The global impact of COVID-19 pandemic on the incidence of pediatric new-onset type 1 diabetes and ketoacidosis: A systematic review and meta-analysis

Running head: Pediatric new-onset type 1 diabetes and COVID-19.

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DATA AVAILABILITY STATEMENT: All data relevant to the study are included in the article or uploaded as supplementary information. The data are available by accessing the published studies listed in Table1.

Abstract

Objective: Viral infections may increase the risk of developing type 1 diabetes (T1D), and recent reports suggest that Coronavirus Disease 2019 (COVID-19) might have increased incidence of pediatric T1D and/or diabetic ketoacidosis (DKA). Therefore, this meta-analysis aims to estimate the risk of global pediatric new-onset T1D, DKA, and severe DKA before and after the COVID-19 pandemic.

Methods: A systematic search of MEDLINE/PubMed, CINAHL, Scopus, and EMBASE was conducted for articles published up to March 2022. A random-effects meta-analysis was performed to compare the relative risk of T1D and DKA among pediatric patients with T1D between the COVID-19 pre-pandemic and pandemic periods. We also compared glucose and HbA1c values in children who were newly diagnosed with T1D before and after the COVID-19 pandemic.

Results: The global incidence rate of T1D in the 2019 period was 19.73 per 100,000 children and 32.39 per 100,000 in the 2020 period. Compared with pre-COVID-19 pandemic, the number of worldwide pediatric new-onset T1D, DKA, and severe DKA during the first year of the COVID-19 pandemic increased by 9.5%, 25%, and 19.5%, respectively. Compared with pre-COVID-19 pandemic levels, the median glucose, and HbA1c values in newly diagnosed T1D children after the COVID-19 pandemic increased by 6.43% and 6.42%, respectively.

Conclusion: The COVID-19 pandemic has significantly increased the risk of global pediatric newonset T1D, DKA, and severe DKA. Moreover, higher glucose and HbA1c values in newly diagnosed T1D children after the COVID-19 pandemic mandates targeted measures to raise public and physician awareness.

Abbreviations: COVID-19, coronavirus disease 2019; T1D, Type 1 diabetes; DKA, diabetic ketoacidosis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; HbA1c, Glycosylated hemoglobin; ACE2, Angiotensin converting enzyme 2; NOS, Newcastle–Ottawa Scale; ER, event rate; RR, risk ratio; SMD, standard mean difference; CI, confidence interval.

1. Introduction

Type 1 diabetes (T1D) is an autoimmune disorder with a permissive genetic background that various environmental factors such as food chemicals, viral infections, etc. act as autoimmune

stimuli and eventually lead to partial or complete destruction of pancreatic b-cells as a result of insulin deficiency ¹. Numerous studies have reported the involvement of various viruses such as enteroviruses, Coxsackie B, Coxsackie A, Echo, cytomegalovirus, rotaviruses, retroviruses, etc. in the pathogenesis of T1D ²⁻⁴. The causative agent of the current epidemic, COVID-19, is a positive-sense single-stranded RNA virus that acts on various organs in the body after entering human cells by binding to the angiotensin converting enzyme 2 (ACE2). ACE2 binds to the membranes of various cells in the body, such as islets of Langerhans ⁵.

Numerous types of diabetes including new-onset diabetes and metabolic complications such as diabetic ketoacidosis (DKA) and hyperosmolarity have been observed in patients with COVID-19 ⁶. DKA is one of the most common and life-threatening acute complications of T1D. Ketoacidosis is the first manifestation of T1D or occurs when the need for insulin increases during illness or stress as well as when insulin intake decreases ⁷. Psychiatric disorders, stress, lower socioeconomic status, and elevated glycosylated hemoglobin (HbA1C) levels increase the risk of DKA⁸. Infection is one of the most important predisposing factors for DKA in diabetic patients. Insufficiency of insulin injection also leads these patients to ketoacidosis ⁹. Diabetic ketoacidosis and its associated cerebral edema are the leading cause of hospitalization and mortality in diabetic children and adolescents and children under the age of 5 years are at higher risk for developing DKA¹⁰. Despite the association between T1D and DKA with infection during COVID-19 epidemics, different findings have been reported. Gottesman et al. (2021) reported an increase in the incidence of newonset T1D among US children during the COVID-19 pandemic¹¹. In contrast, Ho et al. (2021)¹² reported no change and Rabboneet al. (2020)¹³ reported a decrease in T1D frequency. Despite different outcomes in the development of new-onset T1D, these studies have shown a significant increase in DKA and severe DKA in the diagnosis of diabetes in children and adolescents during

the COVID-19 pandemic ¹¹⁻¹⁴. Alfayez el al. (2022) recently published a systematic review and meta-analysis reported the risk of DKA and severe DKA during the COVID-19 pandemic versus the prior-to-COVID-19 period among pediatric patients with T1D and showed that risk of DKA and severe DKA increased significantly during the pandemic ¹⁵. Although, they did not perform any analysis on the number and rate of newly diagnosed children with T1D and the levels of glucose and HbA1c before and after the COVID-19 pandemic. Additionally, they did not identify all relevant studies in their search strategy and five relevant reports ¹⁶⁻²⁰ were missed in their analyses. Moreover, they included a study by Danne et al. which does not report the risk of DKA and severe DKA among newly diagnosed patients ²¹. To date, several studies have reported childhood T1D as a new beginning in the COVID-19 pandemic. Given the dire consequences of childhood T1D, this study reviews and summarizes studies on the prevalence of childhood T1D during COVID-19.

