Systematic Review / Meta-analysis

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Immediate impacts of COVID-19 vaccination on glycemic control in type 1 diabetes mellitus: a systematic review and meta-analysis

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Objective: COVID-19 vaccination is recommended in diabetic patients since diabetes is associated with worse clinical outcomes in COVID-19 infection. The safety profile of different types of COVID-19 vaccines, especially on glycemic control, can be explored due to availability of data from continuous glucose monitoring (CGM) devices. This meta-analysis aimed to quantify the impact of COVID-19 vaccination on glycemic control in patients with type 1 diabetes mellitus (T1DM).

Methods: A systematic search of PubMed, Embase, and Google Scholar was conducted using a search strategy for studies published till January 2023 in English language. Comparative observational studies reporting glycemic control obtained from CGM before and after COVID-19 vaccination in T1DM patients were included. The primary outcome was time in range (TIR) metric of proportion of glucose results falling within the range: 3.9–10 mmol/l. Other outcomes were time above range (TAR) (> 10 mmol/l), time below range (TBR) (< 3.9 mmol/l), coefficient of variation (CV), and mean blood glucose levels. The pooled outcomes were compared pre-vaccination and post-vaccination using Hedges' g (HG) with 95% CI.

Results: A total of seven studies (632 participants) were included in the meta-analysis. COVID-19 vaccination caused small and statistically insignificant decrease in TIR after both the first (HG = 0.21, 95% CI: – 0.02 to 0.44, $P = 0.07$) and second dose (HG = 0.09, 95% CI: – 0.04 to 0.21, $P = 0.19$). Likewise, TAR was not affected after neither first (HG = – 0.09, 95% CI: – 0.22 to 0.03, $P = 0.12$) nor second vaccine dose (HG = – 0.07, 95% CI: – 0.21 to 0.06, $P = 0.30$). Likewise, TBR, mean blood glucose levels, and CV were not significantly altered following uptake of either of the doses.

Conclusion: COVID-19 vaccination has an excellent safety profile in T1DM patients owing to its minimal impacts on immediate glycemic control.

Keywords: adverse drug reactions, continuous glucose monitoring, COVID-19, time in range, vaccination

Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by the selective destruction of insulin-producing beta cells in the pancreas by immune cells[1]. Apart from the inability to regulate blood sugar levels, an increased risk of serious infections also exists for T1DM patients[2]. Patients with T1DM have been found to develop severe outcomes during a SARS-CoV-2 infection, with a hazard ratio of 1.58 when compared to those without the disease[2].

The vaccination against COVID-19 is ongoing worldwide. The various types of COVID-19 vaccines include DNA vaccines, mRNA vaccines, non-replicating viral vector vaccines, inactivated vaccines, live attenuated vaccines, subunit vaccines, and trained immunity-based vaccines[3]. The vaccines can cause local adverse effects like pain, tenderness, redness, and swelling at the site of injection and systemic effects like fever, headache, rash, myalgia, and arthralgia. Some other less common adverse events following immunization (AEFI) are thrombosis and thrombocytopenia,

HIGHLIGHTS

- The COVID-19 vaccination caused small and statistically insignificant decrease in time in range (TIR) after both the first and second doses.
- The time below range, time above range mean blood glucose levels, were not significantly altered following vaccine uptake.
- COVID-19 vaccination has an excellent safety profile in in type 1 diabetes mellitus patients owing to its minimal impacts on immediate glycemic control.

