Review Paper

Variation of Newly Diagnosed Type 1 Diabetes Mellitus Cases During Covid-19 Pandemic: A Review Paper

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ABSTRACT

Background Type 1 diabetes mellitus (T1DM) is one of the chronic diseases that timely and correct management affects the outcome of these patients. COVID-19 is an acute respiratory infection that has created a disproportionate situation for individuals and healthcare systems. The resulting pandemic is associated with delayed presentation of patients as well as increased frequency and severity of acute complications.

Objectives This review study aims to investigate the incidence, initial presentation, frequency, and severity of diabetic ketoacidosis (DKA) as well as changes in demographic findings, such as age and sex in newly diagnosed T1DM children and adolescents during the COVID-19 pandemic.

Methods The search was conducted in different databases, using the keywords: T1DM, COVID-19, pediatrics, and incidence to find the related articles published in English from December 31, 2019, to March 3, 2022.

Results There is no clear evidence for increase in the incidence of T1DM and the frequency and severity of DKA in female and younger people during the pandemic compared to the pre-pandemic period. Further studies with larger sample sizes are needed to better understand the role of pandemic on disease incidence and acute complications.

Conclusion: To reduce the incidence of DKA and speed up the diagnosis of T1DM during the pandemic, people should be informed about their symptoms.

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Introduction

Type 1 diabetes mellitus (T1DM) is one of the most common metabolic diseases of childhood, which occurs during an autoimmune process against beta cells and has observed an increasing trend of new cases in recent years [1]. The findings they presented most often included polyuria, weight loss, and polydipsia. However, diabetic ketoacidosis (DKA), an acute, life-threatening complication, deserves special attention and has a variable prevalence among patients [2].

The role of viruses in the progression to type 1 diabetes has been identified by affecting beta cell and immune system function [3, 4]. COVID-19 is an acute infectious disease with rapid respiratory infections and is often asymptomatic in children [5]. Several studies have reported increased frequency and intensity of diabetic ketoacidosis (DKA) during the pandemic, which may be justified by delayed symptom onset due to the absence of the healthcare system [6, 7].

Due to the restrictions placed on people during the pandemic and delays in referral to the health system, newly diagnosed T1DM cases should be properly screened to determine the impact of Covid-19 [8]. This review examined the characteristics of newly diagnosed children and adolescents with T1DM, including demographics (age and sex), clinical manifestations, and the incidence, severity, and frequency of DKA caused by the Covid-19 pandemic.

Methods

This is a review study. A search was conducted in databases, such as PubMed, Scopus, Web of Science, and Science Direct using the Keywords T1DM, COVID-19, pediatrics, and incidence to find the related articles published in English from December 31, 2019, to March 3, 2022.

Inclusion criteria

Children and adolescents (<18 years of age) newly diagnosed with type 1 diabetes during the pandemic. Studies were with designs, including cohorts, case-control, observational cohorts, mini-reviews, meta-analyses, and systematic reviews.

Exclusion criteria

Articles did not meet our study design criteria (e.g. observational non-cohort studies, narrative reviews, case studies [case reports and case series], books, cross-sectional studies, randomized controlled trials [RCTs], editorials, news, posters), and animal study. Patients whose age range did not match the age limits of our study, studies in which patients were not segregated by date, and type of diabetes during the pandemic were also excluded.

The initial screening of selected articles based on title/abstract is consistent with our inclusion criteria. Based on the searched database, 322 articles were extracted, of which 273 articles remained after removing duplication (49 articles). Thirty-nine articles were selected for full-text review by assessing the findings of the included articles, including incidence, initial presentation, frequency and severity of DKA, and demographic findings of newly diagnosed T1DM cases younger than 18 years of age, three of these articles were not available in full text. From the remaining articles, five original articles, including two observational cohort studies, two single-center cohort studies, and one multicenter cohort study, were selected according to the inclusion criteria.

The full-text analysis of the articles was performed on the variables mentioned during the pandemic compared to newly diagnosed cases before the pandemic. In addition, studies reviewed that did not meet inclusion criteria related to study design were excluded. Article scanning was performed to identify included articles by two independent researchers to avoid missing articles. Figure 1 shows the selection of items included.

