Review Paper

Glycemic Fluctuations of Children and Adolescence Type 1 Diabetes Mellitus and the Impressive Aspects of SARS-CoV-2 Since the Onset of Pandemic Lockdown: A Review Paper

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ABSTRACT

Background: The COVID-19 pandemic limited the daily activities of children and adolescents with type 1 diabetes mellitus, and several factors are impacting ongoing care. The role of pandemics on glycemic control is unknown. We plan to assess the glycemic status and the factors that influence it during the pandemic.

Objectives: Our goal was to examine the impact of COVID-19 quarantine on the glycemic control of children and adolescents with type 1 diabetes mellitus.

Methods: Databases including PubMed, Scopus, Web of Science, and Science Direct, with English-type articles extracted from December 31, 2019, to March 3, 2022, were searched. The article review was based on factors influencing glycemic control in type 1 diabetes mellitus cases younger than 18 years of age during the pandemic period such as psychological factors, telemedicine role, lifestyle changes, various diabetes technology (cost, availability...), caregivers' role, and socioeconomic factors.

Results: We scanned 573 articles as an initial search for titles/abstracts and full-text reviews, and 54 articles remained after title/abstract screening for full-text assessment among which 14 articles (cohort studies) were included. Most studies reported glycemic improvement based on blood glucose metrics while some studies reported stable glycemic control. Although the pre-pandemic glucose profile is important, factors such as telemedicine, diabetes technology, and lifestyle play a more tangible role in improving glycemic control during the pandemic.

Conclusions: Overall, the studies did not contain strong evidence that glycemic control worsened in children and adolescents with type 1 diabetes mellitus during the pandemic. Although the assessment was conducted over a short period, long-term multicenter studies would be useful for a more precise assessment of the mentioned potential factors.

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Introduction

In 2019, the COVID-19 pandemic led to a quarantine that restricted the daily lives of patients, especially type 1 diabetes (T1DM) [1]. Indeed, the role that the pandemic has played is related to patient adherence to treatment caused by changes in daily routines [2, 3]. COVID-19-induced lifestyle changes, including dietary habits, physical activity, sleep disturbances, mental health issues, and screen time, are associated with poor glycemic control [4, 5].

In addition to the factors that have worsened glycemic control during the pandemic, some factors have a role in improved glycemic control. Spending most of their daily activities with their parents has caused their treatment regimen and eating habits to be more monitored than usual [6]. The use of televisit has also made it easier for patients to access medical services. Furthermore, diabetes technologies such as insulin pumps and glucose control sensors have made patient findings continuously available in medical centers [7-9].

It is also important to determine the long-term effect of potential factors on glycemic status to better assess their role during a pandemic [1]. This article argued the glycemic status in children and adolescents with known T1DM during the pandemic and compare it with the pandemic period, and the interaction between these factors and glycemic control during the pandemic.

Methods

We conducted a review study to examine factors influencing glycemic control in T1DM cases younger than 18 years of age during the pandemic period. We searched databases including Pubmed, Scopus, Web of Science, and Science Direct from December 31, 2019, to March 3, 2022. Keywords used to search the databases included type 1 diabetes mellitus, COVID-19, pediatric, and glycemic, with English-language articles, entered in our study. Preliminary screening of selected articles was based on title/abstract adjusted for inclusion criteria, factors influencing glycemic control in children and adolescents with known T1DM during the pandemic.

Inclusion criteria

The inclusion criteria were children and adolescents (age <18 years old) with definite T1DM diagnosis >6 months and studies by design 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, and posters), and animal studies. Patients whose age range did not meet the age limits of the study and studies that did not segregate patients by age and type of diabetes during the pandemic were also excluded. Figure 1 shows the process of extracting contained items.

The initial screening of selected articles based on title / abstract consistent with our inclusion criteria was done. Based on the searched database, 573 articles were extracted, of which 376 articles remained after removing duplicates (197 articles). Fifty-four articles were selected for full-text review by assessing the findings of the entered articles encompassed type 1 diabetes mellitus, COVID-19, pediatric, and glycemic findings of known cases of T1DM younger than 18 years of age. Five of these articles were not available in full text. From the remaining articles, 14 original articles (cohort studies) remained according to our study entry criteria.

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

A full-text analysis of the articles was then performed concerning psychology, lifestyle, diabetes technology, caregiver role, and socioeconomic factors affecting glycemic control. Variables extracted from the included articles were author name, study year, study type, study population, sample size, underlying factors, the main outcome, and pre-pandemic and post-pandemic data values. The results of the search process are shown in Table 1.

Results

A total of 14 articles were included in the study. All studies focused on patients who had been diagnosed with T1DM for more than 6 months and younger than 18 years. Factors investigated in these patients included

