3	424	12.12 ± 2.60 109.0 ± 28.4	496	12.47 ± 2.41 112.8 ± 26.3	.0344
	11–14	% mmol/mol	923	12.67 ± 2.88[†,&,a] 115.0 ± 31.5	404	12.3 ± 3.1 110.9 ± 33.4	519	12.97 ± 2.69 118.2 ± 29.5	**.0004**
	15–18	% mmol/mol	295	12.3 ± 2.96[‡,b] 110.9 ± 32.3	153	11.97 ± 3.19 107.3 ± 34.9	142	12.65 ± 2.65 114.8 ± 28.9	.0479
	ANOVA *p* value		**<.0001**						
Hospitalization duration	0–2	Days	226	11.3 ± 4.34[*,†,‡]	98	11.00 ± 3.99	128	11.58 ± 4.59	.3186
	3–6	Days	535	10.5 ± 3.86	229	11.19 ± 3.63	306	10.02 ± 3.96	**.0005**
	7–10	Days	791	10.3 ± 4.26[a]	366	10.14 ± 3.44	425	10.5 ± 4.9	.2214
	11–14	Days	814	10.2 ± 4.13[†]	355	10.4 ± 4	459	9.98 ± 4.23	.1213
	15–18	Days	254	9.9 ± 3.76[‡]	132	10.06 ± 3.73	122	9.72 ± 3.79	.4678
	ANOVA *p* value		**.0010**						
BMI	0–2	kg/m^2	228	15.3 ± 2.11	107	15.28 ± 2.09	121	15.37 ± 2.14	N/A
	3–6	kg/m^2 z-score percentile	609	15.1 ± 2.20 −0.6 ± 1.40 36.5 ± 31.3	271	15.01 ± 2.13 −0.69 ± 1.42 35.1 ± 31.4	338	15.17 ± 2.26 −0.54 ± 1.39 37.7 ± 31.2	.2086
	7–10	kg/m^2 z-score percentile	906	16.8 ± 3.82 −0.3 ± 1.37[a] 43.2 ± 33.45	428	16.67 ± 4.06 −0.35 ± 1.31 41.64 ± 33.24	478	16.95 ± 3.60 −0.27 ± 1.43 44.6 ± 33.6	.4012
	11–14	kg/m^2 z-score percentile	909	18.3 ± 3.77 −0.5 ± 1.56[a] 40.4 ± 32.86	406	18.3 ± 3.6 −0.38 ± 1.3 41.6 ± 32.3	503	18.17 ± 3.87 −0.56 ± 1.73 39.48 ± 33.31	.0910
	15–18	kg/m^2 z-score percentile	289	20.7 ± 4.66 −0.4 ± 1.58 43.6 ± 33.72	151	21.10 ± 4.67 −0.20 ± 1.63 48.15 ± 33.54	138	20.21 ± 4.62 −0.54 ± 1.51 38.6 ± 33.3	.0646
	ANOVA *p* value		**.0010**						
Quantitative traits—Numbers and %									
Characteristic	**Age group**		***N***	**2019/2021**	***N***	**2019/2020**	***N***	**2020/2021**	***p* value**
Gender—Man [*N* (%)]	0–2		266	143 (53.8%)	117	67 (57.3%)	149	76 (51%)	.3096
	3–6		633	319 (50.4%)	276	143 (51.8%)	357	176 (49.3%)	.5308
	7–10		929	457 (49.2%)	432	189 (43.8%)	497	268 (53.9%)	**.0020**
	11–14		934	536 (57.4%)	411	236 (57.4%)	523	300 (57.4%)	.9854
	15–18		299	176 (58.9%)	155	80 (51.6%)	144	96 (66.7%)	**.0082**
	Age groups—*p* value		**.0010**						
Urban residency [*N* (%)]	0–2		242	138 (57.0%)	112	64 (57.1%)	130	74 (56.9%)	.9725
	3–6		574	334 (58.2%)	267	153 (57.3%)	307	181 (59.0%)	.6886
	7–10		839	517 (61.6%)	414	255 (61.6%)	425	262 (61.4%)	.9874
	11–14		859	524 (61.0%)	395	253 (64.1%)	464	271 (58.4%)	.0909
	15–18		273	164 (60.1%)	152	88 (57.9%)	121	75 (62.8%)	.4101
	Age groups—*p* value		.4859						
DKA [*N* (%)]	0–2		266	185 (69.5%)	117	67 (57.3%)	149	118 (79.2%)	**.0001**
	3–6		633	242 (38.2%)	276	90 (32.6%)	357	152 (42.6%)	.0105
	7–10		930	420 (45.2%)	432	162 (37.5%)	498	258 (51.8%)	**<.0001**

TABLE 1 (Continued)

Quantitative traits—Numbers and %								
Characteristic	**Age group**	***N***	**2019/2021**	***N***	**2019/2020**	***N***	**2020/2021**	***p* value**
	11–14	934	407 (43.6%)	411	151 (36.7%)	523	256 (48.9%)	**.0002**
	15–18	299	93 (31.1%)	155	51 (32.9%)	144	42 (29.2%)	.4856
	Age groups—*p* value	**<.0001**						

Note: Superscript symbols (*, †, ‡, [a], [b]) denote statistically significant differences between the groups in post-hoc Bonferroni test. N/A - statistical comparison not performed. Bolded *p*-values are statistically-significant after applying correction for multiple comparisons.

in a similar design to the continuous ones—between the 2019/2020 and 2020/2021 periods in each age subgroup (0–2 years old, 3–6 years old, 7–10 years old, 11–14 years old, 15–18 years old). In some cases, odds ratio (OR) with 95% confidence interval was calculated to help estimate the effect size of an association.

We then assessed the T1D incidence and DKA rate dynamics in more detail by pooling the numbers from all regions into 30-day periods (starting 15 March 2019). On such data, we performed a Pettitt test, which is a series Mann–Whitney *U* test to determine the best split point for a given variable (here: DKA rate) between two periods.

