International Journal of Health Sciences (IJHS)

Special Issue IX

The International Journal of Health Sciences (IJHS), an academic, interdisciplinary, and double-blind peer-reviewed publication ISSN 2550-696X (Online) ISSN 2550-6978 (Print), publishes scholarly articles on international students in tertiary education, secondary education, and other educational settings that make significant contributions to research, policy, and practice in the internationalization of higher education. Articles in the journal are freely available to the public thanks to our institutional sponsors.

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DOI: https://doi.org/10.53730/ijhs.v6nS9.2022

PUBLISHED: 31-12-2023

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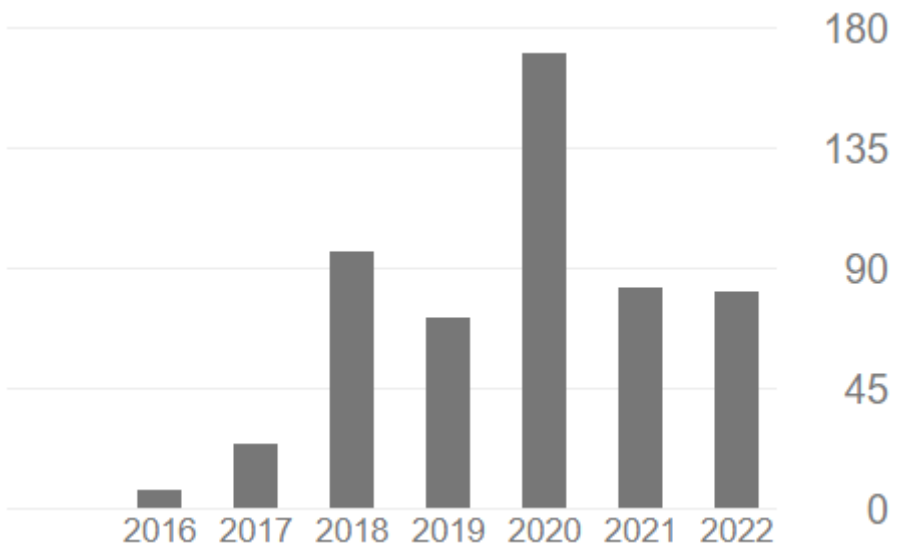

Last updated: 1 January 2023

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How to Cite:
Deakandi, W. Y., Farahdina, F. ., Putri, Q. A. N., Nuzula, T. M., Fedora, K., Aina, Q., Rochmah, N., & Faizi, M. (2022). The glycemic control among type 1 diabetes children pre and during COVID-19 pandemic: A systematic review and meta-analysis. *International Journal of Health Sciences*, *6*(S9), 2171–2182. https://doi.org/10.53730/ijhs.v6nS9.12893

The glycemic control among type 1 diabetes children pre and during COVID-19 pandemic: A systematic review and meta-analysis

Wika Y. Deakandi
Faculty of Medicine, Universitas Islam Malang, Malang, Indonesia

Farahdina Farahdina
Faculty of Medicine, Department of child health, Dr. Soetomo General Hospital, Universitas Airlangga, Surabaya, East Java, Indonesia

Qurrota A. N. Putri
Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Tyas M. Nuzula
Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Katherine Fedora
Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Qorri Aina
Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Nur Rochmah
Faculty of Medicine, Department of child health, Dr. Soetomo General Hospital, Universitas Airlangga, Surabaya, East Java, Indonesia
Corresponding author email: nur-r@fk.unair.ac.id

Muhammad Faizi
Faculty of Medicine, Department of child health, Dr. Soetomo General Hospital, Universitas Airlangga, Surabaya, East Java, Indonesia

***Abstract*--**The impact of the COVID-19 pandemic on glycemic control in Type 1 Diabetes Mellitus (T1DM) patients is still evolving. This study aims to assess the negative effect of the COVID-19 pandemic on mean glucose and glycated hemoglobin (HbA1c) in patients with T1DM. This meta-analysis study using the PRISMA framework method with the search strategy according to the population, intervention, control, and outcome (PICO) model. Relevant articles were searched in 4 databases. The results identified the HbA1c and mean glucose. The