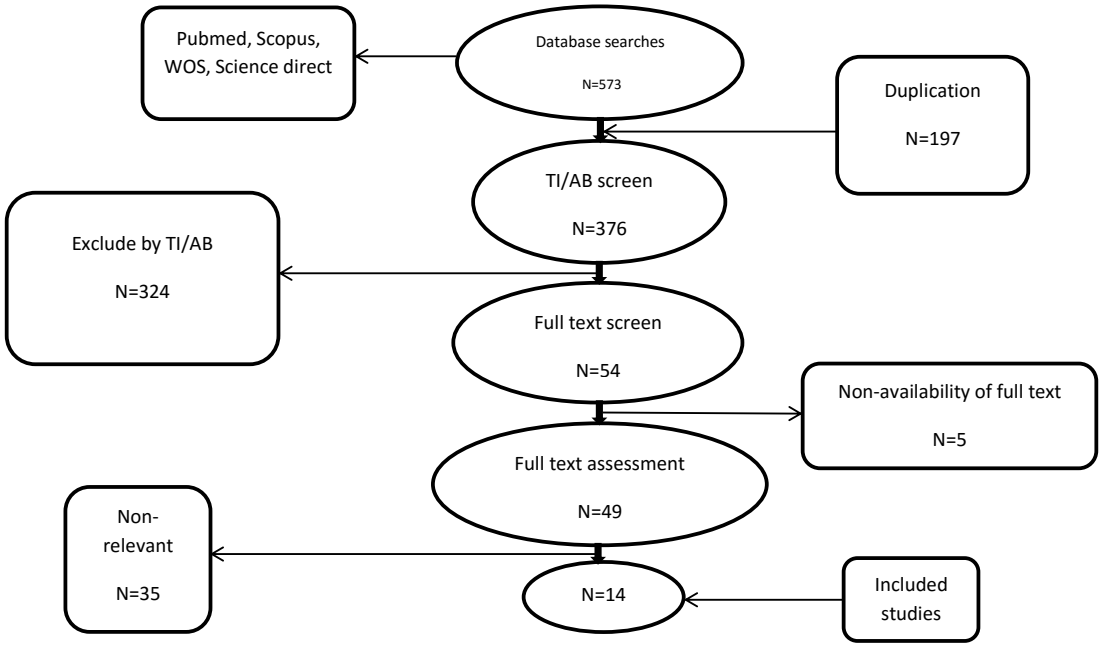

Figure 1. Flowchart of included articles

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psychological factors, the role of telemedicine, lifestyle changes, different diabetes technologies (cost, availability, etc.), caregiver experience, and socioeconomic factors (including BMI, cost, and availability etc.

Studies indicating proper glycemic control

Cusinato et al. represented an improvement in glycemic control during the pandemic over the pre-pandemic period. They found significant reductions in the percentage of time in hyperglycemia (P<0.001), time in hypoglycemia (moderate and severe form) (P=0.002 and

Table 1. Eligible criteria

Criteria	Include	Exclude
Population	Children and adolescence (age <18 y) with definite T1DM diagnosis >6 months	Adult (age ≥18 y) 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 that differentiated between types of diabetes but did not differentiate outcomes. Studies in which T1DM patients complicated with other co-morbidities affecting glycemic control
Intervention and comparators	Psychological factors Telemedicine role Lifestyle changes Various diabetes technology (cost, availability…) Caregivers' role Socioeconomic factors (including body mass index (BMI), cost, and availability…)	If causes other than the pandemic period and COVID-19 influence have affected the interventions listed in the included criteria.
Outcomes	Glycemic control	None
Study type	Cohort Case-control Observational-cohort Mini review Meta-analyses Systematic review	Observational-non-cohort Narrative review Case studies (case series & case report) Book Cross-sectional Randomized controlled trial (RCT) Editorial, news, poster Animal studies

Abbreviations: T1DM: Type 1 diabetes mellitus; BMI: Body mass index; RCT: Randomized controlled trial.

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P=0.001, respectively), GMI (P=0.001) and a significant increase in TIR (P<0.001) [10]. Lazzeroni et al. conducted a retrospective study to investigate the impact of telemedicine and lifestyle on glycemic control in children with T1DM during the quarantine. Mean HbA1c levels ameliorated significantly, 64.4±15.61 mmol/mol before the quarantine and 60.7±11.54 mmol/mol after it (P=0.002) [11]. In a study, Cognigni et al. assessed HbA1c levels in patients <18 years of age during and pre-pandemic. HbA1c altered from 60 mmol/L pre-pandemic to 57 mmol/L during the pandemic (P=0.04) [12]. Tornese et al. designed a study application of the Hybrid closed-loop (HCL) system described three times to compare blood glucose metrics in children; pre-pandemic (first), early pandemic (second), and during lockdown (third), also the effect of PA on glycemic control during these periods. TIR percent augmented at time 3 compared to time 2 (P=0.039). They also indicated a decrease in TBR at time 3 compared to time 2 and time 1 (P=0.044 and P=0.041, respectively) [5]. A summary of values is shown in Table 2.

Table 2. Summary of selected articles findings

Author	Type of Study	Population	Sample Size	Potential factor(s)	Main Results	Pre-pandemic Value	Pandemic Value	Sig.
Cusinato et al. 2021 [10]	A single-center cohort	Adolescents (52 female, 65 male)	117	Psychological	Significant improvement of TIR (70–180 mg/dL) percentage	59%	49%	<0.001
					Significant improvement of time in hyperglycemia	-	-	<0.001
					Significant improvement of GMI	7.6%	7%	0.001
					Significant reduction of time in moderate and severe hypoglycemia	-	-	0.002 and 0.001, respectively
					Significant reduction of TBR (<70 mg/dL)	-	-	0.002
					Significant improvement of time above range (>180 mg/dL)	-	-	<0.001
					Significant lower TIR for cases experiencing anxiety	-	-	0.028
					Significant lower TIR for cases experiencing depression	-	-	0.012
Brener et al. 2020 [6]	An observational multi-center cohort	Aged ≤18 years (54 male, 48 female) (aged <10, children, n=41 and aged ≥10 years, adolescents, n=61)	102	Sociodemographic features	No significant improvement in glucose level (mg/dL) in children	161.2	161.2	0.965
					No significant improvement in glucose SD (mg/dL) level in children	65.6	63.1	0.076
					No significant improvement in TIR percentage in children	61.5%	61.4%	0.944
					Significant improvement in CV	40.5%	39.1%	0.041
					No significant alteration of glucose (mg/dL) level among adolescents	165	161.7	0.116
					Significant alteration of Glucose SD (mg/dL) among adolescents	62.4	54.4	<0.001
					Significant alteration of TIR (>250 mg/dL) percentage among adolescents	11.7%	9.7%	0.009
					Significant alteration of CV among adolescents	37.7%	35.9%	0.009
					Significant lower glucose SD levels among adolescents than children	62.4 mg/dL compared to 65.6mg/dl	54.4mg/dl compared to 63.1(mg/dl)	0.034
					Significant lower CV percentage among adolescents than children	37.7% compared to 40.5%	35.9% compared to 39.1%	0.005