We also performed region-level ("ecological") analyses. The change in T1D incidence or region-specific DKA rate between the periods was assessed using paired *t* test. Subsequently, we checked whether the noted change in regions' DKA rate was associated with their geographic or demographic characteristics—this was done using Spearman's R correlation. Finally, we evaluated the association of DKA rate's increase with COVID-19-related burden of each region. As most indicators (e.g., number of cases, number of positive tests, fraction of positive tests) are highly dependent on testing strategy at a particular time, we chose COVID-19-related deaths (expressed as number by 100,000 population) as the most unbiased measure of pandemic impact. Importantly, it does not only reflect the epidemiological severity of COVID-19, but also the load put on health care system. Given that the largest increase in DKA rate was noted in March 2020, we assessed COVID-19-related deaths both for the entire 2020/2021 period and for the March–April 2020 period only.

3 | RESULTS

The study included 14 pediatric diabetes reference centers, representing 13 out of 16 Polish macroregions (voivodships) inhabited by ~6.5 M children up to 18 years old (88.2% of Polish pediatric population).

Between 15 March 2019 and 15 March 2021, participating centers recorded 3062 cases of new-onset T1D (53.3% boys, mean age at diagnosis 9.5 ± 4.3 years old), 1347 (44%) of whom presented with DKA (mean blood pH 7.15 ± 0.14). Detailed characteristics of the entire group, stratified by age and period, are presented in Tables 1 and S1. Notably, in 1.1% of DKA cases 7% of non-DKA cases pH results were unavailable and the presence of acidosis was ascertained based on documentation. Detailed flow-chart is included as a Figure S1.

Among the recorded new-onset T1D cases, 1391 (45.4%) were diagnosed in the 2019/2020 period and 1671 (54.6%) in the 2020/2021 period. Considering the pediatric population at risk, this corresponds to an observed increase in T1D incidence from 21.55 cases/100000 person-years to 25.90 cases/100000 person-years in children aged 0–18. The increase was consistent among the analyzed regions and statistically significant ($p = .0044$, Figure 1). At the same time, there were 521 DKA cases noted in 2019/2020 (37.5%) and 826 in 2020/2021 (49.4%). The increase was significant both at the patient level ($p < .0001$) and at the observation region level (mean increase across the regions +11.1 ± 7.2%, $p = .0001$, Figure 1). At the national level (considering all new-onset T1D cases diagnosed during each month), the major increase was noted in February 2020, denoting a shift in DKA incidence (minimum *p* value for before/after comparison with Mann–Whitney *U*/Pettitt test noted for February, $p = .00008$, significant even after considering Bonferroni-adjusted threshold of 0.0022, Figure 2). A month after, a nationwide lockdown was introduced, during which the observed DKA incidence reached its peak (60%). Data for subgroups based on patient's age and DKA severity are included in Figure S2).

Among the reported DKA episodes, 15 (1.1%) could not be graded for severity according to ISPAD criteria—the remaining ones were graded as mild in 680 (51.1%) cases, moderate in 371 (27.9%) and severe in 281 children (21.1%). Between the compared periods, we noted a significant shift in DKA severity toward more severe episodes ($p = .0089$, Table 2), which was consistent across almost all age groups (in 15–18 years old the incidence of moderate and severe DKA remained similar or decreased slightly). In line with this observation, the frequency of ICU admissions among DKA cases increased, albeit not significantly (13.6% vs. 17.4%, $p = .0633$), and significantly more children required assisted ventilation (1.3% vs. 3.4%, $p = .0037$, Table 2).

In 11 (0.8%) cases DKA was complicated by thrombosis, with similar incidence in both analyzed periods. In two DKA cases the outcome was fatal. Both deaths outcomes occurred after COVID-19 outbreak, however, due to extremely low counts and zero deaths reported in 2019/2020 no statistical comparison between the periods was made. Both deaths had place in non-referral hospitals prior to transfer to the referral ones in the course of cerebral edema (More detailed case reports in the Data S1).

The change in T1D incidence did not correlate with any of the collected regions' characteristics ($p > .05$). Similarly, the change in