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
Manuscript submitted: 9 May 2022, Manuscript revised: 18 July 2022, Accepted for publication: 27 August 2022

COVID-19 pandemic caused an increase in the HbA1c levels (%) compared to the pre-COVID group with a mean difference of -1.06 (95% CI: -1.44, -0.69; p<0.00001). Meanwhile, the mean glucose (mg/dL) decreased during-COVID-19 pandemic with a mean difference of -2.32 (95% CI: -4.40, -0.23; p=0.03). Ten studies with a total of 1615 subjects contributed for HbA1c analysis (during-COVID-19, n = 615; pre-COVID, n = 1000). A total of 1164 patients from six studies with a mean glucose analysis were included (during-COVID-19, n = 418; pre-COVID, n = 746). This study found that the COVID-19 pandemic significantly increased the levels of HbA1c and decreased mean glucose in patients with T1DM, but further studies need to be evaluated.

***Keywords*---**HbA1c, T1DM, Mean glucose, COVID-19.

Introduction

Type-1 Diabetes Mellitus (T1DM) is a condition of insufficient secretion of insulin caused by autoimmune against beta pancreas. T1DM can be considered one of the most common non-communicable diseases in children. The prevalence of T1DM in the USA was 1.93 /1000 in 2009 and in some central European countries, the annual increase in the incidence rate of T1DM in this period was 3.4% (Shojaeian and Mehri-Ghahfarrokhi, 2018). In Indonesia, the prevalence is predicted to increase approximately sevenfold over a decade from 3.88 to 28.19 per 100 million in 2010. However, there are still many underdiagnosed and misdiagnosed, making it difficult to determine the actual frequency of T1DM among Indonesian children (Pulungan et al., 2021).

T1DM is a chronic condition of an autoimmune disease associated with the specific destruction of the insulin-producing beta pancreas which results in increased glucose and HbA1c level (Sperling et al., 2021). Insulin deficiency leads to lipolysis alteration and an increased level of free fatty acids which inhibit the glucose metabolism in the liver and muscle. In some patients with newly diagnosed T1DM, a part of beta-cells are still functional so with insulin administration, the remaining beta-cell function improves and decreases the demand for additional insulin. When a diabetic patient experiences good glucose control, this stage is referred to as the honeymoon period (Marcdante and Kliegman, 2019).

Coronavirus Disease 2019 (COVID-19) has caused the Indonesian and global public health crisis (Christoforidis et al., 2020). Some studies showed that COVID-19 causes a high mortality and morbidity rate among people with diabetes mellitus. However, there were no hospitalization-required cases of COVID-19 and T1DM. Additionally, this study demonstrated that T1DM patients had higher total blood glucose levels post-COVID-19 than pre-COVID-19 (Lee et al., 2022). In addition to insulin therapy, healthy eating habits, regular daily routines, and even exercise all significantly improve the control of diabetes. The lockdown significantly altered peoples' everyday routines, particularly those of children with T1DM. For children and adolescents with T1DM, these factors may contribute to

increased glycemic control (Christoforidis et al., 2020). The changes in daily routines and the medical aspects of people with T1DM can have a great effect on glycemic control (Duarte et al., 2022). Therefore, it is necessary to make a systematic review and meta-analysis of the differences in glucose and HbA1c levels before and during the pandemic in children with T1DM.

Method

The procedures, such as record collection, extraction of data, quality assessment, and statistical analysis based on the preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) (Page et al., 2021).

Data Sources

A systemic electronic-based literature search was done from 2 to 28 February 2022 to assess the effect of the COVID-19 pandemic on glycemic control in children with T1DM. The search was conducted using the keyword constructed on Medical Subject Heading (meSH) and other additional keywords: (COVID) AND [(pandemic) OR (lockdown) OR (quarantine)] AND (Type 1 Diabetes Mellitus) AND [(glycemic control) OR (glucose level)] AND [(children) OR (pediatric)]. The literature search was performed in PubMed, Embase, Cochrane, and Directory of Open Access Journals (DOAJ) databases.