Author	Type of Study	Population	Sample Size	Potential factor(s)	Main Results	Pre-pandemic Value	Pandemic Value	Sig.
Lazzeroni et al. 2021 [11]	A real-life observational cohort	Pediatric and young Adult (78 male, 61 female)	139	Telemedicine and lifestyle	Significant improvement of mean hba1c mmol/mol) level of post-lockdown than pre-lockdown	64.44±15.61	60.66±11.54	0.002
					No significant increase in insulin doses (IU/kg/day) during the pandemic than pre-pandemic	0.743±0.198	0.759±0.215	0.19
					No significant alteration of mean BMI, or z-score level during the pandemic than pre-pandemic	0.30±0.97	0.35±1.05	0.55
					Significant reduction in mean PA hours/week during the pandemic than pre-pandemic	3.91±3.56	2.13±3.33	<0.001
					No significant difference among variation of hba1c level and daily insulin injection between SBGM vs FGM/CGM methods in the pre- and post-lockdown		Mean±SD: -5.21±18.06 and -3.56±13.21, respectively.	0.70
					No significant alteration of hba1c level variation (between MDI and CSII therapy) in pre and post-lockdown		The mean reduction of -4.91±15.64 mmol/mol and --1.17±8.19 mmol/mol, respectively.	0.07
					No significant alteration of mean hba1c level and daily insulin injection regarding diet and PA variation during a pandemic	-	-	NS
Cognigni et al. 2021 [12]	Cohort	Children and adolescents (25 female, 25 male)	50	Physical activity, telemedicine, lifestyle, diabetes technology	Significant improvement of hba1c level after lockdown than pre-lockdown	7.6%	7.4%	0.04
					Independent correlation between CSII and CGM/FGM methods, physical activity, and telemedicine with hba1c improvement	-	-	-
					No significant alteration between the BMI of post-lockdown and pre-lockdown	0.27 SDS (−0.27–1.18)	0.35 SDS (−0.23–1.29)	0.81
Tornese et al. 2020 [5]	Cohort	Adolescents (8 male, 5 female)	13	In-home PA, telemedicine	Significant increase of TIR (70–180 mg/dL) percent in time 3 than time 2[a]	66%	72%	<0.05
					Significant reduction of TBR (<70 mg/dL) percent in time 3 than time 1 and time 2[a]	2%	1%	<0.05
					No significant alteration in TDD (U/day) of insulin	57	54	>0.05
					Significant improvement of TIR between times 2 and 3 with regular PA[a]	-	-	0.043
					Significant improvement of TIR among patients with regular and non-regular PA at time 3[a]	-	-	0.005

Author	Type of Study	Population	Sample Size	Potential factor(s)	Main Results	Pre-pandemic Value	Pandemic Value	Sig.
Di Dalmazi et al. 2020 [13]	Cohort	(30 children (≤12 y), 24 teenagers (13–17 y), and 76 adults (≥18 y))	130	Diabetes technology (CGM system including CGM with sensors, Dexcom or freestyle libregm, MDI)	Significant reduction of glucose SD in children during the pandemic than pre-pandemic	67.4mg/dL	64.3 mg/dL	0.029
					No significant improvement in CV percent in children during the pandemic than pre-pandemic	37.4%	36.8%	0.069
					No significant increase in TIR percent in children during the pandemic than pre-pandemic	53.3%	53.8%	0.055
					No significant increase of TBR (54–69 mg/dL) percent in children during the pandemic to pre-pandemic	1.2%	1.3%	0.072
					Significant reduction of TBR (<54 mg/dL) percent in children during the pandemic than pre-pandemic	0.4%	0.3%	0.029
					No significant increase of TAR (>250 mg/dL) percent in children during the pandemic than pre-pandemic	14.5%	14.6%	0.74
					Significant alteration of LBG index in children during the pandemic than pre-pandemic	0.5(0.3-0.9)	0.5(0.2-0.6)	0.033
					No significant improvement in any CGM metrics of teenagers	-	-	NS
Predieri et al. 2020 [14]	An observational cohort	Children and adolescents (31 male and 31 female)	62	Telemedicine	Significant increase of mean TIR (70-180 mg/dL) during lockdown than pre-lockdown	60.0±13.1%	62.1±13.7%	0.008
					Significant reduction of TBR (<54 mg/dL) during lockdown than pre-lockdown	0.50±0.63%	0.34±0.53%	0.002
					Significant reduction of TBR (<70 mg/dL) during lockdown than pre-lockdown	2.63±2.37	2.13±2.41	0.001
					Significant reduction of TAR (>180 mg/dL) during lockdown than pre-lockdown	37.8±13.9	35.7±14.4	0.048
					Significant reduction of TAR (>250 mg/dL) during lockdown than pre-lockdown	11.4±7.77	9.74±7.00	<0.001
					Significant reduction of glucose SD (mg/dL) during lockdown than pre-lockdown	60.8±11.8%	57.6±10.8%	<0.0001
					Significant reduction of PA (hour/week) during the pandemic than pre-pandemic	3.27±2.82	0.24±0.59	<0.0001
					No significant reduction of GMI during lockdown than pre-lockdown	7.45±0.74%	7.35±0.72%	0.069
					No significant increase in TDD (IU/kg/day) injection during lockdown compared to pre-lockdown	0.72±0.22	0.74±0.19	0.186
					No presence of a significant relationship between alteration in exercise time and any type of glucose metrics		Median Δ=-2.00 h/week	NS