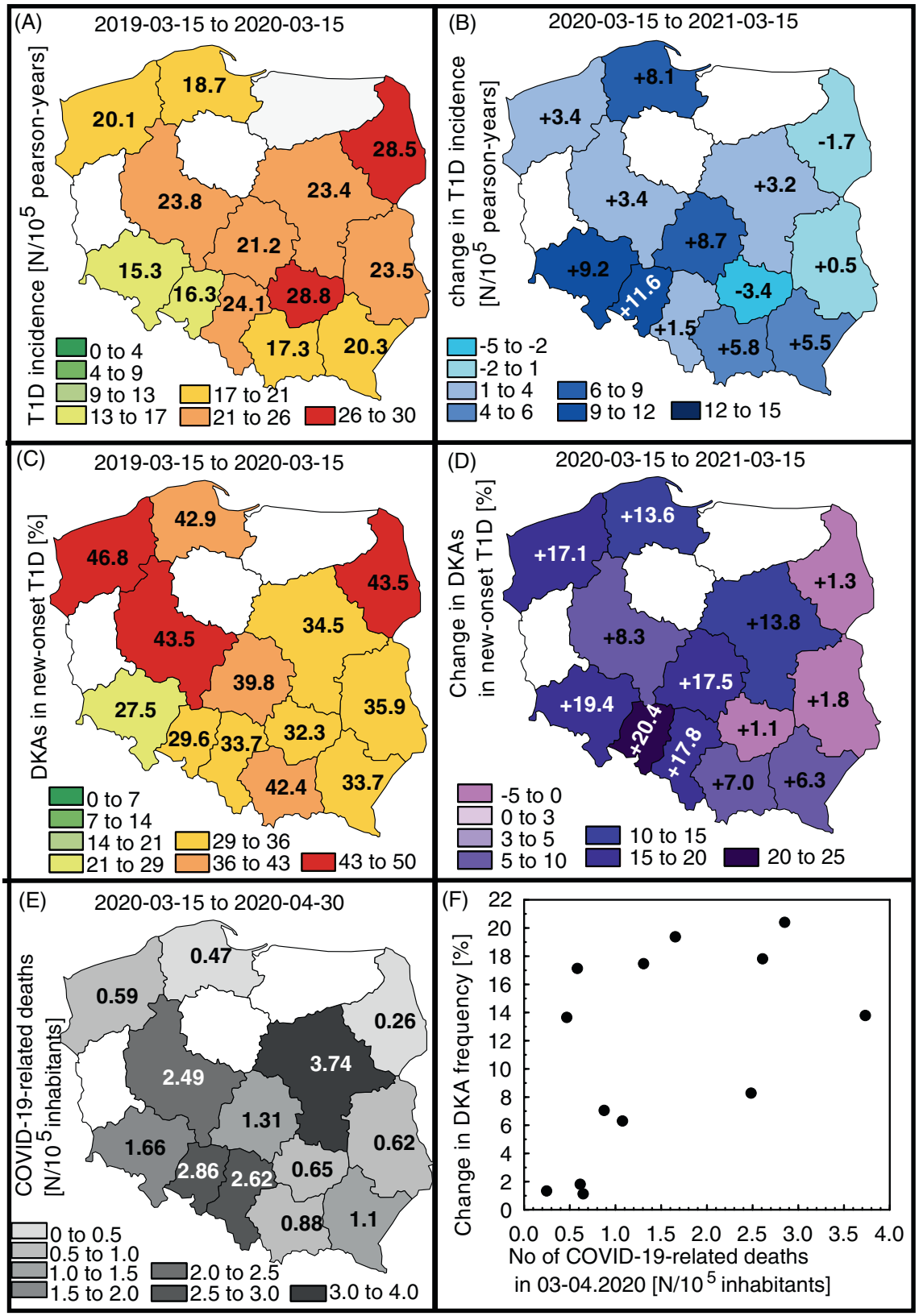

FIGURE 1 Incidence of childhood type 1 diabetes (T1D) in Polish regions between 15 March 2019 and 15 March 2020 (A) and its change in 15 March 2020/15 March 2021 period relative to the preceding year (B). Exact numbers are provided for each region, with additional color-coding below. Frequency of diabetic ketoacidosis (DKA) in new-onset childhood T1D in Polish regions between 15 March 2019 and 15 March 2020 (C) and its change in 15 March 2020/15 March 2021 period relative to the preceding year (D). Exact numbers are provided for each region, with additional color-coding below. Number of COVID-19-related deaths in Polish regions between March and April of 2020 (15 March 2020 to 30 April 2020) (E) and its association with region-specific change in DKA frequency (F). By Spearman correlation coefficient, the association was moderately strong, positive and significant ($R = .6$, $p = .0287$).

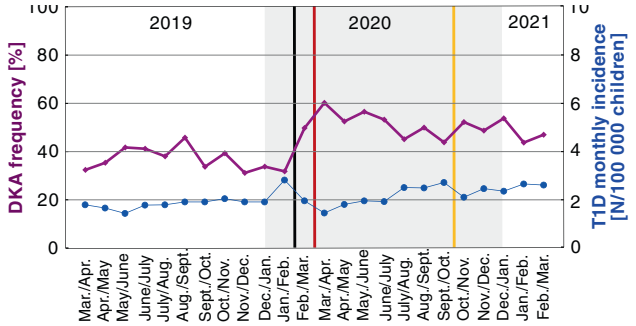

FIGURE 2 Monthly type 1 diabetes (T1D) incidence (blue points and line) and diabetic ketoacidosis (DKA) frequency in new-onset T1D (purple squares and line) in 13 Polish regions between 15 March 2019 and 15 March 2021. Each point represents data aggregated from a 30-day period, encompassing halves of consecutive months. Years are denoted in the upper side, as well as by gray tone. Black line denotes the best statistical division point (based on Pettitt's test), for which two resulting periods (here: 15 March 2019 to 15 February 2020 and 15 February 2020 to 15 March 2021) differ the most in terms of DKA frequency. Red line denotes 15 March 2020, when national lockdown was introduced at the beginning of COVID-19 first wave in Poland. Yellow line marks the beginning of the second wave of pandemic

DKA rates observed between 2019/2020 and 2020/2021 was not associated with regions' size ($R = -.14$, $p = .6286$), population ($R = .25$, $p = .3943$) or children ($R = .24$, $p = .4154$), population density ($R = .38$, $p = .1944$), number of general practitioners and pediatric specialists per 1000 children ($R = -.46$, $p = .1173$) and cumulative COVID-19 death toll for 2020/2021 ($R = -.18$, $p = .5533$). However, it showed a moderate-to-strong correlation with COVID-19 deaths related to the pandemic outbreak (March/April 2020) ($R = .6$, $p = .0287$, Figure 1), urbanization rate ($R = .65$, $p = .0154$) and change in T1D incidence ($R = .7$, $p = .0080$).

Overall, children who developed DKA were younger than those who did not (8.98 ± 4.28 vs. 9.91 ± 4.19, $p < .0001$), presented more pronounced weight loss (body weight z-score: −0.36 ± 1.5 vs. −0.1 ± 1.37, $p < .0001$; BMI z-score: −0.63 ± 1.49 vs. −0.3 ± 1.44, $p < .0001$) and higher blood glucose levels at diagnosis (478 ± 192 vs. 409 ± 156 mg/dl, $p < .0001$) as well as HbA1c [12.7% (116 mmol/mol) ± 2.1% (23 mmol/mol) vs. 11.6% (104 mmol/mol) ± 2.9% (31 mmol/mol), $p < .0001$]. DKA was also associated with a significantly longer hospitalization (10.96 ± 4.06 vs. 9.91 ± 4.1 days, $p < .0001$). Details of those comparisons are presented in Table S1. Importantly, children who had a FDRs with T1D developed DKA at T1D diagnosis less often than those without positive family history [OR = 0.33 (95%CI: 0.24–0.45), $p < .0001$). The effect persisted after adjustment for analysis period in a multivariable logistic regression [OR = 0.32 (0.23–0.44), $p < .0001$), with the interaction assessed as insignificant ($p = .4063$).