Variables extracted from articles include the author's name, study year, study type, study population, sample size, potential factors, main outcomes, and pre- and post-pandemic data values. Table 1 presents the results of the search process.

Results

A total of five articles were selected according to the inclusion criteria, and Table 2 presents the results. All studies focused on patients younger than 18 years diagnosed with T1DM during the COVID-19 period. In the study, outcomes were assessed in terms of patient symptoms, differences in disease incidence compared to pre-pandemic, frequency and severity of DKA, and demographic findings.

Table 1. Eligibility criteria

Criteria	Inclusion	Exclusion
Population	Children and adolescents (age <18 years old) with definite T1DM diagnosis during the pandemic lockdown	Adult (age ≥18 years old) population Studies in which age groups are not segregated between children and adults Studies that do not specify the type of diabetes Studies combining T1DM with other types of diabetes Studies differentiated between types of diabetes but did not differentiate outcomes.
Intervention and comparators	Incidence DKA Initial presentation Demographic findings	If causes other than the pandemic and COVID-19 influence the interventions listed in the inclusion criteria.
Outcomes	Alteration of incidence rate Frequency and severity of DKA Alteration of presentation Demographic variation (age onset, sex predominant)	None
Study type	Cohort Case-control Observational-cohort Mini review Meta-analyses Systematic review	Observational- non-cohort Narrative review Case studies (case series and case report) Book Cross-sectional Randomized controlled trial (RCT) Editorial, news, poster Animal studies

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Abbreviations: T1DM: Type 1 diabetes mellitus; RCT: Randomized controlled trial; DKA: Diabetic ketoacidosis.

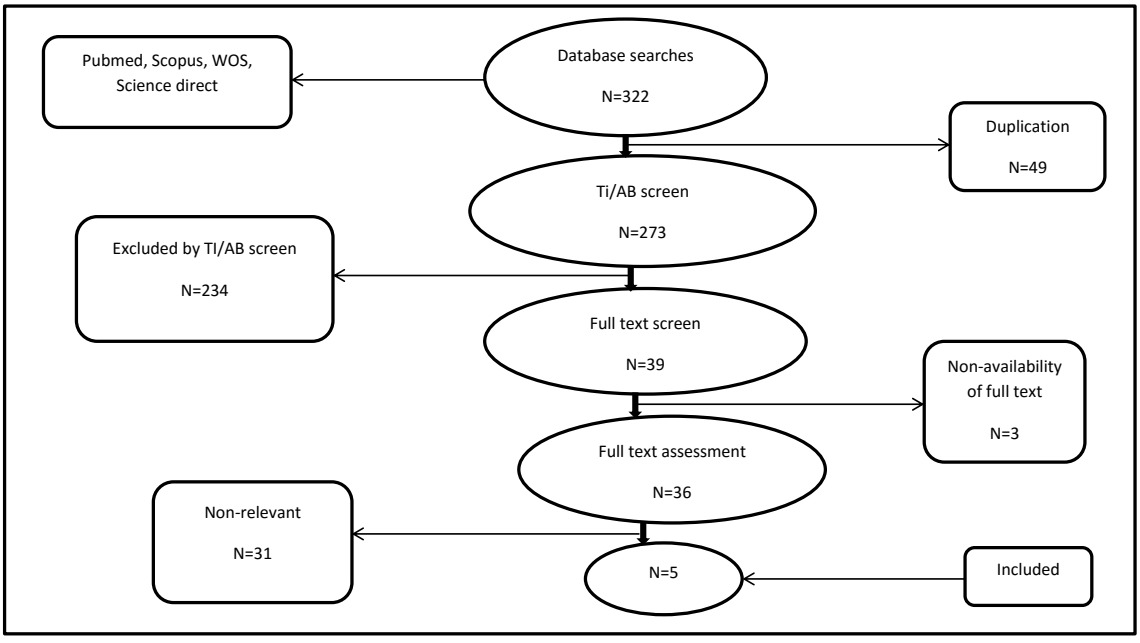

Figure 1. Flowchart of included articles

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Table 2. Summary of selected articles findings