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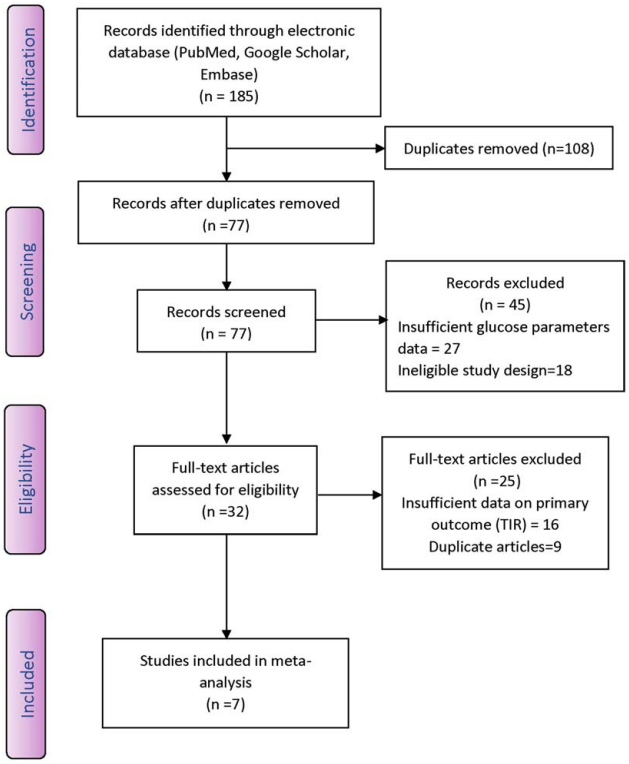

Figure 1. PRISMA Flow diagram of selection of studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

myocarditis or pericarditis, inflammatory myositis, autoimmune diseases such as Guillain-Barré syndrome, and life-threatening allergic reactions known as anaphylaxis[4–6]. All of these reactions are the result of the activation of multiple inflammatory pathways as a response to vaccination. Such reactions could potentially impair glucose control in T1DM patients. Multiple cases of vaccine-induced hyperglycaemia requiring hospitalization have been observed in patients even without a prior history of DM[7,8]. These have led to concerns about the temporary instability of blood glucose levels post-vaccination in T1DM. However, primary prevention remains the mainstay for mitigating the risks associated with COVID-19 since anti-COVID-19 vaccination is associated with a lower fatality risk in T1DM[9].

Continuous glucose monitoring (CGM) devices that display an estimate of interstitial glucose levels, along with trends in direction, are increasingly being adopted for routine care in people with T1DM. The sensor component of the CGM system has the capability to acquire readings at intervals of a few minutes. The CGM system enables the automated transmission of the user's most recent blood sugar readings to a device or mobile platform using Bluetooth technology. A type of CGM called a flash glucose monitor requires the user to wave (scan) the device over the sensor in order to obtain interstitial glucose measurements. In contrast to flash glucose monitoring systems, certain CGM devices provide the capability to establish communication with an insulin pump, a crucial feature for the implementation of closed-loop systems. By utilizing this comprehensive dataset, healthcare professionals may implement enduring modifications in pharmacotherapy tailored to the individual lifestyle of each patient[10]. The safety profile of different COVID-19 vaccines,

Table 1
Characteristics of the studies included in the meta-analysis

Study	Study design	Study site	Sample size	Type of monitoring	Male:female ratio	Age (mean)	Available parameters	Vaccines used
Dicembrini *et al.*[19]	Cohort study	Italy	221	FGM	55:45	49.5[a]	MBGL, CV, TIR, TAR, TBR (pre-vaccination and post-vaccination) of both doses	mRNA-1273
Gouda[21]	Cohort study	Greece	70	CGM	53:47	12.56 ± 3.37	TIR (pre-vaccination and post-vaccination) of both doses, MBGL	mRNA-Pfizer/BioNTech
D' Addio[22]	Cohort study	Italy	150	CGM	55:45	45.9 ± 9.0	TIR, TAR, TBR, CV, MBGL (pre-vaccination and post-vaccination) of both doses	mRNA (BNT162b2, mRNA-1273)
Piccini *et al.*[23]	Cohort study	Italy	39	AHCLs: 24 CGM: 15	AHCLs: 63:37 CGM: 47:53	AHCL: 18.4 ± 2.4 CGM: 18.3 ± 1.5	TIR (pre-vaccination and post-vaccination) of 1st dose CV as a whole (AHCL, CGM) (pre-vaccination and post-vaccination) of first dose	Moderna: 54% Pfizer- BioNTech vaccines: 46% Moderna: 67% Pfizer- BioNTech vaccines: 33%
Heald *et al.*[24]	Cohort study	UK	20	CGM	45:55	53 (26–70)	TIR, TAR, TBR, CV, MBGL (pre-vaccination and post-vaccination) of 1st dose of vaccine	Pfizer/Biontech = 8 Oxford/ AstraZeneca = 12
Heald *et al.*[24]	Cohort study	UK	97	FGM	47:53	44	TIR, TAR, TBR, CV, MBGL (pre-vaccination and post-vaccination) of 1st dose of vaccine	Pfizer/Biontech = 45 Oxford/ AstraZeneca = 52
daD'onofrio[25]	Cohort study	Italy	35	CGM	60:40	36 (27–51)	TIR, TAR, TBR, CV (pre-vaccination and post-vaccination) of both doses	mRNA: BNT162b2