Unfortunately, data on COVID-19 infection status at admission were severely lacking (PCR test results available for $N = 854$ children in 2020/2021, 51.1% of analyzed sample). In this subgroup, 45 children had a positive PCR test at T1D diagnosis, corresponding to 5.3%. The proportion of COVID-19-positive children was higher among those with DKA ($N = 28$, 6.4%) than those without ($N = 17$, 4.1%), but the disproportion was not statistically significant ($p = .1236$). COVID-19 status was also not associated with DKA severity in those who developed DKA ($p = .8399$).

4 | DISCUSSION

We presented comprehensive nationwide data on T1D incidence and DKA frequency in children new-onset T1D in Poland and assessed their change during COVID-19-affected time.

We showed that the first year of COVID-19 pandemic in Poland was associated with increased T1D incidence in children, more frequent presence of DKA at onset and overall shift toward more serious DKA stages, signifying a switch toward less favorable T1D course. The most notable change occurred in the initial period around February/March 2020 and was upheld during second wave in October. Furthermore, we are among the first to report DKA-related deaths during COVID-19 pandemic that were not observed in Poland for more than a dozen previous years.

The overall shift toward more severe DKA stages that we observed in most age groups (with the exception of 15–18 years old) are in line with the majority of existing reports.[16–18] Fortunately, the overall observed increase (+5.4% for moderate and +3.4% for severe DKA) was not as pronounced as in some countries (e.g., 26.8%–42.3% increase for Romania,[19] 5%–45% in Australia[20]). In our cohort, the highest risk for severe DKA was observed in the youngest children (27.3%–29.9%), while the greatest increase was observed in children aged 7–10 years (17%–24.9%). The lack of statistical significance in most subgroup comparisons can be easily explained by the decrease in statistical power resulting from the smaller group size (from ~1300 to 90–400 patients).

Our study did not show a statistically significant increase in ICU admissions for DKA at T1D onset that was noted in other studies.[21,22] The reason for this might be between-country differences in guidelines and standard operating procedures concerning new-onset T1D. In Poland, most DKA cases (even severe ones) are treated in dedicated pediatric diabetology/endocrinology wards by experienced teams, and ICU care is only requested when assisted ventilation or pressors administration is needed. In some regions, the distance and established cooperation between ICU and diabetologist team also play important role. On the other hand, we detected a significant and over two-fold increase in frequency of the use of assisted ventilation, which is another proxy of DKA severity. Finally, we reported 2 deaths that occurred in March–April 2020, increasing the estimated DKA mortality up to 0.2%. Due to the fortunately low number of such events, statistical comparisons were not performed, and any estimates must be treated with caution. Nevertheless, we did not identify any other reports of DKA-related death in developed countries in this period, and similarly we had no data on such events for a more than a dozen years in Poland. Heavily impaired by the Covid-19 outbreak Polish health care system and faulty social behaviors (e.g., delayed first contact with medical professional, failure to recognize diabetes symptoms) may have played a role in these tragic cases and could be targeted as a subject of a widespread educational campaign.

TABLE 2 Course of reported DKA cases

DKA severity (Data available for $N = 1332$)					
Group		**2019/2020**	**2020/2021**	**Change**	***p* value**
All DKA cases	Mild	288 (55.4%)	392 (47.8%)	↓ **−7.8%**	.0089
	Moderate	125 (24.5%)	246 (29.9%)	↑ **+5.4%**	
	Severe	98 (19.2%)	183 (22.3%)	↑ **+3.4%**	
0–2 years old ($N = 183$)	Mild	29 (43.9%)	39 (33.3%)	↓ **−10.6%**	.3381
	Moderate	19 (28.8%)	43 (36.8%)	↑ **+8%**	
	Severe	18 (27.3%)	35 (29.9%)	↑ **+2.6%**	
3–6 years old ($N = 239$)	Mild	56 (62.9%)	85 (56.7%)	↓ **−6.2%**	.4681
	Moderate	17 (19.1%)	39 (26.0%)	↑ **+6.9%**	
	Severe	16 (18.0%)	26 (17.3%)	↓ *−0.7%*	
7–10 years old ($N = 416$)	Mild	95 (59.7%)	120 (46.7%)	↓ **−13%**	.0297
	Moderate	37 (23.3%)	73 (28.4%)	↑ **+5.1%**	
	Severe	27 (17.0%)	64 (24.9%)	↑ **+7.9%**	
11–14 years old ($N = 403$)	Mild	86 (58.1%)	128 (50.2%)	↓ **−7.9%**	.2946
	Moderate	40 (27.0%)	79 (31.0%)	↑ **+4.0%**	
	Severe	22 (14.9%)	48 (18.8%)	↑ **+3.9%**	
15–18 years old ($N = 91$)	Mild	22 (44.9%)	20 (47.6%)	↑ *+2.7%*	.7558
	Moderate	12 (24.5%)	10 (23.8%)	↓ *−0.7%*	
	Severe	15 (30.6%)	12 (28.6%)	↓ *−2.0%*	

DKA treatment and outcomes (Data available for $N = 1347$)				
Procedure or outcome	**2019/2020**	**2020/2021**	**Change**	***p* value**
ICU admission	71 (13.6%)	144 (17.4%)	↑ **+3.8%**	.0633
Mannitol or 3% NaCl treatment	20 (3.8%)	40 (4.8%)	↑ **+1.0%**	.3844
Required assisted ventilation	7 (1.3%)	28 (3.4%)	↑ **+2.1%**	.0337
Complicated by thrombosis	5 (1%)	6 (0.7%)	↓ *−0.3%*	.6431
Fatal outcome	0 (0%)	2 (0.2%)	↑ **+0.2%**	NA

Note: Bold values denote a clinically unfavorable shift, for example, decrease in proportion of least severe DKA cases (mild) or increase in more severe ones (moderate, severe); Italic values denote neutral or positive changes—decreased frequency of moderate and severe DKAs and corresponding increase in mild ones.