Study Selection

The articles included in this analysis were independently screened by two authors (TMN and QA) based on the following eligibility criteria: 1) assessing the impact of the COVID-19 pandemic on glycemic control of T1DM, 2) having required the standard analytic calculation, 3) observational studies. The exclusion criteria were: 1) irrelevant titles and abstracts, 2) incomplete data, 3) literature reviews, editorials, and letters, 4) non-English language articles. The potential covariate in this paper was the COVID-19 pandemic's roles. While the outcome was glycemic control as measured by HbA1c (%) and mean glucose (mg/dL). The covariates were determined after preliminary searching for covariates screening to our study calculations.

Data extraction

The following details were selected from every paper: 1) Author name, 2) publication year, 3) the number of cases and control or sample size, 4) sample's age, 5) ethnicity, 6) main findings, 7) HbA1c (%) in Pre- and during-COVID-19 Pandemic (8) Mean glucose in Pre- and during-COVID-19 Pandemic. Two authors extracted the data to reduce human error and produce highly reliable data (FF and WYD). If a discrepancy was discovered, we had a group discussion.

The quality paper for meta-analysis was evaluated with the New Castle-Ottawa Scale (NOS) which ranged from 0 to 9 points. The NOS had 3 items: selection of patients (4 points), group comparability (2 points), and exposure assessment (3 points). The interpretation was low quality (score ≤ 4), medium quality (score 5-6), or high quality (score ≥ 7). The two researchers (FF and WY) conducted a NOS

assessment, and if discrepancies were identified, discussions were held with the senior researcher (NR and MF).

Statistical analysis

The glycemic control parameter (HbA1c and mean glucose) of T1DM children before and during the pandemic were analyzed as continuous variables using the mean difference and 95% confidence interval (CI). The Z-test was used to assess the overall effect ($p < 0.05$). Before identifying key factors, the measure for data heterogeneity using the I^2 test and publication bias. When heterogeneity was present ($I2 > 50\%$ or $p < 0.10$), a random-effects model was implemented. Contrarily, the fixed-effects model was applied. Egger's tests were used to measure the publication bias ($p < 0.05$). The correlation and effect estimates were then plotted using a forest diagram. Data were analyzed using Review Manager version 5.3 (Revman Cochrane, London). Two independent authors (QAN and KF) conducted a statistical analysis to avoid methodological errors.

Results

Eligible studies

The searching strategy evaluates 135 related studies. There were 114 papers removed due to irrelevant titles and abstracts. In total, 21 papers were included for full-text review. Nine of them were eliminated due to insufficient data ($n = 4$), or review ($n = 4$). Finally, 13 papers were included in this analysis. This paper's selection process is shown in Figure 1 and Table 1 summarizes the baseline parameters.