Author	Type of Study	Population	Sample Size	Potential Variables	Main Result	Pre-pandemic Value	Pandemic Value	Sig.
C. Lawrence [6]	An observational cohort study	Pediatric (24 males, 29 females)	53	DKA, initial presentation, demographic findings, the incidence	Significant increased number of severe DKA during lockdown than pre-lockdown.	5%	45%	<0.003
					No significant difference between new cases of T1DM during lockdown and pre-lockdown (from 2015 to 2019).	11	6-10 (median 9)	NS
					Significantly increased number of DKA during the pandemic.	26%	73%	<0.007
					Decreased frequency of presentations during the pandemic than pre-lockdown	6550	4799	<0.01
					No significant difference in age onset between pandemic and pre-pandemic periods	-	-	NS
					No significant difference between the male sex during the pandemic and pre-pandemic	-		NS
Kaleb T. Bogale [8]	A single-center cohort study	Pediatric (F/M: 171/241)	412	DKA, demographic findings	No significant difference in DKA frequency between pre and post-lockdown.	47%	48%	NS
					No significant difference in DKA severity (mild, moderate to severe) between pre and post-lockdown.	13% for mild DKA and 33% for moderate-severe DKA	14% for mild DKA and 31% for moderate-severe DKA	NS
					No significant alteration of age at presentation between pre-lockdown and post-lockdown	10.0	9.2	NS
					No significant alteration of male sex between pre-lockdown and post-lockdown	58.9%	54.8%	NS
					No significant alteration of BMI percentile between pre-lockdown and post-lockdown	48.9	54.9	NS

Author	Type of Study	Population	Sample Size	Potential Variables	Main Result	Pre-pandemic Value	Pandemic Value	Sig.
Aqeel Alaqeel [9]	A multicenter cohort study	Children (120 males, 140 females)	260	Incidence, DKA, demographic findings	No significant difference in new cases of T1DM between pre and during covid-19.	57	41	0.70
					No significant difference in severe DKA between pre and during covid-19.	4	7	0.13
					Significant increase of DKA frequency between pre and during covid-19.	15	23	<0.001
					No significant difference in age presentation between pre and during covid-19	9.7 years	10 years	0.20
					No significant difference between the male sex during the pandemic and pre-pandemic	69	51	0.60
Anca Andreea Boboc [10]	A single-centre cohort study	Children (M/F:245/214)	459	Incidence, demographic findings, DKA, presentation	Significant increase in mean new cases of T1DM during pandemic than pre-pandemic.	9.4 cases/month	13.2 cases/ month	0.015
					Significant increase of DKA frequency during pandemic than pre-pandemic.	39.42%	65.99%	<0.0001
					Significant increase of severe DKA during the pandemic than pre-pandemic.	26.83%	42.27%	0.016
					No significant alteration of M/F ratio during pandemic and pre-pandemic.	1.04	1.19	0.55
					Significant increase in median age at diagnosis during the pandemic than pre-pandemic.	7 years	7.20years	<0.001
					No significant alteration in median days of symptoms before presentation during the pandemic and pre-pandemic.	24.52±1.83 days	25.39±2.23 days	0.51
					Significant effect of presentation during the pandemic on DKA at diagnosis.	-	-	(OR:3.2, 95%CI 2-5.2, <0.001)
					Significant correlation between DKA at diagnosis with younger age during the pandemic than pre-pandemic.	-	-	(Increase in age by OR 0.94 per year, 95% CI 0.90–0.98)