There was no significant shift in population characteristics of children diagnosed with T1D between the 2019/2020 and 2020/2021 periods in terms of age structure, BMI and urban/rural background, however we noted a slight increase in boys' representation in 7–10- and 15–18-year-olds. This was likely related to a secular trend and of little clinical importance.

In terms of T1D incidence, existing reports remain unclear. Among studies summarizing the first 2–3 months of the pandemic, some reported an increase in T1D incidence while others observed no change.[23] One study[24] also observed a decrease, explained by delayed contact with medical professionals for fear of infection and decreased exposure to non-COVID-19 seasonal viral infections due to school closing. Unfortunately, increasing observation time to second wave (7–12 months) did not reduce uncertainty—in Canada[25] there was no increase in T1D incidence among children adolescents while Romania[19] and Finland[22] experienced upsurges similar to Poland. Moreover, it should be considered that T1D incidence is heavily influenced by different time-trends. For example, Poland has experienced a fluctuating increase over the years,[26] which might explain the increase observed between 2019 and 2021 (although the observed T1D incidence [~30/100000] was lower than predicted ~40/100000, probably due to extrapolation error). Therefore, longer observations and metanalyses might be needed to clearly discern COVID-19 effects on T1D incidence.

We also showed that the presence of DKA was significantly associated with younger age and was more frequent in children without T1D among FDRs. These are well-known risk factors of DKA, and they did not change between COVID-19 unaffected and affected period. In addition, children with DKA presented with significantly lower BMI, higher blood glucose level and higher HbA1c than those without DKA, which reflects possible delay in T1D diagnosis. Importantly, HbA1c increased significantly during the 2020/2021 period compared with the previous year (both in DKA-positive and negative children), suggesting an overall deterioration of pediatric health care.

Furthermore, the DKA frequency increase was higher in regions that were more urbanized, experienced greater increase in T1D incidence and more COVID-19-related deaths during the first months of pandemic.

Overall, it is estimated that between 15% and 70% of children present with DKA at T1D diagnosis. In Poland for the last years this rate was between 25% and 36% and did not show a tendency to increase.[6] Therefore, the increase we observed in 2020/2021 could be cautiously attributed to COVID-19 impact while still considering the usual limitations of observational studies. Such hypothesis can be further reinforced by the notable association between DKA frequency increase and the initial death-toll of COVID-19 in each region. However, it is not clear to what extent our results can be generalized to the international pediatric population.

The first reports covering 1st wave of COVID-19 pandemic were highly variable and included no change in DKA frequency (Italy) or increasing tendencies—some of which did (Germany, Israel, Saudi Arabia, United Kingdom[16–18,23,24,27]) or did not reach statistical significance (United States).[28] Moreover, the noted increase was not always upheld—for example, in the United States it encompassed only first 6 weeks of COVID-19 pandemic.[28]

The studies covering longer periods (first and second wave) are largely consistent with our results, demonstrating an increase in DKA frequency in new-onset T1D cases compared with corresponding pre-pandemic period.[19,22,25,29]

On the other hand, it is possible that DKA frequency can also be affected by country-specific time trends. For example, the SEARCH study[30] noted a statistically significant 2% yearly increase in DKA frequency at T1D onset in the United States (from 35.5% in 2010 to 40.6% in 2016). Furthermore, a study based on The German Diabetes Prospective Follow-up Registry[31] compared the monthly frequency of DKA at T1D onset during COVID-19 pandemic to that estimated from 2000 to 2019 years). In this report, they demonstrated a significant increase in two periods: April to September and December. Moreover, the observed overload was positively correlated during the first wave (first half of 2020) with region-specific weekly COVID-19 incidence and mortality. This report is therefore in strong agreement with our observations, where the year-to-year increase in DKA incidence was correlated with SARS-Co-V-2-related deaths in March/April 2020.

Although the amount of evidence linking COVID-19 and DKA rate is increasing, the question whether the association is causal (and how direct) remains unanswered. First, negative impact of COVID-19 pandemic on access to health care and social behaviors may have resulted in delayed contacts with medical professionals and increase the risk of DKA. In our study DKA rate was strongly correlated with the number of COVID-19-related deaths during March and April 2020. Similar observations were made also in a larger scale by Danne et al.,[10] who showed a marked increase in DKA rate in countries suffering from the highest COVID-19-related mortality during first wave of pandemic. Furthermore, in our study, both DKA-positive and negative children presented higher HbA1c than the reference group from previous 12 months. In the multicenter study in the United Kingdom up to 20% of centers reported clear delays of T1D diagnosis within the first 3 months of COVID-19 pandemic. It is also possible that Sars-CoV-2 infection directly or indirectly initiates or aggravates autoimmune beta cell destruction, resulting in more aggressive T1D course and easier DKA development. According to molecular studies, pancreatic beta cells might be targets of SARS-CoV-2[32–34] and SARS-CoV-2 infection in pancreatic islets cultures has been shown to modulate their morphology and response to glucose changes.[35] In addition, infection-related inflammation[36] might lower insulin sensitivity and aggravate insulin deficiency leading to an earlier DKA. Finally, COVID-19-related isolation policy might have resulted in a decrease in physical activity promoting insulin resistance and accelerating the T1D development. However, those hypotheses were definitely out of scope for our study given its design.