2. Methods

The present systematic review and meta-analysis was carried out in accordance with methodological guidelines from the Cochrane Handbook for Systematic Reviews ²². The findings of the present study were reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Supplementary Material S1) ²³.

2.1. Search strategy

Relevant studies were systematically searched in electronic databases including MEDLINE/ PubMed, CINAHL, Scopus, and EMBASE by two researchers (MA and MK) up to March 2022. The search strategy was as follows: ("severe acute respiratory syndrome coronavirus 2" or "novel coronavirus" or "COVID-19" or "2019-nCoV" or "SARS-CoV-2") and ("type 1 diabetes mellitus" or "diabetes mellitus" or "juvenile onset diabetes" or "insulin dependent diabetes" or "T1D" or "diabetic ketoacidosis" or "diabetic acidosis" or "acidosis") (Supplementary Material S2). Further, in order to find any other eligible articles, we searched all reference lists of included studies. Additionally, language restriction was not considered.

2.2. Eligibility Criteria

The Eligibility criteria followed the PICOs question in the present systematic review and metaanalysis ²⁴. We included studies that evaluated pediatrics' new-onset T1D during the COVID-19 pandemic in 2020 and during the same periods in 2019 which have reported at least one of the following outcomes: the number of children with new-onset T1D, the number of DKA among newly diagnosed children with T1D, and the number of severe DKA among newly diagnosed children with T1D. We also included studies that evaluated the level of hyperglycemia and HbA1c at T1D diagnosis before and after COVID-19 in newly identified children. Moreover, abstracts with insufficient data, and studies with no reported sample size were excluded from the present meta-analysis.

2.3. Data extraction and quality assessment

First, all retrieved articles were screened by two investigators (M.A., M.K.) in multiple levels of title, abstract, and full-text and final studies that met the inclusion criteria were included. Second, the following data were extracted from eligible studies, where available: study design, country, age and gender, T1D diagnosis criteria, and relative outcomes. The quality of included studies were assessed using the Newcastle–Ottawa Scale (NOS)²⁵. In all stages, discrepancies were solved by consensus with a third investigator (Sh.M.) before conducting meta-analysis.

2.4. Statistical analyses

All meta-analyses were conducted using Comprehensive Meta-Analysis Software, version v. 2.0 (CMA, Biostat, Englewood, NJ, USA) and P value less than 0.05 was considered as significant. Dichotomous outcomes were pooled and expressed as logit event rate (ER), risk ratio (RR), and standard mean difference (SMD) with 95% confidence interval (CI) ²⁶. The pooled analysis results were classified based on study types into two categories, cohorts and cross-sectional and the pooled effect sizes were estimated using the random-effect model ²⁷. Moreover, heterogeneity was calculated using Cochran's Q statistics and I². Funnel plots with Egger weighted regression test were used for assessing the potential for publication bias. Finally, the overall pooled effect size of the respective outcomes was re-estimated by the one study removed methods to perform sensitivity analysis ²⁸.

3. Results3.1. Study identification and characteristics

A total of 4344 potentially relevant articles were identified in our literature search. Five hundred and eighty-nine studies remained after removing duplicates. After screening titles and abstracts, 448 research articles were excluded. Of 41 obtained research articles, another 15 articles were excluded. Finally, twenty-six qualified articles met the eligibility criteria and were included in the meta-analysis (Figure 1). The characteristics of the included studies for meta-analysis are listed in Table 1. Data on newly diagnosed T1D among children during the COVID-19 pandemic period in all included studies were compared with those diagnosed during the same period in the previous year. The COVID-19 year in all included studies was defined as finding the first case of COVID-19 infected patient in the country. Publication ranged from 2020 to 2022 from most European countries, Saudi Arabia, Kuwait, Turkey, US, UK, Australia, Israel, Korea, and Canada. Data regarding the number of children infected by COVID-19 among all new-onset T1D were limited as ten studies did not report any information about the number of diagnosed COVID-19 patients ^{12,14,18,20,29-34}. The number of COVID-19-positive cases in 16 remaining studies was as follows: one case in three studies ³⁵⁻³⁷, two cases in two studies ^{38,39}, four cases in two studies ^{17,40}, eight cases in four studies ^{13,19,41,42}, and no case in five studies ^{16,43-46}. The worldwide incidence rate of diagnosis of T1D in the 2019 period was 19.73 per 100,000 children (18 years and younger) and 32.39 per 100,000 in the 2020 period. Compare with pre COVID-19 pandemic, the number of worldwide pediatric new-onset T1D, DKA, and severe DKA during the first year of COVID-19 pandemic were increased by 9.5%, 25%, and 19.5%, respectively. Compare with pre COVID-19 pandemic, the median glucose (423.5 mg/ dL vs. 397.9 mg/dL) and HbA1c values ($12.26 \pm 1.9\%$ vs. $11.52 \pm 2.3\%$) in newly diagnosed pediatric T1D children after COVID-19 pandemic were increased by 6.43 and 6.42%, respectively. All included studies were of moderate or high quality with NOS scores equal to or greater than 6 (Table 2). The designs of the included studies were

cohort (n = 18) and cross-sectional (n = 8) and we performed a subgroup analysis based on different study types.