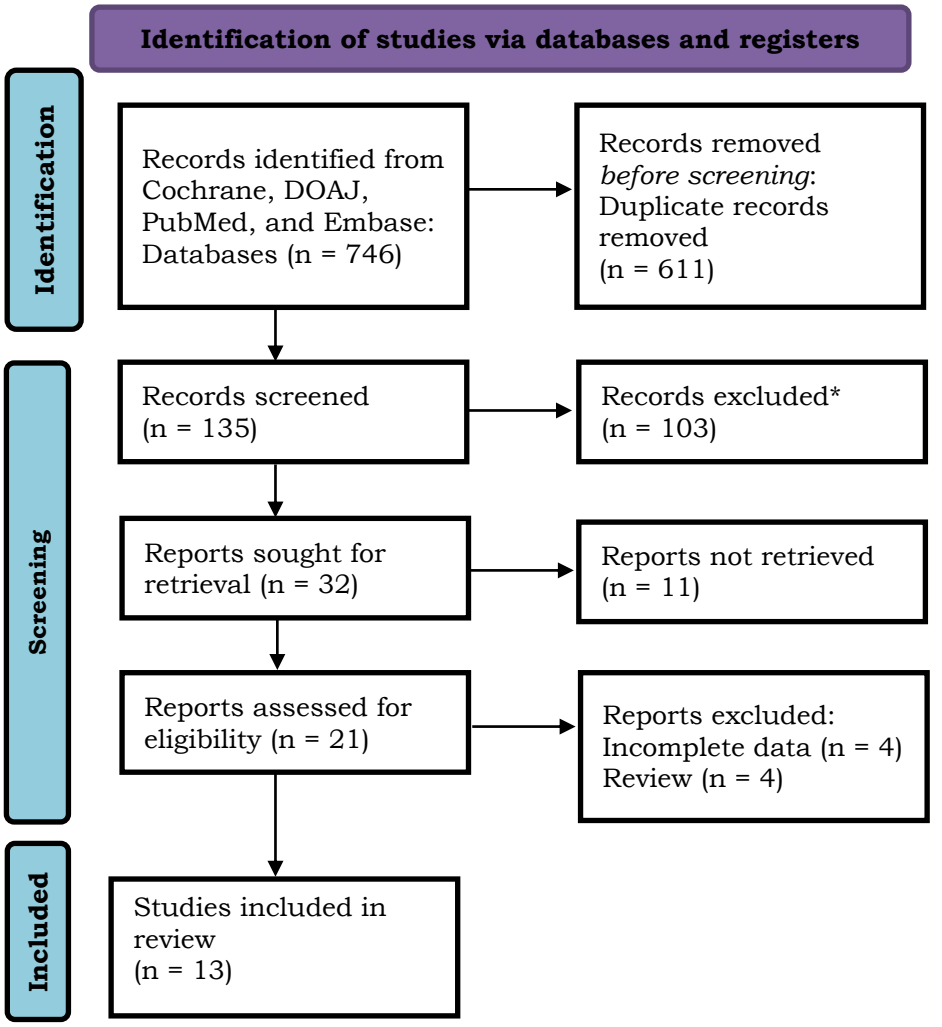


Figure 1. Paper selection pathway

Table 1. Baseline characteristics of articles included in our study

Author & year	Sample size	Gender (male)	Location	Study design	Age (years) (mean ± SD)	NOS	Main findings
Alaqeel et al 202	260	120	Saudi Arabia	Retrospective	9.8 ± 0.2	6	Lockdown affected T1DM children and increased the incidence of DKA.
Bogale et al 2020	412	241	Pennsylvania	Retrospective	10.0 ± 4.29	7	A similar frequency of DKA was seen in newly diagnosed children with T1DM.
Brener et al 2020	102	54	Israel	Retrospective	11.2 ± 3.8	7	During the COVID-19 pandemic, CGM in T1DM patients remained mostly steady.
Cheng et al 2021	93	44	Malaysia	Retrospective	11.08 ± 3.47	6	Adverse impact on HbA1C mostly seen in T2DM patient
Christoforidis et al 2020	34	16	Greece	Retrospective	11.37 ± 4.45	7	The mean glucose levels did not differ from the COVID-19 pandemic lockdown.
Duarte et al 2022	100	59	Portugal	Retrospective	12.5 ± 4	7	Only the 10–13 age group showed a significant change in glycemic control before and after lockdown.
Elhenawy 2021	115	56	Egypt	Retrospective	-	7	In children with T1DM, the lockdown had a negative effect on glycemic control.
Kostopoulou et al 2021	38	21	Greece	Prospective	9.44 ± 3.72	7	The severity of newly diagnosed T1DM increased in the first year of the COVID-19 pandemic.
Lee et al 2021	45	23	Korea	Retrospective	15.83 ± 6.13	8	Children with T1DM had an increase in blood glucose levels.
Marigliano et al 2021	233	131	Italy	Retrospective	13.9 ± 4.4	7	During the COVID-19 lockdown, children with T1DM had better glycemic control.
McGlacken-Byrne et al 2021	47	24	London	Retrospective	11 ± 2.7	7	During the COVID-19 pandemic, T1DM symptoms were more severe than usual.
Rochmah et al 2021	33	18	Indonesia	Prospective	11.97 ± 2.91	7	During the COVID-19 pandemic, the Quality of Life (QoL) of children with T1DM increased after receiving online

							education.
Tinti et al 2021	66	46	Italy	Retrospective	11.6 ± 4.5	7	During the COVID-19 lockdown, Continuous Glucose Monitoring (CGM) was enhanced.