Author	Type of Study	Population	Sample Size	Potential factor(s)	Main Results	Pre-pandemic Value	Pandemic Value	Sig.
Minuto et al. 2021 [15]	An observational cohort	Children and young patients age : Group 1: ≥6<10 y Group 2: ≥10<14 y Group 3: ≥14<18 y, Group 4: ≥18, which included 7, 42, 58, 95 patients, respectively	202	Telemedicine and PA	Significant reduction of PA hours/ week during lockdown than pre-lockdown	4.36±0.94	0.14±0.38	0.02
					Significant reduction of CV among group 2 during lockdown than pre-lockdown	37.55±6.02%	34.13±5.68%	≤0.0001
					Significant reduction of mean glucose SD (mg/dL) among group 2 during lockdown than pre-lockdown	65±14.01	58.43±11.74	≤0.0001
					Significant improvement of TAR(>250 mg/dL) among the group 2 during lockdown than pre-lockdown	16.36±12.86%	12.74±9.99%	0.01
					Significant reduction of TBR among group 2 during lockdown than pre-lockdown	3.34±3.36%	2.20±2.51%	0.002
					Significant reduction of TBR <54 mg/dL among the group 2 during lockdown than pre-lockdown	0.80±1.17%	0.49±0.94%	0.03
					Significant alteration of glucose SD (mg/dL) among group 3 during lockdown than pre-lockdown	67.33±15.52	63.40±15.08	0.002
					Significant alteration of hba1c among the group during lockdown than pre-lockdown 3	7.95±1.09%	7.76±1.31%	0.03
					Significant alteration of TIR among group 3 during lockdown than pre-lockdown	51.96±16.73%	56.71±19.42%	0.005
					Significant alteration of TAR among group 3 during lockdown than pre-lockdown	45.38±18.01%	40.84±20.75%	0.02
					Significant alteration of TAR (>250 mg/dL) among group 3 during lockdown than pre-lockdown	18.63±12.13%	16.22±15.09%	0.004
Mianowska et al. 2021 [17]	Cohort	21 children and 55 teens (30 girls and 46 boys)	76	Psychological factors (diabetes-related distress) and (caregivers' role).	Significant reduction of PAID score, consequence reduction of DD in girls compared to boys (among teens) during the pandemic	-	Median difference; (-7(-17 to -2.5))	0.028
					No significant changes in PAID score, subsequently DD in children during the pandemic	--	Median difference; -3(-14 to 7)	0.131
					No significant alteration of PAID score, subsequently DD in teens' parents and children's parents		Median difference; 3(-9 to 10) and -5(-9 to 1), respectively	0.376 and 0.227, respectively.
					No significant correlation between PAID score with CGM use	-	-	NS

Author	Type of Study	Population	Sample Size	Potential factor(s)	Main Results	Pre-pandemic Value	Pandemic Value	Sig.
Nwosu et al. 2021 [16]	An observational cohort	Pediatric (57 male and 53 female)	110	Diabetes technology (CGM system)	No significant alteration of hba1c level between the pre and post-pandemic periods		0.18±1.2%	0.13
					Significant improvement in mean glucose level during the pandemic than pre-pandemic	204.05±31.2 mg/dL	195.95±33.0 mg/dL	0.0497
					Significant increase in sensor usage % during the pandemic than pre-pandemic	79.79±23.6	88.68±15.4	0.014
					Significant improvement of point-of-care hba1c during the pandemic than pre-pandemic	8.24±1.1%	7.90±1.1%	0.0012
					Significant improvement of CGM-estimated hba1c during the pandemic than pre-pandemic	8.06±0.8%	7.92±0.7%	0.018
					No significant alteration of CGM estimated A1c for insulin pump usage among CGM users during the pandemic than pre-pandemic	7.83±0.6%	7.63±0.6%	0.48
					Significant improvement of CGM estimated A1c for female sex among CGM users during the pandemic than pre-pandemic	8.07±0.7%	7.89±0.7%	0.035
					No significant alteration of TDI (unit/kg/day) injection during the pandemic than pre-pandemic	0.88±0.3	0.94±0.3	0.48
					No significant alteration of hba1c among non-CGM users during the pandemic than pre-pandemic	9.48±1.9%	9.43±1.6%,	0.86
					Significant increase in TDI injection among non-CGM users during the pandemic than pre-pandemic	--	--	<0.0001
Wu et al. 2021 [18]	An observational cohort	Children and teenagers (23 male and 20 female)	43	Sociodemographic and lifestyle changes	Significant alteration of TIR (39–100 mmol/L) before, during, and post lockdown	74.28±12.13 %	75.35±12.66 mmol/L% during lockdown and 73.60±12.83 mmol/L% post-lockdown	0.081
					No significant alteration in mean glucose level before, during, and post lockdown	7.74±1.19 mmol/L	7.85±1.14 mmol/L during lockdown and 7.70±1.20 post-lockdown	0.368
					No significant alteration of estimated hba1c before, during, and post lockdown	6.47±0.75%	6.54±0.72% during and post lockdown	0.368
					Significant improvement in time <39 % before, during, and post-lockdown	3.70 %	2.91 % during lockdown and 4.95 % post lockdown	0.004

Author	Type of Study	Population	Sample Size	Potential factor(s)	Main Results	Pre-pandemic Value	Pandemic Value	Sig.
Wu et al. 2021 [18]	An observational cohort	Children and teenagers (23 male and 20 female)	43	Sociodemographic and lifestyle changes	Significant improvement in time <3 mmol/L (%) before, during and post lockdown (%)	0.59 %	0.38 mmol/L (%) during lockdown and 0.82 post lockdown	0.008
					No significant improvement in the LBG index before, during, and post-lockdown	1.15	1.03 during lockdown and 1.40 post lockdown	0.020
					Significant improvement in hypoglycemic events before, during, and post lockdown	1.50	0.50 during lockdown and 1.27 post lockdown	0.020
					No significant alteration in time >139 mmol/L (%) of hyperglycemia before, during, and post-lockdown	2.95	1.58 during lockdown and 1.80 post lockdown	0.862
					No significant alteration in time >100 mmol/L of hyperglycemia (%) before, during, and post lockdown	18.68	15.39 during lockdown and 15.84 post lockdown	0.404
					No significant alteration in high blood glucose index before, during, and post lockdown	41.54	41.20 during lockdown and 40.74 post lockdown	0.298
					Significant increase in diabetes management during the lockdown	-	-	<0.001
					Significant increase in snack frequency during the lockdown	-	-	0.018
					Significant increase in sleep duration during the lockdown	-	-	0.024
					Significant reduction of PA time during the lockdown	-	-	0.004
					No significant alteration in anxiety and stress during the lockdown	-	-	NS
					No significant alteration of insulin injection during the lockdown	-	-	NS