3.2. The worldwide impact of COVID-19 pandemic on the incidence of pediatric new-onset type 1 diabetes

Twenty-four studies ^{12-14,16-20,29,31-33,35-46} involving 5671 new T1D patients (2706 new T1D patients in 2019 and 2965 new T1D patients in 2020) reported numbers of pediatric new-onset T1Dbefore and after the COVID-19 pandemic. Overall, the COVID-19 pandemic was significantly associated with an increase in the number of worldwide pediatric newly diagnosed T1D (logit ER= 0.080, 95% CI 0.028 to 0.133, P=0.003; Figure 2A). Significant heterogeneity was observed among the included studies (I²=66%, P=0.0001). According to the study types, the pooled main effect of COVID-19 pandemic in the number of worldwide pediatric newly diagnosed T1D in cohort and cross-sectional studies were logit ER, 0.076 (95% CI: 0.018, 0.135; P=0.010), and logit ER, 0.097 (95% CI: -0.026, 0.221; P=0.123), respectively. Additionally, eight studies ^{12,14,18,29,34,35,42,46} reported incidence rate of T1D before and after the COVID-19 pandemic. Overall pooled analysis showed that COVID-19 pandemic was significantly associated with an increase in incidence rate of diagnosis of T1D in children (overall: logit ER= 0.493, 95% CI 0.289 to 0.697, P=0.001; cohorts: logit ER= 0.494, 95% CI 0.279 to 0.709, P=0.0001; cross-sectionals: logit ER= 0.482, 95% CI -0.166 to 0.129, P=0.145; Figure 2B).

3.3. The worldwide impact of COVID-19 pandemic on the risk incidence of pediatric diabetic ketoacidosis

Twenty-one studies ^{12-14,16,18-20,29-33,35-39,41-44} involving 2648 new T1D patients with DKA and 979 new T1D patients with severe DKA (DKA: 1177 new cases in 2019 and 1471 new cases in 2020; severe DKA: 446 new cases in 2019 and 533 new cases in 2020) were included. The random-effect model showed that COVID-19 pandemic was associated with an elevation in the risk incidence of worldwide pediatric DKA and severe DKA compared with pre-COVID-19 period (RR= 0.064, 95% CI 0.043 to 0.084, P=0.0001, and RR, 0.049 (95% CI: 0.029, 0.066; P=0.0001, respectively; Figure 3). The values of I²=3% (P=0.412) and I²=14% (P=0.26) indicated that no significant heterogeneity exist in the included studies evaluating DKA and severe DKA. The pooled main effects were comparable for the different study designs: RR = 0.068, 95% CI: 0.045, 0.091; P=0.0001 (DKA in cohort studies), RR = 0.049, 95% CI: 0.028, 0.070; P=0.0001 (severe DKA in cohort studies), RR = 0.048, 95% CI: -0.002, 0.093; P=0.059 (DKA in cross-sectional studies), and RR = 0.049, 95% CI: -0.009, 0.106; P=0.096 (severe DKA in cross-sectional studies).

3.4. The worldwide impact of COVID-19 pandemic on the risk of increased hyperglycemia and HbA1c at T1D diagnosis

In total, six studies ^{19,30,33,43-45} included within this meta-analysis, which reported blood glucose and HbA1c levels in children who were newly diagnosed with T1D in 2019 and 2020. There were statistically significant associations between COVID-19 pandemic with elevation in blood glucose and HbA1c levels in pediatric newly diagnosed T1D compared with pre-COVID-19 period (SMD= 0.336, 95% CI 0.074 to 0.598, P=0.012, and SMD= 0.173, 95% CI 0.022 to 0.323, P=0.024, respectively; Figure 4). The SMDs observed for blood glucose in the cohort and cross-sectional studies were 0.169 (95% CI: 0.017, 0.322, P=0.030), and 0.286 (95% CI: -0.595, 1.688, P=0.524), respectively. Additionally, the SMDs observed for HbA1c in the cohort and cross-sectional studies

were 0.378 (95% CI: 0.030, 0.725, P=0.033), and 0.282 (95% CI: -0.117, 0.681, P=0.167), respectively.

3.5. Sensitivity analysis and publication bias

The results of sensitivity analysis showed that the overall pooled estimates of the respective outcomes in all analyses obtained closely resembled preliminary associations. In order to further clarify the publication bias for the included studies, funnel plots suggested no noticeable bias in the studies of the present meta-analysis (Supplementary Material S3). Further, *Begg's* correlation rank and *Egger's* regression did not show significant publication bias (Table 3).

4. Discussion

In the present systematic review and meta-analysis, we performed a pooled analysis to evaluate and compare the effects of the first year of COVID-19 pandemic on the global incidence of T1D, DKA, hyperglycemia, and mean HbA1c levels in children. Based on the results of 26 eligible articles, the present meta-analysis shows that the global new-onset of childhood T1D rate and number have increased in 2020 compared to 2019. In addition, compared to pre-pandemic COVID-19 period, significant increases were observed in global DKA, severe DKA, blood glucose levels, and HbA1c levels in children.

Long-term complications of childhood-onset T1D has been considered as a main cause of death and cardiovascular-associated disease ⁴⁷. More importantly, even before the onset of diabetesrelated complications, young people with T1D are still at a higher risk of mortality ⁴⁸. A systematic review of 13 articles assessing structural changes in the central nervous system in children and adolescents with diabetes concluded that repeated episodes of acute hyperglycemia, e.g., DKA, are associated with detrimental structural changes in the brain ⁴⁹. Additionally, acute diabetic complications including DKA and hyperglycemia were identified as leading causes of death before the age of 30 in a cohort study of 7871 childhood-onset T1D in Norway ⁵⁰. Moreover, the Brecon cohort study of 3642 individuals in Wales showed that a near threefold excess mortality before age 30 which persists in individuals with young onset T1D occurred before age 15 years and ketoacidosis was the most common cause of death in these patients ⁵¹. Further, a nationwide cohort study of 12,652 individuals in the Swedish pediatric diabetes quality registry from 2006 to 2014 showed that higher mean HbA1c during childhood was associated with higher diabetes-related premature mortality in young people (< 30 years of age) ⁵². Overall, these studies indicate that hyperglycemia, higher mean HbA1c, and DKA are associated with increased risk of mortality in individuals with young onset T1D before the age of 30 years.