AHCL, advanced hybrid closed loop; CGM, continuous glucose monitoring; CV, coefficient of variation; FGM, flash glucose monitoring; MBGL, mean blood glucose level; TAR, time above range; TBR, time below range; TIR, time in range.
[a]Median age.

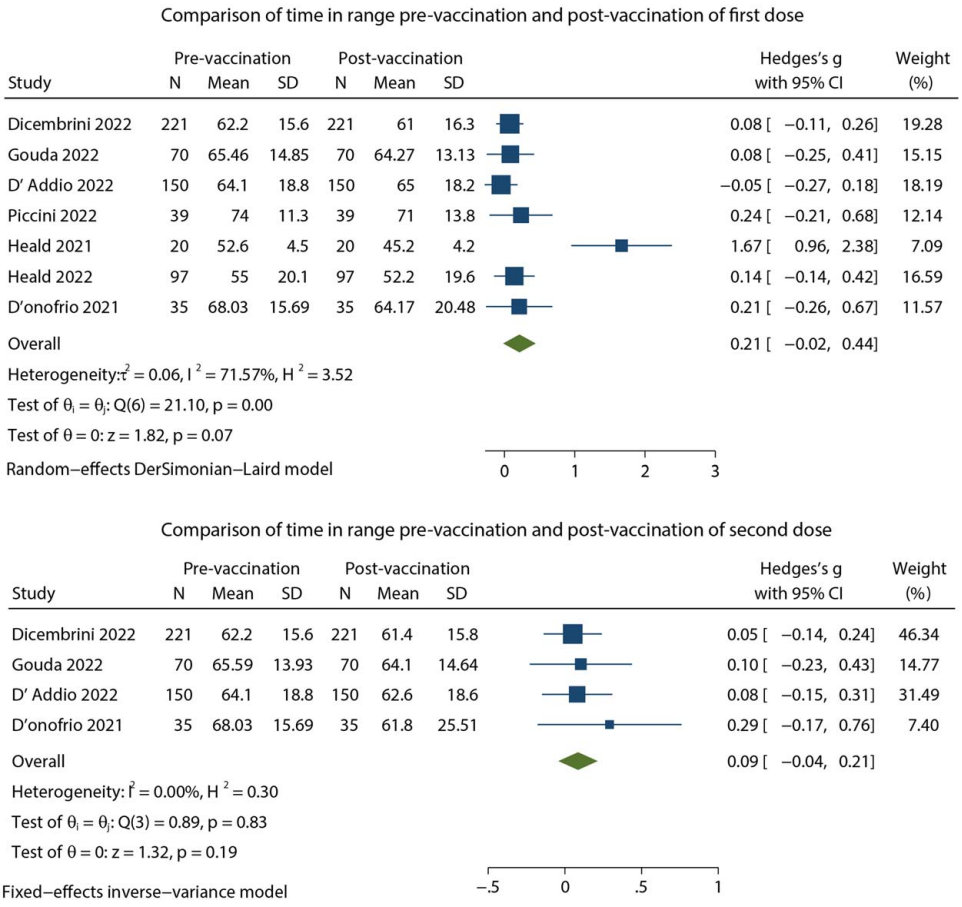

Figure 2. Meta-analysis of comparison of time in range pre-vaccination and post-vaccination.

especially in terms of glycemic control, can be investigated due to the availability of data from CGM. The aim of this meta-analysis was to quantify the immediate impacts of COVID-19 vaccination on glycemic control in T1DM patients.

Methodology

Ethical compliance and guideline

The systematic review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Supplemental Digital Content 1, http://links.lww.com/MS9/A358) 2020 guidelines and criteria[11]. PROSPERO was used to register the review protocol (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023423467). The Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR2, Supplemental Digital Content 2, http://links.lww.com/MS9/A359) checklist, an appraisal tool, was also utilized to assess this study[12]. The overall quality of our review was rated moderate by the AMSTAR2 tool.