Author	Type of Study	Population	Sample Size	Potential Variables	Main Result	Pre-pandemic Value	Pandemic Value	Sig.
Katarzyna Dżygało [11]	An observational cohort study	Children (48 males, 38 females)	86	Incidence, DKA, demographic findings, presentation	No significant difference between new cases of the pandemic period and pre-pandemic one((previous year)	52	34	NS
					No significant alteration in age at diagnosis during the pandemic and pre-pandemic	9.59±4.7years	9.90±4.9years	0.822
					No significant alteration in F/M ratio during the pandemic and pre-pandemic	26/26	12.22	0.192
					No significant alteration of BMI z-score during the pandemic and pre-pandemic period.	–0.31±1.5	–0.36±1.5	0.680
					No significant difference for duration of symptoms (weeks) during COVID-19 and pre-COVID-19.	3.69±3.43	3.09±2.6	0.631
					Significant increase of weight loss (kilogram) at initial presentation during the pandemic.	2.12±2.28	5.11±4.0	0.001
					No significant alteration of DKA frequency between two periods.	29	18	0.276
					Significant increase of severe DKA during pandemic and pre-pandemic.	6	11	0.026
					Significant increase of both moderate and severe DKA during pandemic and pre-pandemic.	13	17	0.022

Abbreviations: DKA: Diabetic ketoacidosis; NS: Not significant; T1DM: Type 1 diabetes mellitus; F/M: Female/male; SD: Standard deviation; BMI; Body mass index.

Incidence

Lawrence et al. in their study showed that the number of new cases of T1DM during the pandemic was not significant compared to pre-pandemic (2015-2019) (6 to 10 patients in pre-lockdown compared to 11 ones during the pandemic) [6]. Alaqeel et al. reported that the incidence of T1DM during the pandemic was similar to pre- pandemic and non-significant (106 vs 154) [9]. A study by Boboc et al. found a significant increase in new cases per month, 13.2 vs. 9.4 (P=0.015) during the pandemic compared to pre-pandemic [10]. In a study by Dżygało et al. severe form of DKA in children with T1DM during the pandemic was assessed. They reported 34 new cases during the pandemic compared to 52 new cases before the pandemic (the previous year) [11].

Demographic findings

In Lawrence et al.'s study, male gender difference among new T1DM cases during lockdown was not significant compared to pre-lockdown (27% during the pandemic compared to 33%-63% range in the pre-lockdown period). The mean age of patients also did not change between the two study periods (ranging from 8.0±4.3 years in the lockdown phase to 7.9±4.0 to 10.2±5.4 years in the pre-lockdown phase) [6]. Bogale et al. compared DKA rates in children with T1DM between the two periods of the study. They argued that the mean age of newly diagnosed children during the pandemic did not differ significantly from pre- pandemic (9.2 years vs. 10 years). The comparison of male patients during the pandemic has not altered significantly different from pre- pandemic (54.8% vs. 58.9%). Also, the mean body mass index (BMI) percentile during the pandemic was 54.9 compared to 48.9 pre- pandemic, which was not significant. They reported a significant association between patients aged 0-3 years and 13-19 years with DKA at the time of diagnosis (P=0.003 and 0.009, respectively), but the correlation between the male sex and DKA at diagnosis was not significant (P=0.34). The relationship between BMI at diagnosis (15^{th}-85^{th} percentile) and DKA was not significant (P=0.21) [8].

Alaqeel et al. discussed the age of patients at the time of diagnosis (during the pandemic) and the male sex was not significantly different from pre- pandemic (P=0.2 and 0.6, respectively) [9]. Boboc et al. studied new patients with T1DM during the pandemic. They indicated that the male/female ratio did not change significantly compared to the pre- pandemic period (P=0.55). Furthermore, the age of patients at diagnosis during the pandemic was significantly higher than pre-pandemic (P<0.001) [10]. Another study conducted by Dżygało et al. reported no significant difference in the female/male ratio between the pandemic and pre-pandemic periods (P=0.192). The mean age of patients at diagnosis was older during the pandemic and was not significant (P=0.822). By reviewing BMI z-score of patients, this value did not change significantly between the two periods (P=0.680) [11].