Given the accepted theory of the pathogenesis of T1D¹ and the global increasing incidence of severe T1D, DKA, and severe DKA in children during the recent pandemic, it can be hypothesized that SARS-CoV-2 is probably a stimulus for the autoimmune system, especially for pancreatic autoimmunity, and the initiation of T1D. Therefore, this hypothesis can be a common cause between these two diseases and raising awareness about this issue is recommended. Although, further research is needed to demonstrate this hypothesis.

T1D is a multifactorial disease and in addition to environmental stimuli (food, stress, etc.), exposure to infectious agents such as viruses in genetically predisposed individuals can trigger the disease 53,54 . It has been shown that the RNA virus carrying COVID-19 may damage pancreatic β -cells 35,55 . Several hypotheses have been proposed for the association between COVID-19 and higher incidence rate of T1D. Diabetes increases the risk of infections, including viral infections,

due to its innate immunodeficiency on neutrophil chemotaxis phagocytosis and cellular immunity 56 . Inflammatory markers of COVID-19 enter the cell through the binding of the COVID-19 spike protein using the enzyme ACE2. The mechanism of this process is a decrease in the expression of ACE2 induced by COVID-19, which eventually leads to cell damage, inflammation and respiratory failure. Pancreatic β -cells are affected by the enzyme ACE2, and this direct link puts diabetics at greater risk for COVID-19 and finally the infection can cause new diabetes 57 .

It is essential that all non-diabetic patients (especially those at high risk for metabolic disease) be evaluated for the possibility of developing new-onset diabetes. Other factors such as unknown biological factors, avoidance, limited access or delay in seeking medical care, fear of seeing a doctor because of the risk of infection, and failure to recognize DKA symptoms, and stress may be involved in combating the COVID-19 pandemic. It is clearly worrying that T1D and DKA remain undiagnosed during the limited interaction of patients referred to health care centers. Another interesting finding in the data collected in this study was the higher HbA1c during the pandemic among the new T1D, which could be due to delays and limitations in medical care etc. Owing to rising T1D and DKA rates, public awareness of the symptoms of the disease in the public, improvement of telemedicine technology due to concerns about COVID-19 in hospitals and quarantine, warning to take the milder symptoms of the onset of new diabetes seriously is warranted.

Results of the present meta-analysis must be interpreted in light of its limitations. First, the present systematic review and meta-analysis only covered the first wave of the COVID-19 pandemic and future studies should evaluate the number of childhood new-onset T1D in 2021 and 2022. Second, data regarding the number of children infected by COVID-19 among all new-onset T1D are limited and this make it difficult to attribute such an increase in T1D, DKA, and severe DKA to COVID-

19 infection. Third, our findings should be interpreted with caution since our meta-analysis did not capture the unexpected confounders, time-varying exposure such as multifactorial environmental stimuli (i.e., food, stress, and outdoor environmental factor), and different ethnic effect. Finally, the criteria used for the T1D diagnosis varied between studies and should be consistent in future studies.

5. Conclusion

The results of the present meta-analysis demonstrate a global significant increase in the incidence of childhood new-onset T1D, DKA, and severe DKA with elevated hyperglycemia and mean HbA1c levels at T1D diagnosis in the first year of the COVID-19 pandemic compared to pre-COVID-19 period. Due to this fact, physicians should consider this issue in all non-diabetic children and monitor their blood sugar and HbA1C when accepting them for proper and early management. Based on these findings, continuous and repeated educational diabetes awareness should be delivered to physicians, caregivers and the public to improve health outcomes in the world and change trends in childhood T1D and DKA.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Masoud Rahmati and Jae II Shin developed the idea and designed the study and had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Masoud Rahmati and Maryam Keshvari ran the search strategy; Masoud Rahmati and Maryam Keshvari selected articles and extracted data; Masoud Rahmati evaluated the quality of the literature. Masoud Rahmati, Maryam Keshvari, Shahrzad Mirnasuri, Dong K Yon, Seung Won Lee, Jae II Shin and Lee Smith wrote the manuscript. All listed authors reviewed and approved the final manuscript.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information. The data are available by accessing the published studies listed in Table1.

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Figure Legends

Figure 1. PRISMA flow diagram of study selection.

Figure 2. Forest plot of the logit event rates of numbers (A) and incidence (B) of pediatric newonset T1D before and after the COVID-19 pandemic.

Figure 3. Forest plot of the risk of global pediatric DKA (A) and severe DKA (B) before and after the COVID-19 pandemic.