Publication search strategy

A systematic search of medical databases (PubMed, Embase, and Google Scholar) was conducted independently by two reviewers using thesame search strategy for studies published till January 2023 in English. A database search was conducted using Boolean logic, and the Boolean search operators "AND" and "OR" were utilized to connect search words. Relevant articles were screened from the bibliography of the retrieved articles. The following keywords were used to search: SARS-CoV-2, caccination, glycemic control, diabetes mellitus, continuous glucose monitoring. The corresponding MeSH terms of these keywords were also used to search the articles in the databases. A detailed search strategy used in the literature review can be accessed in Appendix 1 of the Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/A360. Since this is a meta-analysis, the need for ethical approval and informed consent is not mandatory. The ethical approval for each of the studies included in this study can be obtained from the original publications.

Selection strategy

Any comparative observational studies reporting on the immediate (within 14 days of vaccination) continuous glycemic control in the form of time in range% (TIR%) before and after COVID-19 vaccination in T1DM patients were included. Full-text irretrievable articles, editorials, letters, case series, case reports, opinion-based articles, and animal studies were excluded.

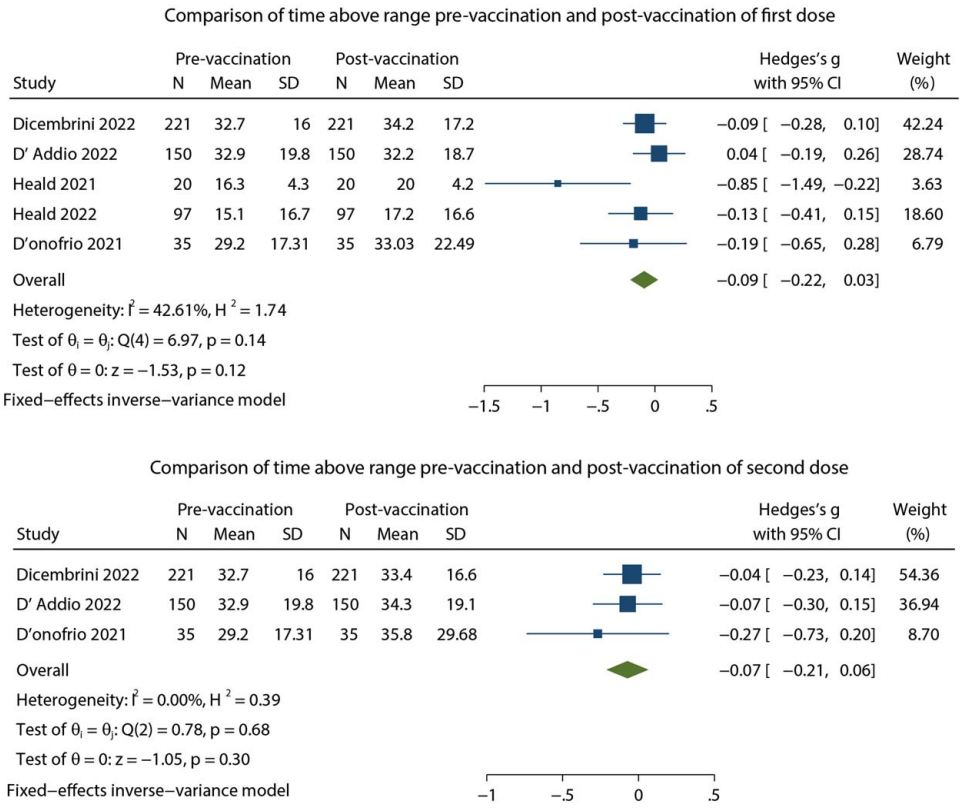

Figure 3. Meta-analysis of comparison of time above range pre-vaccination and post-vaccination.