Note, CGM, Continuous Glucose Monitoring

Data Synthesis

This study included 13 papers assessing the effect of the COVID-19 pandemic on glycemic control of T1DM. The effect of the COVID-19 pandemic is measured by decreasing HbA1C and mean glucose levels. This pooled analysis found that COVID-19 pandemic affects the reduction of HbA1c (mean diff: -1.06 [95%CI: -1.44, -0.69], p < 0.00001) and mean glucose (mean diff: -2.32 [95%CI: -4.40, -0.23], p = 0.03). The overview of the association between the COVID-19 pandemic and outcome variables in the present study is presented in Table 2.

Source of Heterogeneity

This analysis found heterogeneity in HbA1C variables; therefore, a random effect model was used. While there was no evidence of heterogeneity in the mean glucose variables, therefore a fixed-effect model was used. The result of heterogeneity among studies is shown in Table 2.

Potential Publication Bias

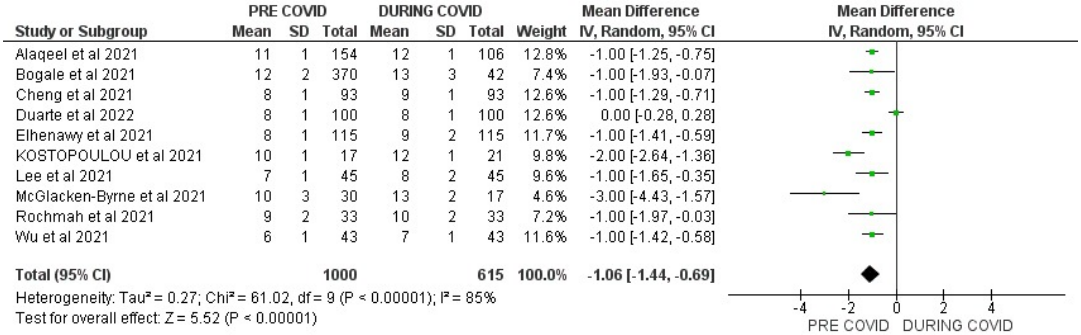
Egger's test was used to examine the publication bias in the studies. There was no publication bias in this study and the result was shown in Table 2.

Table 2. Summary of the glycemic control in children with T1DM pre and during the COVID-19 pandemic

Parameters	Outcome measure		Std diff in mean / Odds Ratio in number of events	95%CI	pE	pHet	p
	Pre pandemic	During pandemic					
HbA1C (%)	8.9 ± 1.3	13 ± 2.6	-1.06	-1.44- -0.69	0.390	<0.0000001	<0.0000001
Mean Glucose (mg/dL)	222.16 ± 57.33	218 ± 59.5	-2.32	-4.40 - -0.23	0.239	0.04	0.03

Note, data were presented in mean ± SD; CI, confidence int

a)



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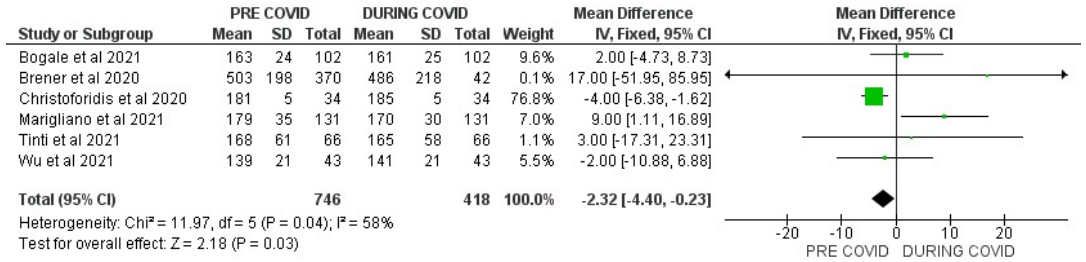