Figure 4. Forest plot of risk of pediatric hyperglycemia (A) and elevated HbA1c (B) before and after the COVID-19 pandemic

<u> </u>	ъ.	a ,	Age	Gender.	Analyzed	T1D		Severe DKA	C	Outcome		
Study	Design	Country	(year)	n (F)	periods during the pandemic*	diagnosis criteria	DKA diagnosis	diagnosis	Group	2019, n	2020, n	
Alaqeel et al.	Cohort	Saudi	9.8 ± 0.2	154 (85)	March to June	ADA	pH level < 7.3	pH level < 7.1	New-onset T1D	57	41	
2021 ³⁸		Arabia			in 2020		Bicarbonate level	Bicarbonate level	DKA	15	23	
							<15 mmol/L	<5 mmol/L	Severe DKA	4	7	
Al-Abdulrazzaq	Cohort	Kuwait	8 ± 2.3	303 (153)	February to	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	303	324	
et al. 2021^{29}					February of		Bicarbonate level	Bicarbonate level	DKA	113	166	
A.1 . 1	G 1		ND	50 (26)	2020 and 2021		<15 mmol/L	<5 mmol/L	Severe DKA	33	60	
Atlas et al.	Cohort	Australia	NR	58 (26)	February and	NR	pH level < 7.3	pH level < 7.1	New-onset TID	89	58	
202110					May in 2020		Bicarbonate level	Bicarbonate level		41	30 12	
Dohoo ot ol	Cabort	Domonio	72+02	147 (72)	Marah ta	ICDAD	<15 mmol/L	<5 mmol/L	Severe DKA	15	13	
2021^{41}	Conort	Komama	7.2 ± 0.2	147 (72)	Fobruary of	ISPAD	pn level < 7.5 Bicarbonata laval	Pricerbonate level	DKA	115	147	
2021					2020 and 2021		<15 mmol/I	<5 mmol/I	DKA Savara DKA	33	125	
Rogale et al	Cohort	US	92 + 45	42 (19)	Ianuary to	NR	~ 15 mmol/L nH level < 7.3	\sim nH level < 7.1	New-onset T1D	NR	41	
2021^{30}	Conort	05).2 ± 4.5	42 (17)	September in	MIX	Bicarbonate level	Bicarbonate level	DKA	172	20	
2021					2020		<15 mmol/L	<5 mmol/L	Severe DKA	123	13	
Dilek et al.	Cross-	Turkey	10 ± 7.4	74 (39)	March to March	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	46	74	
2021 ³⁵	sectional			(27)	of 2020 and		Bicarbonate level	Bicarbonate level	DKA	27	68	
					2021		<15 mmol/L	<5 mmol/L	Severe DKA	4	15	
Dżygało et al.	Cohort	Poland	9.9 ± 4.9	34 (12)	March to May	WHO	pH level < 7.3	pH level < 7.1	New-onset T1D	52	34	
202043					in 2020		Bicarbonate level	Bicarbonate level	DKA	29	18	
							<15 mmol/L	<5 mmol/L	Severe DKA	6	11	
Goldman et al.	Cohort	Israel	9.9 ± 2.8	146 (59)	March to June	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	113	146	
2022^{36}					in 2020		Bicarbonate level	Bicarbonate level	DKA	44	85	
							<15 mmol/L	<5 mmol/L	Severe DKA	6	11	
Gottesman et al.	Cross-	US	9.8 ± 0.2	187 (NR)	March to March	NR	NR	NR	New-onset T1D	119	187	
2022 17	sectional				of 2020 and				DKA	47	93	
	C 1 /	LIC.	.10	72 (11)	2021	104	111 1.72	XX 1 1 . 7 1	Severe DKA	NR	NR	
Hawkes et al. 2021^{39}	Cohort	US	<18	73 (NR)	March to July in	ADA	pH level < 7.3	pH level < 7.1	New-onset TID	92	73	
202155					2020		Bicarbonate level	Bicarbonate level		33 11	35 11	
Harrara at al	Cohort	Spain	08 1 1 4	27(17)	Ionuomi to	ICDAD	<13 IIIII01/L	< 3 IIIII0I/L	New onset T1D	22	27	
2022^{18}	Conort	Span	9.0 ± 1.4	57 (17)	January of 2020	ISFAD	$\frac{1}{1000} = \frac{1}{1000} = 1$	$\frac{\text{pirevel} < 7.1}{\text{Bicarbonate level}}$	DKA	13	12	
2022					and 2021		<15 mmol/I	<5 mmol/I	Severe DKA	5	2	
Ho et al. 2021 ¹²	Cohort	Canada	6-18	107 (61)	March to	DCCP	rH level < 7.3	rH level < 7.1	New-onset T1D	114	107	
110 Ct ull 2021	Conort	Cuntudu	0 10	107 (01)	August in 2020	Deel	Bicarbonate level	Bicarbonate level	DKA	52	73	
					1108000 11 2020		<15 mmol/L	<5 mmol/L	Severe DKA	3	8	
Jacob et al.	Cross-	Israel	12 ± 2.7	86 (NR)	March to May	ADA	pH level < 7.3	pH level < 7.1	New-onset T1D	80	86	
202131	sectional			~ /	in 2020		Bicarbonate level	Bicarbonate level	DKA	31	46	
							<15 mmol/L	<5 mmol/L	Severe DKA	14	16	
Kamrath et al.	Cohort	Germany	6-18	532 (205)	March to May	NR	NR	NR	New-onset T1D	503	532	
2020^{14}		-			in 2020				DKA	123	238	
									Severe DKA	70	103	

 Table 1. General characteristics of included studies.

(Continues)

Table 1. Continued.