Data extraction and quality assessment

Abstract screening and data extraction were performed independently by two researchers. Microsoft Excel version 2016 was used to extract the data from the original studies. The primary outcome was the TIR metric of proportion of glucose results falling within the range of 3.9–10 mmol/l. Other outcomes were time above range (TAR) (> 10 mmol/l), time below range (TBR) (< 3.9 mmol/l), coefficient of variation (CV), and mean blood glucose levels. The Newcastle-Ottawa Scale (https://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf) was used to assess the quality of each study, which were classified into three categories: selection[5], comparability[2], and exposure[3] (https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Two reviewers evaluated the study separately, and any discrepancies were resolved by discussion with the third reviewer. Studies with a score of 5 or above were considered eligible for inclusion, while those with a score greater than 7 were regarded as being of high quality. The details of quality assessment of the included studies are presented in Appendix 2 of the Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/A360.

Statistical analysis

Statistical analysis was performed using STATA version 17.0 (StataCorp). The pooled outcomes were compared pre- and post-vaccination using Hedges' g (HG) with a 95% CI. The data were pooled using either a random-effects or fixed-effects model. Statistical heterogeneity across the studies was assessed using the I^2 index (0–40%: not important; 30–60%: moderate heterogeneity; 50–90%: substantial heterogeneity; 75–100%: considerable heterogeneity), which indicates the percentage of total discrepancy due to variation in data[12]. When I^2 reached up to 50%, meta-analysis was performed using a fixed-effect model. When I^2 was greater than 50%, meta-analysis was performed using DerSimonian and Laird's random-effects model[13]. To illustrate the overall weighted mean estimations with 95% CIs, forest plots with 95% CIs were generated. Subgroup analysis was performed on the basis of country of study population, type of glucose monitoring system, and sample size of the study.

Statistical significance was defined as a *P* value of less than 0.05. Moreover, a sensitivity analysis was performed by omitting each individual study sequentially to check the stability and robustness of the pooled outcomes. Additionally, publication bias was estimated using Begg's correlation test and Egger's linear regression test. A *p* value greater than 0.05, along with the observation of symmetry in the funnel plot, indicated the absence of significant publication bias.

Results

Study characteristics

In total, 185 relevant articles were identified after a thorough database search. After the exclusion of duplicates and the articles that could not meet inclusion criteria, a total of seven studies were included in the meta-analysis. The systematic selection process of the articles included in the review has been illustrated with the