Author	Type of Study	Population	Sample Size	Potential factor(s)	Main Results	Pre-pandemic Value	Pandemic Value	Sig.
Lombardo et al. 2021 [19]	An observational cohort	Pediatric	85	Diabetes technology (CGM system), telemedicine	Significant improvement of TIR during the lockdown than pre-lockdown	62.7±13%	66.6±12.9%	<0.001
					Significant improvement of TAR during the lockdown than pre-lockdown	33.5±13.4%	29.6±13.3%	<0.001
					Significant improvement of CV during the lockdown than pre-lockdown	36.9±6.2%	36±5.8%	0.003
					Significant improvement of GMI during the lockdown than pre-lockdown	7.1±0.6%	7±0.6%	<0.001
					Significant improvement of TIR among patients aged 5-9 years during the lockdown than pre-lockdown	59.7±13.4%	64.3±13.3%	<0.001
					Significant improvement of TAR among patients aged 5-9 years during the lockdown than pre-lockdown	35.9±14.4%	31.4±14.9%	<0.001
					Significant improvement of GMI among patients aged 5-9 years during the lockdown than pre-lockdown	7.2±0.6%	6.9±0.6%	0.008
					Significant improvement of TIR among patients aged 10-14 years during the lockdown than pre-lockdown	63.5±11.2%	66.7±11%	0.004
					Significant improvement of TAR among patients aged 10-14 years during the lockdown than pre-lockdown	33.1±11.8%	29.6±11%	0.003
					Significant improvement of GMI among patients aged 10-14 years during the lockdown than pre-lockdown	7.2±0.6%	7.1±0.6%	0.016
					Significant improvement of TIR among patients aged 15-18 years during the lockdown than pre-lockdown	64.9±15.2%	69.4±15.4%	0.001
					Significant improvement of TAR among patients aged 15-18 years during the lockdown than pre-lockdown	31.1±14.9%	27.5±15.2%	0.007
					Significant improvement of CV among patients aged 15-18 years during the lockdown than pre-lockdown	35.5±8.3%	34.8±7.2%	0.041
					Significant improvement of TIR among the MDI group during the lockdown than pre-lockdown	58±15.6%	63.7±15.1%	0.004
					Significant improvement of TAR among the MDI group during the lockdown than pre-lockdown	39.2±17%	33±16.8%	0.004

Author	Type of Study	Population	Sample Size	Potential factor(s)	Main Results	Pre-pandemic Value	Pandemic Value	Sig.
Lombardo et al. 2021 [19]	An observational cohort	Pediatric	85	Diabetes technology (CGM system), telemedicine	Significant improvement of GMI among MDI group during the lockdown than pre-lockdown	7.3±0.7%	7±0.7%	0.024
					Significant improvement of TIR among the CSII group during the lockdown than pre-lockdown	63.2±10.9%	65.9±10.3%	0.002
					Significant improvement of TAR among the CSII group during the lockdown than pre-lockdown	32.5±12.2%	29.6±11.2%	0.002
					Significant improvement of GMI among CSII group during the lockdown than pre-lockdown	7.1±0.7%	7±0.6%	0.003
					Significant improvement of TIR among the HCL group during the lockdown than pre-lockdown	64.6±12.6%	68.5±13.2%	<0.001
					Significant improvement of TAR among the HCL group during the lockdown than pre-lockdown	31.5±11.8%	28.1±2.8%	0.001
					Significant improvement of CV among the HCL group during the lockdown than pre-lockdown	36.9±7.5%	35.4±6.6%	0.005
Braune et al. 2021 [20]	Cohort	Children (10 male, 18 female)	28	Diabetes technology (CGM system), telemedicine	No significant alteration of hba1c level % after 3- and 6-month remote consultations	7.5%	7.7% and 7.6%, respectively	0.43 and 0.42,
					Significant improvement of TIR after 3- and 6-month remote consultations	46.9%	57.5% and 56.3%, respectively	0.001 and 0.02,
					Significant improvement of time in hyperglycemia after 3- and 6-month remote consultations	48%	37.9% and 40%, respectively	0.004 and 0.02,
					No significant alteration of time in hypoglycemia after 3- and 6-month remote consultations	5.1%	4.7% and 3.7%, respectively	0.21 and 0.08,
					Significant improvement in psychosocial health after 6 months of remote consultations	72.5	78	0.04

Author	Type of Study	Population	Sample Size	Potential factor(s)	Main Results	Pre-pandemic Value	Pandemic Value	Sig.
Tinti et al. 2021 [21]	Cohort	Children and adolescents (46 male, 20 female)	66	Diabetes technology (CGM system), telemedicine, PA	Significant reduction of mean glucose during the lockdown	168±61 mg/dL	165±58 mg/dL	<0.05
					Significant reduction of TAR during the lockdown	37.8±14%	35.2±15%	0.004
					Significant reduction of CV during the lockdown	36±5%	35±5%	0.003
					Significant reduction of PA hours during the lockdown	6.1±3.3 hour	2.7±3.1 hour	<0.001
					Significant increase in daily insulin injection during lockdown	0.79±0.25 UI/kg/day	0.87±0.31 UI/kg/day	0.004
					Significant increase of TIR during lockdown	59.7±13%	62.5±14%	0.001
					Significant increase in CGM use during lockdown	87±17%	92±10%	0.006
					No significant alteration of TBR during the lockdown	2.5±2.3%	2.3±2.5%	0.177
					No significant alteration of GMI during the lockdown	7.5±0.9%	7.4±0.8%	0.05
					No significant alteration of TIR, TBR, TAR, CV, or daily insulin injection after remote consultation	-	-	NS