Ct. 1	D '	G (Age	Gender.	Analyzed	T1D		Severe DKA	Outcome			
Study	Design	Country	(year)	n (F)	periods during the pandemic*	diagnosis criteria	DKA diagnosis	diagnosis	Group	2019, n	2020, n	
Kostopoulou et	Cohort	Greece	8.3 ± 0.9	21 (12)	March to	NR	pH level < 7.3	pH level < 7.1	New-onset T1D	17	21	
al. 2021 ³²					February of		Bicarbonate level	Bicarbonate level	DKA	6	14	
					2020 and 2021		<15 mmol/L	<5 mmol/L	Severe DKA	1	9	
Lawrence et al.	Cohort	Australia	8 ± 4.3	11 (8)	March to May	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	9	11	
2021^{44}					in 2020		Bicarbonate level	Bicarbonate level	DKA	2	8	
							<15 mmol/L	<5 mmol/L	Severe DKA	1	5	
Lee et al. 2021^{33}	Cross-	Korea	12 ± 6.5	10 (9)	February to	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	10	10	
	sectional				February of		Bicarbonate level	Bicarbonate level	DKA	4	6	
					2020 and 2021		<15 mmol/L	<5 mmol/L	Severe DKA	0	1	
Mameli et al.	Cohort	Italy	8.5 ± 4.2	256 (110)	March to	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	231	256	
2021^{42}					December in		Bicarbonate level	Bicarbonate level	DKA	65	91	
					2020		<15 mmol/L	<5 mmol/L	Severe DKA	24	39	
Marks et al.	Cohort	US	10 ± 4.3	182 (81)	March to	ADA	pH level < 7.3	pH level < 7.1	New-onset T1D	158	182	
202119					March of 2020		Bicarbonate level	Bicarbonate level	DKA	82	105	
					and 2021		<15 mmol/L	<5 mmol/L	Severe DKA	27	51	
McGlacken-	Cross-	UK	$10.3 \pm$	17 (8)	March to June	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	30	17	
Byrne et al.	sectional		6.5		in 2020		Bicarbonate level	Bicarbonate level	DKA	9	13	
202137							<15 mmol/L	<5 mmol/L	Severe DKA	3	8	
Modarelli et al.	Cohort	US	9.8 ± 0.2	46 (16)	April to March	ADA	pH level < 7.3	pH level < 7.1	New-onset T1D	31	46	
2022^{45}					of 2020 and		Bicarbonate level	Bicarbonate level	DKA	NR	NR	
					2021		<15 mmol/L	<5 mmol/L	Severe DKA	NR	NR	
Rabbone et al.	Cross-	Italy	0-14	160 (NR)	February to	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	208	160	
2020^{13}	sectional				April in 2020		Bicarbonate level	Bicarbonate level	DKA	86	61	
							<15 mmol/L	<5 mmol/L	Severe DKA	31	27	
Salmi et al.	Cross-	Finland	10 ± 2.3	20 (9)	April to	NR	NR	NR	New-onset T1D	57	84	
202246	sectional				October in				DKA	NR	NR	
		-			2020				Severe DKA	5	13	
Sellers et al.	Cohort	Canada	9.8 ± 0.2	260 (NR)	March to July	NR	pH level < 7.3	pH level < 7.1	New-onset T1D	236	260	
2021^{20}					in 2020		Bicarbonate level	Bicarbonate level	DKA	86	143	
							<15 mmol/L	<5 mmol/L	Severe DKA	29	69	
Unsworth et al.	Cohort	UK	12 ± 6	30 (8)	March to June	ISPAD	pH level < 7.3	pH level < 7.1	New-onset T1D	15	30	
202040					in 2020		Bicarbonate level	Bicarbonate level	DKA	NR	NR	
× 71 1	2	. .	0.14		• •		<15 mmol/L	<5 mmol/L	Severe DKA	NR	NR	
Vlad et al.	Cross-	Romania	0-14	NR	January to June	NR	NR	NR	New-onset T1D	11.4**	13.3**	
202154	sectional				ın 2020				DKA	NR	NR	
									Severe DKA	NR	NR	

ISPAD, International Society of Paediatric and Adolescent diabetes; WHO, World Health Organization; ADA, American Diabetes Association; DCCP, Diabetes Canada Clinical Practice; NR, Not reported. * The COVID-19 pandemic period in all included studies were compared with those diagnosed during the same period in the previous year. ** This study only reported the rate of incidence.