In our study we also noted that having a FDRs with T1D was a strong protective factor against developing DKA at T1D onset, which was consistent both pre-COVID-19 and during 2020/2021. This was in line with observation by Ho et al.,[25] who noted a significant increase in DKA rate among those without T1D in FDRs (75.2% in 2020 vs. 46.9% in 2019).

This study contributes important and clinically relevant data to the rapidly growing field of research on COVID-19 interactions with T1D. Thanks to several strengths of the design we hope to provide reliable, reproducible and generalizable results. First, this was a multicenter study including 14 reference pediatric diabetes care centers, which minimizes the risk of center-specific bias. Second, we included centers providing care for almost 90% of Polish children with T1D, which ensures that collected data reliably reflect the underlying population. Moreover, in terms of projecting our results to other groups, Polish people are ethnically homogenous, and all enjoy the same level of access to public health care. Therefore, we expect that our results might be most relatable for other countries with similar population structure and health care policy. Finally, this is one of currently emerging studies with a 12-month observation window covering both first and second COVID-19 wave. This allowed us to account for seasonal variability of T1D and show that in Poland DKA change was abrupt rather than gradual.

On the other hand, this study has some limitations that might limit wider applicability of our results. First, although we the study included almost 90% of Polish pediatric population, three regions were not included in the study. This was due to the fact that these regions lack departments dedicated to pediatric diabetes care. As a result, new T1D cases in these regions are disseminated among local hospitals or are referred to neighboring regions (such cases were not included in this analysis), which could be result in underreporting and be a source of bias. Second, our observation covered only 2 years, which prevented us from gaining insight into possible long-term tendencies and region-specific dynamics. However, such data were not collected due to resource limitation. In addition, our division of time periods for assessment (15 March 2020) was based on the introduction of national lockdown and might not be optimal. Given existing reports, COVID-19 cases are likely to have occurred before that time and public behaviors might have changed as well (e.g., starting to avoid contact with medical facilities). This in fact might be visible in our data, as the initial increase in DKA rate was noted about a month before the official

restrictions. Moreover, not all patients had full data concerning key biochemical features forcing us to rely on documentation reports. We also were not able to collect complete data on SARS-CoV-2 infection status during T1D onset, which limits analyses in this regard and introduces a risk of bias. Some of our analyses were also limited in power. This was the case for region-level analyses, as those were performed on ecological (aggregated) data. Such an approach limits statistical power due to smaller sample size (14 regions) and is susceptible to other sources of bias.[37] Therefore, the results associating DKA with COVID-19 burden should be treated with caution until confirmed by a more in-depth analysis (using, e.g., multi-level modeling). Finally, this was a retrospective study, which prevented us from collecting more detailed data, such as what was the time interval between the patient's first contact with health care (e.g., consultation with GP) and T1D diagnosis and insulin administration. We also acknowledge that unforeseen confounding factors may have affected our results.

In conclusion, the first year of COVID-19 pandemic in Poland in a direct comparison with a preceding year clearly shows an increase in DKA rate among new cases of pediatric T1D cases and points at overall worsening of its course. While the increased incidence of T1D cannot be easily linked with SARS-CoV-2 infection, the increased frequency of DKA at diagnosis and a shift toward its more severe stages seem to be directly or indirectly related to COVID-19 impact. It is therefore important to promote the knowledge about the increased odds of DKA at T1D diagnosis onset during COVID-19 pandemic both among society and first-line clinicians. Finally, even during health care system overload due to COVID-19 (or other events), children presenting signs and symptoms of new-onset T1D and/or DKA should have prompt access to experienced diagnostic and therapeutic teams.

AUTHOR CONTRIBUTIONS

Agnieszka Szypowska and Iwona Pietrzak designed the study; all authors consulted and approved the data collection protocol and contributed relevant data from participating centers; Arkadiusz Michalak performed statistical analysis, Arkadiusz Michalak, Sebastian Seget and Iwona Pietrzak assessed the results and prepared manuscript; all authors reviewed, commented and approved the final paper.

ACKNOWLEDGMENTS

Authors would like to thank all medical staff (physicians, nurses, educators) providing medical care to children with type 1 diabetes in the participating centers, as well as students and other faculty who assisted in reviewing patients' medical charts and data collection. In particular, we would like to acknowledge: Joanna Zarębska, Anna Dolbecka (The Independent Public Clinical Hospital no. 6 of the Medical University of Silesia in Katowice), Aleksandra Wodniak, Sławomir Rak, Aleksandra Wypyszewska, Andrzej Kalus (Department of Pediatrics, University Clinical Hospital in Opole), Bożena Banecka, Robert Piekarski, Anna Bury, Beata Łukasik-Wysocka, Iga Rosołowska (Lublin Clinical Hospital), Beata Mianowska, Anna Baranowska- Jażwiecka (Department of Pediatrics, Diabetology, Endocrinology and Nephrology, Medical University of Lodz), Zofia Klucznik (Central Clinical Hospital of Medical University of Lodz), Katarzyna Celej (Childrens Memorial Health Institute), Agnieszka Polkowska, Maciej Szabłowski, Michał Okruszko (Medical University of Białystok), Irena Jałowiec, Kinga Maciąg-Gralec (Regional Polyclinical Hospital in Kielce).