Figure 2. Forest Plot of the glycemic control in children with T1DM before and during COVID-19 Pandemic a) HbA1c b) Mean glucose

Discussion

A total of thirteen studies examined the association between HbA1c and mean glucose in T1DM in the pandemic era. This meta-analysis showed that HbA1c and mean glucose levels were lower before than after the pandemic era. Lockdown in the pandemic era hurts glycemic control in T1DM children (Elhenawy and Eltonbary, 2021), especially 10-13 years of age.[7] However, the severity of T1DM also increases during the pandemic era (Kostopoulou et al., 2021 and Mc-Glacken-Bryne et al., 2021). T1DM is a disease caused by the immune system against host cells, particularly beta-cell. This immune cell identified beta-cell as antigens and the proinflammatory responses initiated. Beta-cell destruction occurs as a result of the immune system being exposed to beta-cell antigens by the antigen-presenting cells (APCs). The necrosis of this cell induces the antigen to initiate destruction on another part of beta cells. This process led to increasing the mean glucose level in T1DM in children (Saberzadh-Ardestani et al., 2018). HbA1c level showed glucose attached to haemoglobin has been over the past three months and may be more understandable to T1DM children (Sikaris, 2009).

A study by Aleqeel et al showed that lockdown impacted children with T1DM and led to more complications such as DKA (Alqeel et al., 2021). However, another study found that there were no changes in the risk of diabetes complications among paediatric patients with T1DM and that T2DM patients were more likely to experience negative effects (Bogale et al., 2021 and Cheng et al., 2021). DKA is caused by three conditions which are increased glucose, ketone, and anion gap which is caused by increased gluconeogenesis; glycogenolysis, and decreased glucose uptake by the internal organ, muscle, and adipose tissue (Gosmanov et al., 2000).

Some factors contribute to the mean glucose and HbA1 in T1DM during the pandemic era. In the pandemic era, children with T1DM reduce physical activity and dietary compliance at home (Grabia et al., 2021). The restrictions on daily life such as school attendance also led to a sedentary lifestyle. COVID-19 lockdown causes difficulty in measuring self-blood glucose due to difficulty to get blood sugar measuring devices and insulin injections (Lee et al., 2022). Other factors such as restricted medication, lack of follow-up, stress, and anxiety caused by lockdown also increase the glucose level. Factors associated with the parents also can contribute to the glycemic control of the children. High socioeconomic status, knowledge, and disease awareness are associated with good conditions in T1DM children (Pal, 2021).

T1DM children need glucose monitoring to prevent complications. Continuous Glucose Monitoring (CGM) in patients with T1DM was relatively stable during the COVID-19 pandemic (Brener et al., 2020) and also improve the glycemic control in T1DM during lockdown (Tinti et al., 2021). During the pandemic era, most children used smartphones to study in the classroom virtually. Online education about T1DM to children can increase their quality of life (Rochmah et al., 2021). Further research is needed to know the effective method to control the glucose and HbA1c level in children with T1DM.

According to the author's knowledge, this is the first systematic review and meta-analysis that evaluate the glycemic control among T1DM children pre and during the COVID-19 pandemic. This study also has some limitations. Firstly, some of the studies have small subjects that can cause different signification. Secondly, this study didn't analyse the treatment strategy and complications during the pandemic era. We recommend more studies with a larger sample and studies about treatment strategies and complications during pandemics.

Conclusion

The COVID-19 pandemic effect increases the level of HbA1c and decreases the mean glucose level in children with T1DM. However, more studies need to be evaluated.

Acknowledgment
None

Funding
None

Competing interest
No conflicts of interest related to this work

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