Cohort study	Selection (4)				Compara	ability (2)	Outcome (3)			Total
Author	Representativeness of exposed cohort	Selection based on national registry data	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of study	Study control for diabetic risk factors	Adjustment of incidence rate for age	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Alageel et al. 2021 ³⁸	1	1	1	1	1	0	1	1	1	8
Al-Abdulrazzaq et al. 2021 ²⁹	1	1	1	1	1	1	1	1	1	9
Atlas et al. 2021 ¹⁶	1	0	0	1	0	0	1	1	1	5
Boboc et al. 2021 ⁴¹	1	0	1	1	1	0	1	1	1	7
Bogale et al. 2021^{30}	1	1	0	1	1	0	1	1	1	7
Dżygało et al. 2020^{43}	1	0	1	1	1	0	1	1	1	7
Goldman et al 2022^{36}	1	Ĩ	1	1	Ō	Õ	1	1	1	7
Hawkes et al. 2021^{39}	1	0	1	1	ŏ	Ő	1	1	1	6
Herrero et al 2022^{18}	1	Õ	1	1	ŏ	1	1	1	1	7
Ho at al. 2021^{12}	1	1	1	1	0	1	1	1	1	8
Kompath at al. 2020^{14}	1	1	1	1	0	1	1	1	1	7
Kallfatti et al. 2020	1	1	0	1	0	1	1	1	1	6
2021^{32}	1	0	0	1	1	0	1	1	1	0
Lawrence et al. 2021^{44}	1	0	1	1	1	0	1	1	1	1
Mameli et al. 2021 ⁴²	1	1	1	1	0	1	1	1	1	8
Marks et al. 2021 ¹⁹	1	1	1	1	1	0	1	1	1	8
$\begin{array}{llllllllllllllllllllllllllllllllllll$	1	1	1	1	1	0	1	1	1	8
Sellers et al. 2021 ²⁰	1	1	0	1	0	0	1	1	1	6
Unsworth et al. 2020^{40}	1	1	1	1	0	0	1	1	1	7
Cross-sectional study	Selection (5)				Compara	ability (2)	Outcome (3)			Total
Author	Representativeness of the sample	Sample size	Selection based on national registry data	Ascertainment of exposure	The subj outcome compara the study analysis. factors a	ects in different groups are ble, based on design or Confounding re controlled.	Assessment of t	he outcome	Statistical test	
Dilek et al. 2021 ³⁵	1	1	0	2	2		1		1	8
Gottesman et al. 2022 ¹⁷	1	1	1	1	1		1		1	7
Jacob et al. 2021^{31}	1	1	1	2	0		1		1	7
Lee et al. 2021^{33}	1	1	Ō	2	1		1		1	7
McGlacken-Byrne et	1	1	ĩ	$\overline{2}$	1		ī		1	8
al. 2021^{37}	1	1	1	2	1		1		1	ō
Raddone et al. 2020^{15}	1	1	1	<u>∠</u>	1		1		1	ð
Saimi et al. 2022^{40}	1	1	1	1	2		1		1	8
viad et al. 2021^{54}	1	1	1	1	1		1		1	/

 Table 2. Summary of the Newcastle-Ottawa scale for bias assessment of included studies.

Risk factors	Effect measures	Number of study	Z-Value	p-Value	Effect size (95% CI)	Heterogeneity		<i>Begg's</i> test P- value	<i>Egger's</i> test P- value
						I^2	P-value		
New-onset T1D						_			
Cohorts	Event rate	18	2.582	0.010	0.076 (0.018-0.135)	56%	0.002	0.235	0.414
Cross-sectionals	Event rate	6	1.541	0.123	0.097 (-0.026-0.221)	83%	0.0001	0.425	0.468
Overall	Event rate	24	2.992	0.003	0.080 (0.028-0.133)	66%	0.0001	0.327	0.443
T1D incidence rate									
Cohorts	Event rate	6	4.510	0.0001	0.494 (0.279-0.709)	71%	0.004	0.286	0.198
Cross-sectionals	Event rate	2	1.459	0.145	0.482 (-0.166-0.129)	0%	0.444	NA	NA
Overall	Event rate	8	4.740	0.0001	0.493 (0.289-0.697)	61%	0.012	0.211	0.108
Risk of DKA									
Cohorts	Risk ratio	15	6.223	0.0001	1.108 (1.073-1.145)	0%	0.456	0.480	0.915
Cross-sectionals	Risk ratio	6	1.677	0.093	1.067 (0.989-1.150)	9%	0.356	0.132	0.112
Overall	Risk ratio	21	6.380	0.0001	1.102 (1.069-1.135)	3%	0.414	0.216	0.437
Risk of Severe DKA									
Cohorts	Risk ratio	16	4.567	0.0001	1.056 (1.032-1.081)	14%	0.289	0.471	0.449
Cross-sectionals	Risk ratio	5	1.568	0.117	1.050 (0.988-1.117)	11%	0.342	0.052	0.117
Overall	Risk ratio	21	4.825	0.0001	1.055 (0.033-1.079)	9%	0.334	0.183	0.209
Risk of higher glucose									
Cohorts	SMD	5	2.176	0.030	0.169 (0.017-0.322)	42%	0.136	1	0.970
Cross-sectionals	SMD	1	0.637	0.524	0.282 (-0.595-1.188)	0%	1	NA	NA
Overall	SMD	6	2.253	0.024	0.173 (0.022-0.323)	29%	0.216	0.573	0.945
Risk of higher HbA1c									
Cohorts	SMD	10	2.131	0.033	0.378 (0.030-0.725)	89%	0.0001	0.531	0.350
Cross-sectionals	SMD	4	1.383	0.167	0.282 (-0.117-0.681)	67%	0.025	0.174	0.172
Overall	SMD	14	2.515	0.012	0.336 (0.074-0.598)	86%	0.0001	0.139	0.182

Table 3. Results of the subgroup analysis based on study design.



Figure 1. PRISMA flow diagram of study selection.

A: The numbers of pediatric new-onset T1D before and after the COVID-19 pandemic.



B: Incidence rate of T1D before and after the COVID-19 pandemic.

Study name	Subgroup within study			Statistics fo	or each s	tudy			Logit event rate and 95% CI				
		Logit event rate	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value					
Al-Abdulrazzaq, 202	1 Cohort	0.067	0.227	0.051	-0.378	0.512	0.295	0.768					
Herrero, 2020	Cohort	0.956	0.163	0.027	0.637	1.275	5.871	0.000					
Ho, 2021	Cohort	-0.071	0.442	0.195	-0.937	0.794	-0.162	0.872					_
Kamrath et al. 2020	Cohort	0.053	0.296	0.088	-0.528	0.633	0.178	0.859					
Mameli et al. 2021	Cohort	0.134	0.366	0.134	-0.584	0.851	0.365	0.715		-			
Salmi, 2022	Cohort	1.174	0.673	0.453	-0.145	2.493	1.745	0.081			_		
		0.494	0.110	0.012	0.279	0.709	4.510	0.000					
Dilek, 2021	Cross-sectional	0.806	0.538	0.289	-0.248	1.861	1.499	0.134		1			-8
/lad, 2021	Cross-sectional	0.285	0.419	0.175	-0.535	1.106	0.681	0.496					
		0.482	0.330	0.109	-0.166	1.129	1.459	0.145					
		0.493	0.104	0.011	0.289	0.697	4.740	0.000					
									-1.00	-0.50	0.00	0.50	

Favours 2019 Favours 2020

Figure 2.