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Abbreviations: TIR: Time in range; GMI: Glucose management indicator; TBR: Time below range; TAR: Time above range; SD: Standard deviation; CV: Coefficient of variation; BMI: Body mass index; PA: Physical activity; SBGM: Self-monitoring of blood glucose; FGM: Flash glucose monitoring, CGM: Continuous glucose monitoring; SDS: Standard deviation score; MDI: Multiple daily injections; CSII: Continuous subcutaneous insulin infusion; TDD, total daily dose; LBG, low blood glucose; TDI, total daily insulin; PAID: Problems areas in diabetes; DD: Diabetes-related distress; HCL: Hybrid closed-loop.

[a]Time 3: During the lockdown, Time 2: Early pandemic (during restrictions), Time 1: Before the pandemic.

Dalmazi et al. used the CGM method to study the impacts of the pandemic on the glycemic index in children, adolescents, and adults. In children aged ≤12 years of age, LBGI, glucose SD, and TBR (<54 mg/dL) decreased significantly after the pandemic [13]. In another study, Predieri et al. using televisits noted that Italian T1DM children experienced better glycemic profiles during the pandemic. TIR, TAR, and TBR values improved significantly from 60.5% to 63.5%, 37.3% to 34.1%, and 1.85% to 1.45%, respectively (P=0.008, 0.048, and 0.001, respectively) [14]. Minuto et al. investigated the role of quarantine and PA on glycemic control in children. They divided the children into 4 groups: 6≤ age <10, 10≤ age <14, 14≤ age <18 y and age ≥18 y. Outcomes in patients 6≤ age <10 y did not show a significant change during quarantine compared to pre-quarantine. In the age group of 10≤ age <14 y, glycemic metrics including CV, glucose SD, TAR (>250 mg/dL), TBR, and TBR (<54 mg/dL) indicated significant improvement during the pandemic period (P≤0.0001, P≤0.0001, P=0.01, P=0.002, and P=0.03, respectively). In the age group of 14≤ age <18 y; glycemic metrics including glucose SD, HbA1c, TIR, TAR, TAR (>250 mg/dL) significantly improved (P=0.002, P=0.03, P=0.005, P=0.02, and P=0.004, respectively) [15].

The hypoglycemia index in Wu et al. study encompassed time <3.9 mmol/L (P=0.004), time <3 mmol/L (P=0.008), LGBI (P=0.020), and hypoglycemia events (P=0.020) were ameliorated during pandemic [18]. Lombardo et al. used

CGM metrics to evaluate the glycemic control of children during the pandemic. They reported that the pandemic values of TIR (P<0.001), TAR (P<0.001), CV (P=0.003), and GMI (P<0.001) augmented compared to pre-pandemic, but no significant changes in TBR have been reported [19]. A study by Braune et al. investigated the effect of distance counseling on glycemic control in children. The amount of TIR changed after 3 months (P=0.001) and 6 months (P=0.02) visits. Time in hyperglycemia at 3 months (P=0.004) and 6 months (P=0.02) were reduced (P=0.02) [20]. Tinti et al studied the glucose metrics of children with T1DM during the pandemic. They pointed to augmentation of TIR (P=0.001), TAR (P=0.004), CV (P=0.003), and mean glucose (P<0.05) indexes but there were no significant changes in TBR and GMI values [21].

Studies indicating stable glycemic control

According to the CGM metrics, pediatric T1DM demonstrated fairly stable glycemic control in a study published by Avivit Brener et al. Metrics such as glucose, glucose SD, CV, and TIR (from devices such as Dexcom G4, Medtronic Enlite Sensor, Dexcom G5, or FGM) showed significant changes during the quarantine compared to the pre-quarantine. They stated that the mean delta TIR was significant for poor (delta-TIR <-3%), stable (−3% ≤ delta-TIR ≤3%), and improved TIR (delta-TIR >3%) (values; -8.2±3.7, 0.3±1.9 and 8.7±4.9, respectively, P<0.001). However, the delta TIR during the pandemic period has not altered significantly [6]. Nwosu et al. investigated glycemic control in pediatrics during a pandemic. Their glucose control did not change significantly (P=0.13) [16]. Mianowska et al. studied the psychological factors and burdens associated with diabetes-related distress (DD) during a pandemic period in children and teens with T1DM. They assessed problem areas in diabetes (PAID) score in patients and their parents to compare DD before and after the pandemic. There was not a significant relationship between HbA1c and PAID score between the two periods in children (P=0.109), their parents, teens, and their parents [17].

The results of Wu et al. study provided evidence in support of modest variability in glycemic control in children by assessing CGM metrics. TIR, mean glucose, estimated HbA1c, time in hyperglycemia, glucose variability including CV, SD, mean amplitude of glucose excursion [22], mean of daily differences (MODD), and prolonged hypoglycemia did not alter significantly during the pandemic [18]. By reviewing remote consultation and CGM metrics, Braune et al. pointed out that time in hypoglycemia and HbA1c levels both after 3 and 6 months did not change significantly [20].