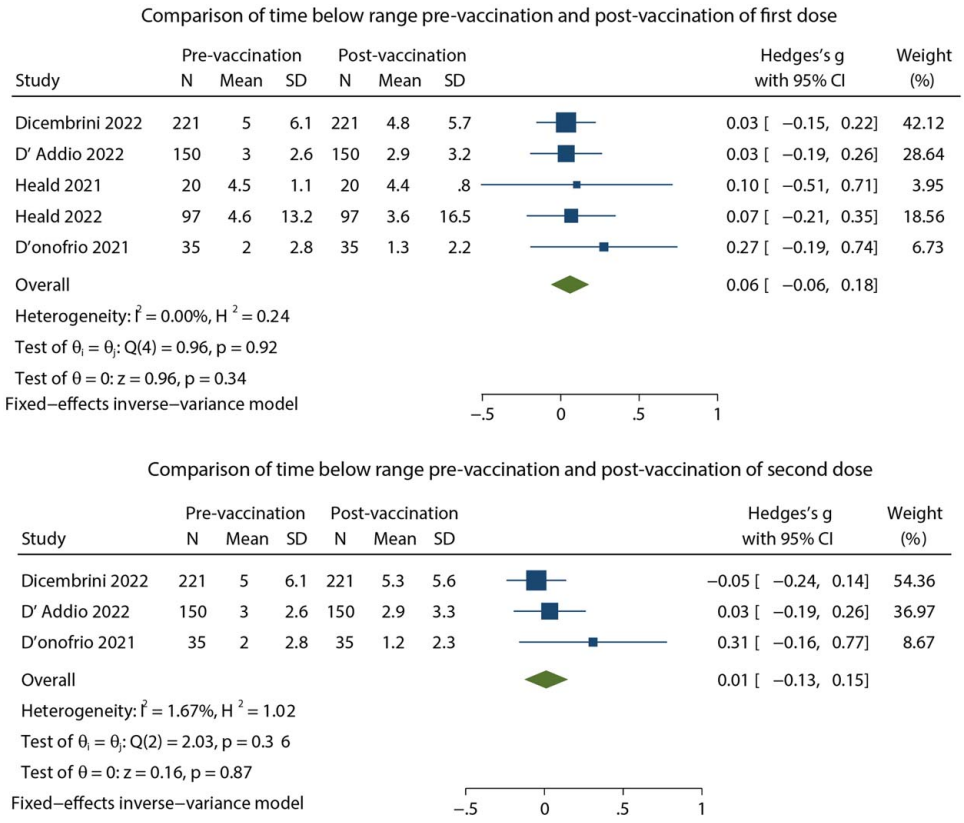

Figure 4. Meta-analysis of comparison of time below range pre-vaccination and post-vaccination.

flow diagram in Figure 1. All seven studies were retrospective observational studies. Four studies were conducted in Italy[14–17], two in the United Kingdom (UK)[18,19], and one in Greece[20]. All of them are monocentric studies. The studies were conducted in 2021 and 2022. The total sample size was 632, ranging from 20 to 221. Three studies utilized conventional CGM systems[15,17,20]; three studies used flash glucose monitoring[14,18,19]; and one study assessed patients under both CGM and an advanced hybrid closed-loop (AHCL) system[16]. The effect of the COVID-19 vaccination on various glycemic parameters is described below. The details of the studies are provided in Table 1.

Pooled outcomes of meta-analysis

Time in range

The COVID-19 vaccination had no significant influence on TIR after both the first and second doses. The COVID-19 vaccination caused a small and statistically insignificant decrease in TIR after both first (HG = 0.21, 95% CI: − 0.02 to 0.45, P = 0.07, I^2 = 71.57) and second dose of vaccination (HG = 0.09, 95% CI: − 0.04 to 0.21, P = 0.19, I^2 = 0%) (Fig. 2).

Other parameters

TAR was not increased after either the first (HG = − 0.09, 95% CI: − 0.22 to 0.03, P = 0.12, I^2 = 42.61%) or the second dose of the vaccines (HG = − 0.07, 95% CI: − 0.21 to 0.06, P = 0.30, I^2 = 0%) (Fig. 3). Likewise, TBR and CV were not significantly affected by either of the doses (Fig. 4 and Fig. 5). Similarly, the mean blood glucose levels were not significantly altered, suggesting that, on average, patients' blood glucose levels remained relatively fairly stable. Neither the first (HG = − 0.14, 95% CI: − 0.39 to 0.12, P = 0.29, I^2 = 69.51%) nor the second dose (HG = − 0.05, 95% CI: − 0.19 to 0.10, P = 0.51, I^2 = 0%) had a significant impact on blood glucose level in the T1DM patients (Fig. 6).

Sensitivity analysis, subgroup analysis, and publication bias of studies

For sensitivity analysis, we sequentially excluded a single study from the pooled analysis and recalculated the summary HG to check whether the summary HGs were significantly influenced by any study. The recalculated HGs were similar (P > 0.05) indicating the stability of analysis. The details of sensitivity analysis are provided in Appendix 3 of the Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/A360.

We performed subgroup analysis based on the study site, the type of glucose monitoring system, and the sample size of the studies. There were no significant differences in TIR values before and after vaccination with 1st dose based on the location of the study (P = 0.14). Likewise, the size of the study (more than 100 or less than 100 participants) did not significantly affect the pre- and post-vaccination TIR values of the first dose (P = 0.07). Similarly, the type of glucose monitoring system used (continuous glucose monitoring, flash glucose monitoring, or advanced hybrid closed-loop system) did not significantly impact pre-