Presentation

In a study conducted by Lawrence et al., the difference in symptoms in patients aged <18 years of age between lockdown and pre-lockdown was 27% and was significant (P<0.01). Non-DKA presentations were also significantly reduced during the pandemic (3 presentations during lockdown versus 4–8 presentations before lockdown, P<0.05) [6]. On the other hand, in Bogale et al.'s study, non-DKA presentation at the time of diagnosis did not change significantly during the pandemic compared to pre- pandemic, 52.4% vs. 53.5% [8]. Boboc et al analyzed the time of T1DM diagnosis and concluded that a significant correlation was observed between the developmental role of DKA at diagnosis (P<0.001). Also, among DKA cases; they observed a significant relationship between increased DKA intensity and presentation (P=0.024) [10]. Dżygało et al. found in their study that polyuria and polydipsia were the most common symptoms both during and pre-pandemic, and the difference between the two periods was not significant. They also noted greater weight loss during the pandemic than pre-pandemic, which was significant (P=0.0006) [11].

Diabetic ketoacidosis (DKA)

In a study conducted by Lawrence et al., the presentation of the new T1DM was assessed. They reported a significant increase in the frequency of DKA during the pandemic and a more severe form of DKA than pre-pandemic (P<0.007 and P<0.003, respectively) [6]. On the other hand, Bogale et al. reported that the DKA rate during the pandemic was not significantly different from pre-pandemic (47.6% vs. 46.5%). Also, no significant difference was observed in the severity of DKA between the two periods, including mild form (14.3% vs. 13.2%) and moderate to severe one (31% vs. 33.2%). Based on multivariate analysis, no relationship between DKA at diagnosis and duration of COVID-19 was evident (P=0.89). The relationship between HbA1c >10% and DKA at diagnosis was significant during the pandemic [8]. Alaqeel et al. compared the frequency of DKA and

the incidence of newly diagnosed T1DM patients during pandemic and pre- pandemic. They discussed that the DKA frequency was higher during the pandemic, which was significant (P<0.001), but severe DKA did not alter significantly (P=0.13). A significant relationship was observed between DKA at diagnosis and duration of lockdown, patient age, and male sex (P=0.01, 0.00, and 0.00, respectively). Severe DKA was significantly correlated with age and male sex (P=0.01 and 0.04, respectively), but not with lockdown duration (P=0.22) [9].

The frequency of DKA in Boboc et al. study was higher during pandemics than pre-pandemic (P<0.0001). Also, the severe form of DKA increased significantly during the pandemic (P=0.016). The average age of patients with DKA was significantly lower than those without DKA (P=0.006). They found no significant difference in the mean age of severe DKA and male sex [10]. On the other hand, in a study conducted by Dżygało et al., the DKA rate at diagnosis did not alter significantly during the pandemic than pre-pandemic (P=0.276). Severe DKA was higher during the pandemic (P=0.026). Also, moderate to severe DKA increased significantly (P=0.022) [11].

Study limitations

The study design should not be region-specific as it does not reflect changes in disease incidence during the pandemic. To more accurately assess the frequency and severity of DKA in newly diagnosed patients, studies with large sample sizes are much better for further investigate factors that may predispose patients to DKA. Comprehensive multicenter studies are needed to better judge potential factors.

Conclusion

This article focuses on evaluating and comparing studies examining the characteristics of children and adolescents with newly diagnosed T1DM during the pandemic period compared to pre-pandemic period. By reviewing five studies according to our study criteria, the incidence, disease onset, frequency, and severity of DKA, and demographic findings, including age and sex differences between pandemic and pre-pandemic were evaluated.

Although the incidence of diabetes varies by region type [12], the prevalence is highest among children younger than 15 years of age in Finland and Sardinia, with 65-37 per 100,000 children in this age group [12, 13]. The incidence of this disease varies by race but is reported to be 22.3 per 100,000 children and adolescents in the United States [14]. In 2017, a multiethnic study of children aged 0-19 years found that the disease had the highest prevalence in non-Hispanic individuals (White adolescents, 2.79 cases per 1000 children), followed by Blacks (2.18), Hispanics (1.56), and Asians (0.76) respectively [15]. A key issue in assessing changes in disease incidence during the pandemic is the need to consider the organization and burden of health systems caused by COVID-19 because a striking relationship is observed between them. Our assessment must be multicenter, as referral patients from other centers may influence our assessment (indeed, the degree of pandemic involvement in the healthcare system depends on the incidence rate) [10]. Another aspect to consider about disease incidence is the change in patients' lifestyles during the pandemic. Despite COVID-19 spurring progression to T1DM, the rate of new diagnoses has reportedly declined early in the pandemic. The reduction in incidence can be explained by the fact that the strict quarantine conditions reduced an individual's exposure to COVID-19 as a trigger to develop T1DM early in the pandemic [10]. Multicenter assessments should be conducted by race in each region to better assess the role of disease incidence and pandemics.