Studies indicating glycemic control and psychological factors

Cusinato et al. studied the role of psychological factors such as anxiety and depression on glycemic control in T1DM during the pandemic. They claimed that these factors worsen glycemic control through significant reductions in TIR, depression (−0.22±0.09, P=0.012), and anxiety (−0.20±0.09, P=0.028) [10]. On the other hand, Mianowska et al. discussed that no significant relationship exists between the difficulties of the pandemic and PAID score in children, their parents, teens, and their parents. Although there was no significant correlation between pre-pandemic concerns and PAID scores among children, teens, and their parents, there was a significant correlation only in children's parents (P=0.021) [17]. In another report designed by Wu et al., psychological factors such as anxiety and stress in children did not alter significantly during the pandemic compared to the pre-pandemic period [18]. The psychosocial health score in Braune et al. study significantly upgraded after 6 months of remote consultation (P=0.04), but the physical health score did not reflect significant changes after 6 months [20].

Studies indicating glycemic control and lifestyle changes

According to a study by Lazzeroni et al., no significant increase in PA hour/week was observed in 15% of individuals who repeated telemedicine usage during the pandemic. A significant reduction in PA hour/week was also reported (P<0.001). Mean BMI z-score findings also indicated a non-significant decrease in scores during the pandemic. In general, they reported no significant changes in HbA1c level and daily insulin injections related to PA and dietary factors [11]. Cognigni et al. indicated that BMI scores in children with T1DM increased during the pandemic, but it was not significant. However, a significant relationship was observed between BMI and meal frequency (P=0.01). They found no significant correlations between BMI, PA, increased meal frequency, and pre-pandemic HbA1c levels [12]. Tornese et al. noted having or not having a routine PA at time 3 caused a significant change in TIR percentage (P=0.005). Moreover, children with routine PA had a marked difference in TIR between time 2 and time 3, in which the TIR of time 3 increased more than time 2 [5].

Predieri et al. presented PA hours decreased during the pandemic (P<0. 0001); but, the number of insulin injections did not alter significantly. Also, there was no discernible relationship between PA hours and CGM metrics. PA hours during the pandemic were reduced in

children in both puberty and pre-puberty groups (both P<0.05) [14]. In a study by Minuto et al. all 3 age groups such as 6≤ age <10 y, 10≤ age <14 , and 1≤ age <18 y showed changes in PA before and after the pandemic (P were 0.02, ≤0.0001, ≤0.0001, respectively). Children with PA ≥3 hours per week compared with those without PA had significant improvement in glycemic metrics including glucose SD, HbA1c, TIR, TAR, TAR (>250 mg/dL), and mean glucose (P=0.02, 0.002, 0.0001, 0.001, 0.002 and, 0.002, respectively) [15].

In a study by Mianowska et al., no significant relationship was observed between PAID score and BMI z-score in children, their parents, teens, and their parents [17]. By investigating the lifestyle of the patients in the Wu et al. study, sleep time (P=0.024), frequency of snacks (P=0.018), and time spent on diabetes management increased during the pandemic (P<0.001). They claimed that PA time decreased during the pandemic (P=0.004) [18]. In another study, Tinti et al. presented a reduction of PA hours in children during the pandemic (P<0.001) [21].

Studies indicating glycemic control and different diabetes technology (cost and availability)

Aiming to compare glucose monitoring devices' efficacy during the pandemic; Lazzeroni et al. did not find any significant variation between CGM or FGM and SMBG by evaluating daily insulin injections and HbA1c levels. Also, in patients treated with insulin injections, increased HbA1c levels were observed in patients undergoing MDI or insulin pump therapy compared to those treated with SAP (P=0.035). MDI treatment was also shown to be more effective than CSII in reducing HbA1c level which was not significant [11]. A significant association between diabetes technology including CSII and FGM / CGM methods with HbA1c improvement was not concluded, according to Cognigni et al. study [12]. In a study by Predieri et al. between MDI and CSII treatment groups, TAR (>250 mg/dL, P<0.001) was decreased in the MDI group, and CV (P<0.001) and TBR (<70 mg/dL, P<0.0001) were reduced in the CSII group [14].

In another study designed by Nwosu et al. HbA1c level of patients with or without insulin pump users was not significantly reduced. In this regard, there was a correlation between improved HbA1c and CGM usage (P=0.019). Their results reflected metrics of point-of-care A1C (P=0.0012), CGM-estimated A1C (P=0.0076), mean glucose (P=0.022), and sensor usage (P=0.012) was enhanced. Daily insulin injections in CGM users did not change significantly. Conversely, in the patients not using CGM, HbA1c level did not reduce significantly after the pandemic, but daily insulin injections showed a significant increase (P<0.0001) [16]. Mianowska et al. presented that there was not a significant correlation between the type of glucose monitoring including CGM or SMBG and PAID score variations in children, their parents, teens, and their parents. The relationship between PAID score and the sort of insulin therapy (MDI or CSII) of children, their parents, teens, and their parents was also not significant [17].

Wu et al. found no significant difference in insulin injection in children during the pandemic. Patient use of outpatient clinics decreased significantly (P=0.002), whereas the use of online medical services increased (P=0.011) [18]. Correlation between type of insulin treatment and CGM metric by Lombardo et al study; TIR and TAR augmented during the pandemic in the MDI group (P of both=0.004) but TBR, CV, and GMI did not alter significantly. TIR (P=0.002), TAR (P=0.002), and GMI (P=0.003) values ameliorated in the CSII group; but changes were not significant for TBR and CV metrics. In the HCL group, patients experienced an improvement in TIR (P<0.001), TAR (P=0.001), and CV (P=0.005) during the pandemic, while TBR and GMI did not alter significantly [19]. Despite, the increase in CGM use in children with T1DM during the pandemic period (P=0.006), insulin injection was raised according to Tinti et al. study (P=0.004) [21].

Studies indicating glycemic control and socioeconomic factors (including age and sociodemographic, cost, insulin availability, etc.)