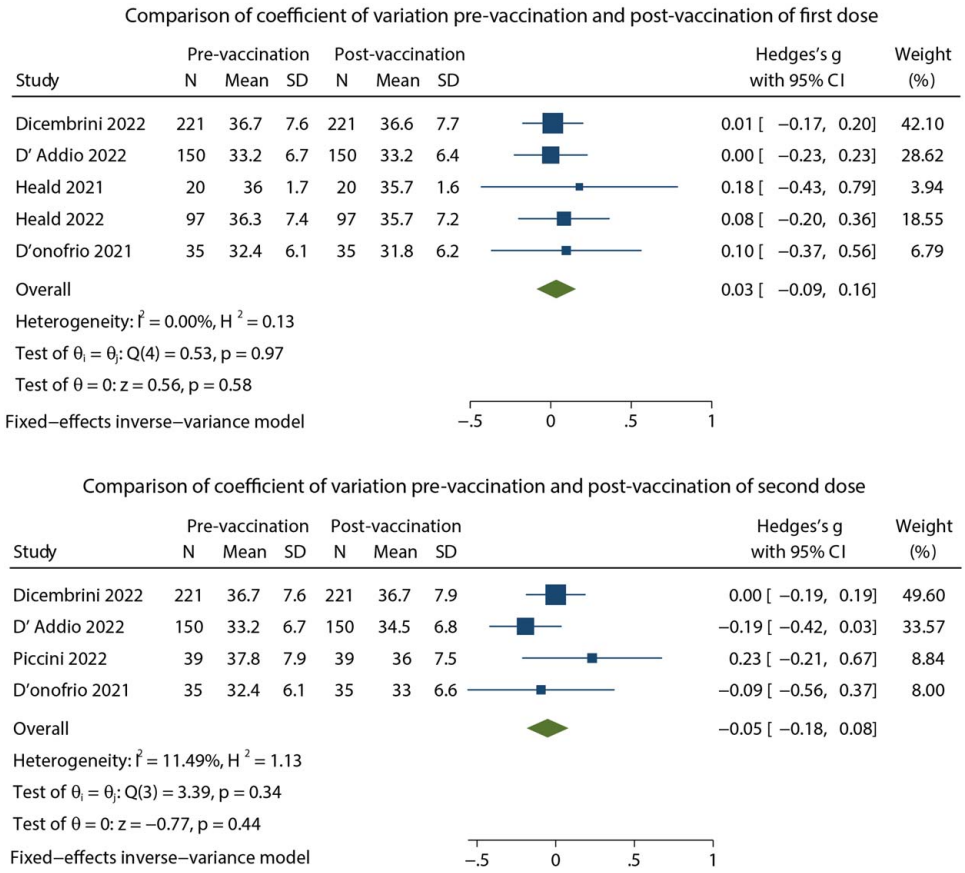

Figure 5. Meta-analysis of comparison of coefficient of variation pre-vaccination and post-vaccination.

vaccination and post-vaccination TIR values ($P = 0.43$). The details of the subgroup analysis are provided in the forest plots in Appendix 4 of the Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/A360.

A funnel plot was generated from the data, as shown in Appendix 5 of the Supplementary File, Supplemental Digital Content 3, http://links.lww.com/MS9/A360, which is a symmetrical funnel plot. However, Begg's test and Egger's test showed significant publication bias in the meta-analysis ($P = 0.0163$ for Begg's test and $P = 0.0012$ for Egger's test).

Discussion

To the best of our current knowledge, this is the inaugural meta-analysis that has evaluated the immediate effects of the COVID-19 vaccination on glycemic control in patients with T1DM. The findings of our study indicated that there was a minimal and statistically insignificant alteration in glucose control parameters like TIR, TAR, TBR, CV, and MBGL after both the first and second doses of the vaccines. Hence, the COVID-19 vaccination demonstrated a commendable safety profile in terms of glucose control in T1DM patients. Even if fluctuations in glucose values occur following vaccination, the fluctuations are mild, short-lived, tolerable, and do not require insulin dose adjustment. This meta-analysis adds to the literature and provides useful information for healthcare providers to counsel and manage people with T1DM who receive the vaccination in the future.