The most common symptoms of childhood T1DM are polydipsia, polyuria, and weight loss, with 90% of cases initially complaining of polydipsia and polyuria [16]. The DKA rate as the first manifestation of T1DM is approximately 30% (DKA ranges from 15%-67%) [2, 17, 18]. DKA is most common in children under the age of 6 or children of low socioeconomic status. Approximately 50% of new T1DM cases are in her children younger than 3 years who present with DKA [2]. The question of the rate and severity of her DKA increase during the pandemic is that, in addition to the need to consider the role of the virus, the limitations of the pandemic are also vital. Another question that needs further clarification during a pandemic is to what extent the increased frequency and severity of DKA are related to the role of the pandemic and to what extent it is related to patient demographics (age and gender). Little evidence suggests a role for demographic findings in patient DKA during the pandemic. Therefore, conducting research focused on this area can clarify the role of the pandemic in the frequency and severity of her DKA in newly diagnosed patients. Looking at demographics and the pandemic period separately can provide a good guide to a more accurate estimate of the number of patients presenting their first presentation of DKA during the pandemic period, which is more specific, also it may be more tangible.

T1DM is the most common form of childhood diabetes, with approximately 75% of T1DM cases occurring during this period. It is estimated that about 80% of new T1DM cases in the United States are younger than 19 years of age [15, 19]. The age onset of T1DM in childhood has two peaks: 4-6 years and 10-14 years [20-22], with approximately 45% of cases diagnosed under 10 years of age [23]. Examining the sex distribution of T1DM in childhood does not give a clear picture of the dominant sex [15, 19]. Comparison of patient demographics during pandemics indicated that reported results were often inconclusive; therefore, it is not possible to adequately assess the role of the pandemic in age and sex changes. Younger children have been reported to have shorter onset duration and faster progression to T1DM diagnosis [11]. We also recommend larger studies with different age groups to more accurately assess age differences between the pandemic and pre-pandemic periods. For sex differences between the two periods, pandemic limitations that lead to undesirable matching between men and women should be considered. Therefore, it is expected that gender differences will not be noticed much.

Symptoms, including weight loss, emesis, polyuria, etc. are in favor of diabetes mellitus. These symptoms may also indicate a viral cause. This misconception leads to late diagnosis of T1DM and early progression to DKA. Restrictions during quarantine, protection from COVID-19 exposure, and lack of access to medical teams are some of the potential factors delaying the diagnosis of T1DM [11]. The reason for the increased DKA rate during the pandemic period was not due to COVID-19 infection, but rather the delay in presentation caused by the disruption of daily life during the pandemic period, including the reduction in face-to-face contact (with friends and relatives), prohibition of referring to the clinic due to COVID-19 infection, online learning, etc. [6]. Delay in presentation has been reported to be proportional to the increase DKA rate at diagnosis [24]. Therefore appropriate strategies should focus on raising awareness that televisit is an appropriate solution. Social media can be used to educate and deliver programs to keep patients and their parents in touch with the healthcare system during the lockdown and prevent DKA rates from rising [6]. It can be concluded that to reduce the incidence of DKA and delay the diagnosis of T1DM, it is necessary to give people warning signals so that they can focus on informing them about their diabetes symptoms.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contributions

Conceptualization and design, data validation, drafting the manuscript: Daniel Zamanfar and Mobin Ghazaiean; Methodology, data analysis, interpretation, article writing and final approval: All authors.

Conflicts of interest

The authors declared no conflict of interest.

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