A: Risk of global pediatric DKA before and after the COVID-19 pandemic.

B: Risk of global pediatric Severe DKA before and after the COVID-19 pandemic.

Study name	Subgroup within s	tudy	Statist	ics for e	each stud	ly		Risk	ratio and 95% Cl
		Risk ratio	Lower limit	Upper limit	Z-Value	p-Value			
Al-Abdulrazzaq, 2021	Cohort	1.069	1.011	1.130	2.343	0.019	1		l-a-
Alaqeel, 2021	Cohort	1.030	0.759	1.397	0.189	0.850			
Atlas, 2020	Cohort	1.068	0.935	1.220	0.973	0.331			
Boboc, 2021	Cohort	0.990	0.882	1.111	-0.173	0.863		h a start a st	
Dzygalo, 2020	Cohort	1.187	0.983	1.432	1.786	0.074			
Goldman, 2022	Cohort	1.021	0.962	1.084	0.687	0.492			- b
Hawkes, 2021	Cohort	1.028	0.924	1.143	0.504	0.614			
Herrero, 2020	Cohort	0.866	0.718	1.044	-1.506	0.132			
Ho, 2021	Cohort	1.047	0.988	1.110	1.559	0.119			+
Kamrath, 2020	Cohort	1.048	1.001	1.097	1.995	0.046			
Kostopoulou, 2021	Cohort	1.349	1.041	1.749	2.261	0.024			
Lawrence, 2021	Cohort	1.309	0.887	1.933	1.355	0.175			
Mameli, 2021	Cohort	1.044	0.984	1.108	1.413	0.158			+
Marks, 2021	Cohort	1.093	0.999	1.197	1.936	0.053			
Salmi, 2022	Cohort	1.062	0.953	1.182	1.090	0.276			
Sellers, 2021	Cohort	1.127	1.051	1.208	3.352	0.001			
		1.056	1.032	1.081	4.567	0.000			•
Dilek, 2021	Cross-sectional	1.106	0.977	1.253	1.597	0.110			
Jacob, 2021	Cross-sectional	1.009	0.896	1.137	0.154	0.878			
Lee, 2022	Cross-sectional	1.091	0.850	1.400	0.683	0.495			
McGlacken-Byrne, 202	2Cross-sectional	1.337	1.001	1.786	1.964	0.050			
Rabbone, 2020	Cross-sectional	1.017	0.942	1.098	0.435	0.663			
		1.050	0.988	1.117	1.568	0.117			
		1.055	1.033	1.079	4.825	0.000			٠
							0.5		1
								Favours 201	9 Favours 2

2

A: Risk of pediatric hyperglycemia before and after the COVID-19 pandemic.



B: Risk of pediatric elevated HbA1c before and after the COVID-19 pandemic.

Study name	Subgroup within study			Statistics f	or each s	study			Std diff in means and 95% Cl
		Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
Al-Abdulrazzaq, 2021	Cohort	0.227	0.080	0.006	0.069	0.384	2.825	0.005	
Alaqeel el al. 2021	Cohort	0.250	0.206	0.042	-0.153	0.653	1.217	0.224	
Boboc, 2021	Cohort	0.769	0.130	0.017	0.515	1.023	5.932	0.000	
Bogale, 2021	Cohort	0.084	0.162	0.026	-0.234	0.401	0.517	0.605	
Dzygalo, 2020	Cohort	0.219	0.221	0.049	-0.214	0.653	0.991	0.322	
Kostopoulou, 2021	Cohort	4.118	0.574	0.330	2.993	5.244	7.173	0.000	
Lawrence, 2021	Cohort	0.068	0.450	0.202	-0.813	0.949	0.152	0.879	
Marks, 2021	Cohort	-0.250	0.109	0.012	-0.464	-0.036	-2.290	0.022	
Modarelli, 2022	Cohort	-0.250	0.233	0.054	-0.707	0.207	-1.072	0.284	
Salmi, 2022	Cohort	0.335	0.468	0.219	-0.582	1.252	0.716	0.474	
		0.378	0.177	0.031	0.030	0.725	2.131	0.033	
Dilek, 2021	Cross-sectional	0.183	0.188	0.035	-0.186	0.552	0.972	0.331	
Gottesman et al. 2022	Cross-sectional	-0.054	0.117	0.014	-0.284	0.176	-0.464	0.643	
Lee, 2022	Cross-sectional	0.398	0.452	0.204	-0.487	1.284	0.882	0.378	
McGlacken-Byrne, 202	21Cross-sectional	0.941	0.319	0.102	0.317	1.566	2.954	0.003	
8		0.282	0.204	0.041	-0.117	0.681	1.383	0.167	
		0.336	0.134	0.018	0.074	0.598	2.515	0.012	
									-1.00 -0.50 0.00 0.50 1.0
									Favours 2019 Favours 2020

Figure 4.