CONFLICT OF INTEREST

The authors declare no conflict of interest that might have influenced the current work.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pedi.13379.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Iwona Pietrzak https://orcid.org/0000-0001-5582-1787
Arkadiusz Michalak https://orcid.org/0000-0002-6088-9636
Sebastian Seget https://orcid.org/0000-0002-1917-6351
Maria Bednarska https://orcid.org/0000-0002-0240-459X
Iwona Beń-Skowronek https://orcid.org/0000-0002-3003-8507
Artur Bossowski https://orcid.org/0000-0002-6316-5342
Agata Chobot https://orcid.org/0000-0002-9622-4433
Katarzyna Dżygało https://orcid.org/0000-0002-0707-2184
Barbara Głowińska-Olszewska https://orcid.org/0000-0002-6699-2503
Martyna Górnicka https://orcid.org/0000-0003-2162-451X
Anita Horodnicka-Józwa https://orcid.org/0000-0001-8900-614X
Katarzyna Jakubek-Kipa https://orcid.org/0000-0003-2314-6398
Przemysława Jarosz-Chobot https://orcid.org/0000-0002-1120-0994
Katarzyna Marcinkiewicz https://orcid.org/0000-0001-9572-0278
Artur Mazur https://orcid.org/0000-0001-5393-3515
Małgorzata Myśliwiec https://orcid.org/0000-0002-1533-8544
Joanna Nazim https://orcid.org/0000-0002-6885-7305
Elżbieta Niechciał https://orcid.org/0000-0003-3245-8131
Anna Noczyńska https://orcid.org/0000-0002-6712-2673
Ewa Rusak https://orcid.org/0000-0002-4422-7704
Monika Seifert https://orcid.org/0000-0002-8556-0204
Anna Skowronek https://orcid.org/0000-0003-4653-6954
Agnieszka Szypowska https://orcid.org/0000-0002-3407-3174
Paulina Wais https://orcid.org/0000-0002-1580-5894
Mieczysław Walczak https://orcid.org/0000-0003-1664-8525
Anna Wołoszyn-Durkiewicz https://orcid.org/0000-0003-2099-9707
Marta Wysocka-Mincewicz https://orcid.org/0000-0001-8213-9759
Agnieszka Zubkiewicz-Kucharska https://orcid.org/0000-0002-6641-6776
Agnieszka Szadkowska https://orcid.org/0000-0002-8281-4408