In a study designed by Cusinato et al., the interaction between psychological factors and glycemic control during a pandemic was analyzed. They argued that there was no correlation between demographic features such as age, gender, and TIR alteration [10]. By measuring CGM metrics from children during COVID-19 pandemic, Avivit Brener et al. found a relationship between age and lower socioeconomic condition according to delta-TIR and delta-mean glucose (F=4.416, P=0.019 and F=4.459, P=0.018), respectively. A higher CV value was also reported for cases <10 years compared to ≥10 years (P=0.005). They showed a correlation between TIR and patients' age, with cases with improved TIR being older than those with poor or stable TIR (P=0.028) [6]. According to Lazzeroni et al. there was no significant difference in HbA1c values between men and women [11]. Similar to previous studies, the relationship between HbA1c improvement with age and sex of patients in Cognigni et al. study was not significant [12].

Evaluating CGM metrics in children with T1DM during the pandemic, Predieri et al. argued that there was no correlation between gender differences and glycemic control. They also reported an increase in TIR (70-180 mg/dL, P=0.003), and TAR (>180 mg/dL, P=0.024) in pre-pubertal children, whereas reduced TBR (<70 mg/dL, P=0.003) in the pubertal group [14]. According to Nwosu et al., changes in HbA1c levels in children between males and females during and pre-pandemic were not significant. The change in CGM-estimated A1c was significant in females (P=0.03), unlike in males [16].

A comparison of PAID scores between males and females by Mianowska et al. was not significant for children during and pre-pandemic, their parents, and teens' parents, but not for teens (P=0.028). By ascertaining the interaction between age and PAID score they found no significant relationship between changes in PAID score and age of children, teens, and their parents, but this relationship was significant for children's parents (P=0.032) [17]. Lombardo et al. demonstrated that TIR (P<0.001), TAR (P<0.001), and GMI (P=0.008) improved in children aged 5-9 years, whereas TBR and CV did not change significantly. A significant increase was also found in TIR (P=0.004), TAR (P=0.003), and GMI values in children aged 10-14 years (P=0.016), whereas changes were not significant in TBR and CV. For children aged 15-18 years, TIR (P=0.001) and TAR values ameliorated (P=0.007), but changes in TBR, CV, and GMI metrics were not significant [19].

Discussion

In general, the interaction between glycemic control and pandemics in children with T1DM depends on lifestyle (including diet, physical activity, personal hygiene, etc.), family financial and emotional support, demographic findings, diabetes technology, and mental state [10]. This article reviewed studies focusing on the potential impact of the COVID-19 pandemic on glycemic control in children and adolescents with T1DM under 18 years of age. These potential factors generally include factors such as psychology telemedicine, lifestyle, diabetes technology, caregiver role, and socioeconomic factors. Although some studies reported stable glycemic control during the pandemic, most studies represented good glycemic control according to glucose profiles and CGM metrics. The pandemic inadvertently led to a healthier quality of life, greater use of diabetes technologies, and more accurate monitoring of diabetes care telemedicine displayed a special role in their glycemic improvement.

Although age was not clearly associated with glycemic control in T1DM during the pandemic period, glucose variability was observed between different age groups. Considerably, patients in the age range of toddlers are under family support; patients in a range of adolescents have better self-care while patients between these two groups have variable glycemic control due to their function and nutritional status. Executive behavior is a key factor during the pandemic period, patients in this age group would be expected to experience greater glucose excursions and poorer glycemic than other groups [6]. A meaningful reduction in PAID score was observed in teens during the pandemic, with the female sex experiencing a further decrease. However, children did not experience meaningful alteration of DD. They argued that pandemic-related stress did not interfere with their disease management owing to the caregivers' role [17].

The pandemic has created limitations in patients and their care, especially in the evaluation of glycemic control [6]. Adolescents are expected to experience better metabolic control than younger people due to their adaptability to pandemic conditions and their favorable relationship with telemedicine [11]. CGM users reported their insulin dose was adjusted by their caregivers despite changes in lifestyle and PA during the pandemic [21]. Also, the different situation of patients such as method availability and diabetes technology is important because it reduces the stress associated with diabetes management by improving glucose metrics [23]. Considerably, misinterpretation of glycemic control analyses should be taken into account due to the short duration of the pandemic. For example, to assess the role of CGM during a pandemic, efficacy should be studied over time among CGM and non-CGM users [6].

COVID-19 is a risk factor for mental health and has been demonstrated to increase problems for children during the pandemic. Restrictions caused by the pandemic induced various psychological changes such as depression, anger, sleep disturbances, and anxiety. [24]. Socioeconomic status directly impacts the role of caregivers and has a two-way relationship with patient health status. Therefore, healthcare systems should consider programs to manage these conditions [25]. As a result, psychological problems have a role in the patient's health status and the caregiver's role. Therefore, to clarify the role of these factors in influencing glycemic control, it is better to investigate these factors in the long run [10].

Consuming high-calorie diets, reducing daily activities, increasing screen time, and decreasing PA time are the factors disrupting proper metabolic profiles [25, 26]. An important point is to maintain PA and adequate nutrition, the proper implementation of which requires pa-

tient attention which is as important as insulin therapy and the supportive role of caregivers [26, 27]. During a pandemic, patients should share their condition with their medical team. A strict diet and PA under the strict supervision of a medical team have a significant impact on metabolic control. An important thing is dietary habits and PA should not be self-reported and having accurate criteria is a suitable solution.

Conclusion

Overall, children and adolescents experienced adequate glycemic control during the pandemic period, in which telemedicine played an important role. Management of lifestyle, PA, diabetes technology, psychosocial health, and socioeconomic status are also potential factors for improving glycemic control.

Study Limitations

Large age-specific studies over longer periods are needed to more accurately determine the glycemic status of patients and the impact of the pandemic. Further studies considering the pre-, during-, and post-pandemic periods will also help to better assess the effects of quarantine on glycemic control in these patients. Also, evaluation of the outcomes of self-reported data such as PA and eating habits should be analyzed more cautiously.

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

Conflicts of interest

The authors declared no conflict of interest.

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