REFERENCES

1. Desai D, Mehta D, Mathias P, Menon G, Schubart UK. Health care utilization and burden of diabetic ketoacidosis in the U.S. over the past decade: a nationwide analysis. *Diabetes Care*. 2018;41(8):1631-1638. doi:10.2337/DC17-1379
2. Duca LM, Reboussin BA, Pihoker C, et al. Diabetic ketoacidosis at diagnosis of type 1 diabetes and glycemic control over time: the SEARCH for diabetes in youth study. *Pediatr Diabetes*. 2019;20(2):172-179. doi:10.1111/PEDI.12809
3. Aye T, Mazaika PK, Mauras N, et al. Impact of early diabetic ketoacidosis on the developing brain. *Diabetes Care*. 2019;42(3):443-449. doi:10.2337/DC18-1405
4. Saydah SH, Shrestha SS, Zhang P, Zhou X, Imperatore G. Medical costs among youth younger than 20 years of age with and without diabetic ketoacidosis at the time of diabetes diagnosis. *Diabetes Care*. 2019;42(12):2256-2261. doi:10.2337/DC19-1041
5. Chiavaroli V, Derraik JGB, Jalaludin MY, et al. Partial remission in type 1 diabetes and associated factors: analysis based on the insulin dose-adjusted hemoglobin A1c in children and adolescents from a regional diabetes center, Auckland, New Zealand. *Pediatr Diabetes*. 2019;20(7):892-900. doi:10.1111/PEDI.12881
6. Szypowska A, Ramotowska A, Grzechnik-Gryziak M, Szypowski W, Pasierb A, Piechowiak K. High frequency of diabetic ketoacidosis in children with newly diagnosed type 1 diabetes. *J Diabetes Res*. 2016;2016:1-5. doi:10.1155/2016/9582793
7. Małachowska B, Małachowska K, Pietrzyk J, Fendler W, Rzeznik D, Mlynarski W. Accessibility of the reference center as a protective factor against ketoacidosis at the onset of diabetes in children. *J Pediatr Endocrinol Metab*. 2014;27(11–12):1137-1143. doi:10.1515/JPEM-2014-0067
8. Chumięcki M, Prokopowicz Z, Deja R, Jarosz-Chobot P. Frequency and clinical manifestation of diabetic ketoacidosis in children with newly diagnosed type 1 diabetes. *Pediatr Endocrinol Diabetes Metab*. 2013;19(4):143-147.
9. Bogusława O-B, Grażyna D, Przemysława J-C, Ewa O-B. The occurrence and analysis of chosen risk factors of DKA among children with new onset of DMT1. *Pediatr Endocrinol Diabetes Metab*. 2007;13(2):85-90.
10. Danne T, Lanzinger S, De Bock M, et al. A worldwide perspective on COVID-19 and diabetes management in 22,820 children from the SWEET project: diabetic ketoacidosis rates increase and glycemic control is maintained. *Diabetes Technol Ther*. 2021;23(9):632-641. doi:10.1089/DIA.2021.0110
11. Dżygało K, Nowaczyk J, Szwilling A, Kowalska A. Increased frequency of severe diabetic ketoacidosis at type 1 diabetes onset among children during COVID-19 pandemic lockdown: an observational cohort study. *Pediatr Endocrinol Diabetes Metab*. 2020;26(4):167-175. doi:10.5114/PEDM.2020.101003
12. Araszkiewicz A, Bandurska-Stankiewicz E, Borys S, et al. 2021 guidelines on the management of patients with diabetes. A position of diabetes Poland. *Clin Diabetol*. 2021;10(1):1-113. doi:10.5603/DK.2021.0001
13. 2022 Guidelines on the management of patients with diabetes. A position of diabetes Poland. *Curr Top Diabetes* 2022;2(1):1–134.
14. Wolfsdorf JI, Glaser N, Agus M, et al. ISPAD clinical practice consensus guidelines 2018: diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatr Diabetes*. 2018;19(Suppl 27):155-177. doi:10.1111/PEDI.12701
15. Kułaga Z, Litwin M, Tkaczyk M, et al. Polish 2010 growth references for school-aged children and adolescents. *Eur J Pediatr*. 2011;170(5):599-609. doi:10.1007/s00431-010-1329-x
16. Kamrath C, Mönkemöller K, Biester T, et al. Ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the COVID-19 pandemic in Germany. *JAMA*. 2020;324(8):801-804. doi:10.1001/JAMA.2020.13445
17. McGlacken-Byrne SM, Drew SEV, Turner K, Peters C, Amin R. The SARS-CoV-2 pandemic is associated with increased severity of presentation of childhood onset type 1 diabetes mellitus: a multi-centre study of the first COVID-19 wave. *Diabet Med*. 2021;38(9):e14640. doi:10.1111/DME.14640
18. Jacob R, Weiser G, Krupik D, et al. Diabetic ketoacidosis at emergency department presentation during the first months of the SARS-CoV-2 pandemic in Israel: a multicenter cross-sectional study. *Diabetes Ther*. 2021;12(5):1569-1574. doi:10.1007/S13300-021-01049-3
19. Boboc AA, Novac CN, Ilie MT, et al. The impact of SARS-CoV-2 pandemic on the new cases of T1DM in children. A single-centre cohort study. *J Pers Med*. 2021;11(6):551. doi:10.3390/JPM11060551
20. Lawrence C, Seckold R, Smart C, et al. Increased paediatric presentations of severe diabetic ketoacidosis in an Australian tertiary centre during the COVID-19 pandemic. *Diabet Med*. 2021;38(1):e14417. doi:10.1111/DME.14417
21. Al-Abdulrazzaq D, Alkandari A, Alhusaini F, et al. Higher rates of diabetic ketoacidosis and admission to the paediatric intensive care unit among newly diagnosed children with type 1 diabetes in Kuwait during the COVID-19 pandemic. *Diabetes Metab Res Rev*. 2021;25:e3506. doi:10.1002/DMRR.3506
22. Salmi H, Heinonen S, Hästbacka J, et al. New-onset type 1 diabetes in Finnish children during the COVID-19 pandemic. *Arch Dis Child*. 2021;107:180-185. doi:10.1136/ARCHDISCHILD-2020-321220
23. Alaqeel A, Aljuraibah F, Alsuhaibani M, et al. The impact of COVID-19 pandemic lockdown on the incidence of new-onset type 1 diabetes and ketoacidosis among Saudi children. *Front Endocrinol (Lausanne)*. 2021;12:669302. doi:10.3389/FENDO.2021.669302
24. Rabbone I, Schiaffini R, Cherubini V, Maffeis C, Scaramuzza A. Has COVID-19 delayed the diagnosis and worsened the presentation of type 1 diabetes in children? *Diabetes Care*. 2020;43(11):2870-2872. doi:10.2337/DC20-1321
25. Ho J, Rosolowsky E, Pacaud D, et al. Diabetic ketoacidosis at type 1 diabetes diagnosis in children during the COVID-19 pandemic. *Pediatr Diabetes*. 2021;22(4):552-557. doi:10.1111/PEDI.13205
26. Chobot A, Polanska J, Brandt A, et al. Updated 24-year trend of type 1 diabetes incidence in children in Poland reveals a sinusoidal pattern and sustained increase. *Diabet Med*. 2017;34(9):1252-1258. doi:10.1111/DME.13345
27. Goldman S, Pinhas-Hamiel O, Weinberg A, et al. Alarming increase in ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the first wave of the COVID-19 pandemic in Israel. *Pediatr Diabetes*. 2021;14:10-18. doi:10.1111/PEDI.13296
28. Hawkes CP, Willi SM. A trend towards an early increase in ketoacidosis at presentation of paediatric type 1 diabetes during the coronavirus-2019 pandemic. *Diabet Med*. 2021;38(4):e14461. doi:10.1111/DME.14461
29. Kostopoulou E, Eliopoulou MI, Rojas Gil AP, Chrysis D. Impact of COVID-19 on new-onset type 1 diabetes mellitus—a one-year prospective study. *Eur Rev Med Pharmacol Sci*. 2021;25(19):5928-5935. doi:10.26355/EURREV_202110_26869
30. Jensen ET, Stafford JM, Saydah S, et al. Increase in prevalence of diabetic ketoacidosis at diagnosis among youth with type 1 diabetes: the SEARCH for diabetes in youth study. *Diabetes Care*. 2021;44(7):1573-1578. doi:10.2337/DC20-0389
31. Kamrath C, Rosenbauer J, Eckert AJ, et al. Incidence of COVID-19 and risk of diabetic ketoacidosis in new-onset type 1 diabetes. *Pediatrics*. 2021;148(3):e2021050856. doi:10.1542/PEDS.2021-050856
32. Yang L, Han Y, Nilsson-Payant BE, et al. A human pluripotent stem cell-based platform to study SARS-CoV-2 tropism and model virus infection in human cells and organoids. *Cell Stem Cell*. 2020;27(1):125-136.e7. doi:10.1016/J.STEM.2020.06.015
33. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol*. 2010;47(3):193-199. doi:10.1007/S00592-009-0109-4

34. Cantuti-Castelvetri L, Ojha R, Pedro LD, et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science*. 2020;370(6518):856-860. doi:10.1126/SCIENCE.ABD2985
35. Müller JA, Groß R, Conzelmann C, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nat Metab*. 2021;3(2):149-165. doi:10.1038/S42255-021-00347-1
36. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. *Nat Rev Endocrinol*. 2021;17(1):11-30. doi:10.1038/S41574-020-00435-4
37. Saunders C, Abel G. Ecological studies: use with caution. *Br J Gen Pract*. 2014;64(619):65-66. doi:10.3399/BJGP14X676979

SUPPORTING INFORMATION

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

How to cite this article: Pietrzak I, Michalak A, Seget S, et al. Diabetic ketoacidosis incidence among children with new-onset type 1 diabetes in Poland and its association with COVID-19 outbreak—Two-year cross-sectional national observation by PolPeDiab Study Group. *Pediatr Diabetes*. 2022;1-12. doi:10.1111/pedi.13379