Primary prevention based on vaccination is the key strategy to dampen the risks associated with COVID-19 in patients with T1DM[14]. Individuals diagnosed with T1DM are classified as a population at heightened risk and are strongly advised to undergo immunization against COVID-19 in order to mitigate the likelihood of developing severe manifestations of the illness[15]. In relation to its effectiveness, a recent study has demonstrated that the administration of two doses of the vaccine in T1DM patients yields comparable efficacy results to those observed in individuals without this condition[16]. Despite its unmatched importance to the patients, one of the possible effects of the COVID-19 vaccination could be fluctuations in glycemic levels. Vaccine hesitancy among individuals with diabetes is a noteworthy phenomenon that warrants attention. It appears to be more prevalent in those who exhibit lower levels of adherence to medical prescriptions and/or demonstrate diminished concerns regarding their overall health[17]. Some patients justify their refusal of vaccination on concerns regarding immediate adverse reactions, particularly blood glucose instabilities. The perturbations in glucose levels in T1DM following vaccination could be due to immune system activation or to stress related to the vaccine itself. There have been documented instances of worsening glycemic control following administration of COVID-19 vaccines in three individuals diagnosed with type 2 diabetes who were on treatment with oral hypoglycaemia medicines and insulin[18]. If the COVID-19 vaccinations are implicated in glucose level perturbations, this might lead to an increase in vaccine hesitancy in patients[19]. Hence, it is

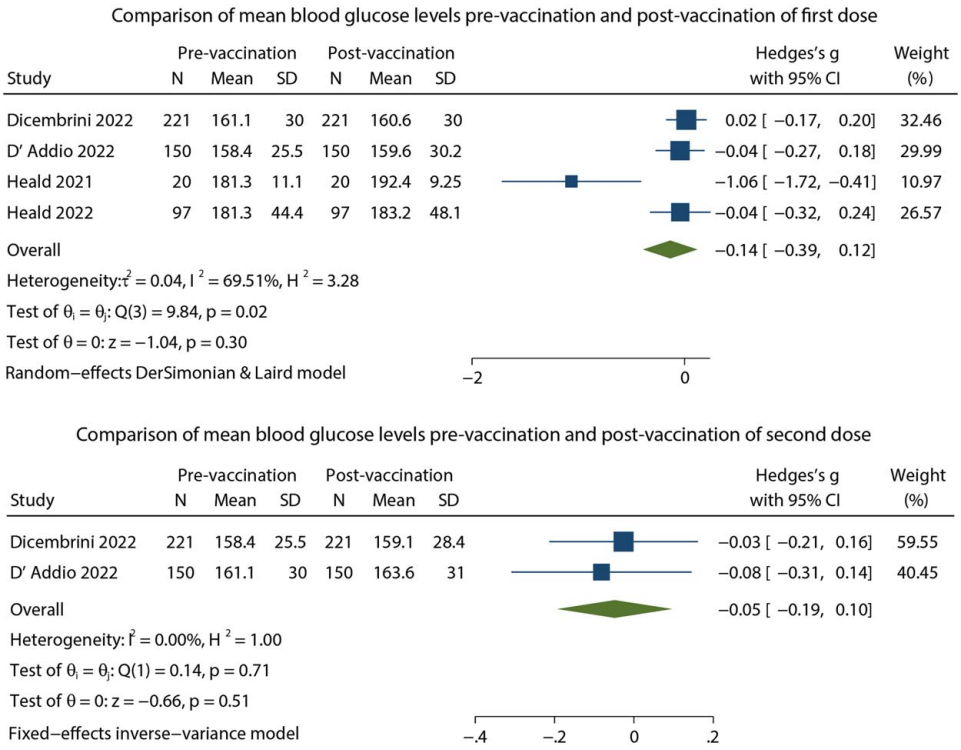

Figure 6. Meta-analysis of comparison of mean blood glucose levels pre-vaccination and post-vaccination.

absolutely essential to endorse the uptake of vaccination in these patients while keeping them informed of the possibility of mild fluctuations in glycemic control.

The mechanism of action for RNA-based COVID-19 vaccines involves the activation of various pattern recognition receptors due to their structural resemblance to pathogenic agents. This phenomenon involves the utilization of both adaptive and innate anti-viral mechanisms[26]. The process of vaccination leads to the generation of a substantial quantity of neutralizing antibodies targeting the SARS-CoV-2 virus. Furthermore, it is worth noting that there is a substantial augmentation in the population of antigen-specific polyfunctional CD4 and CD8 T cells subsequent to the administration of the second dose[27]. The administration of vaccines elicits a chain of immune responses, leading to the activation of several inflammatory pathways at once. The administration of the COVID-19 vaccine elicits an immunological response, wherein the immune system is stimulated to a lesser extent compared to an actual COVID-19 infection, hence inducing a milder stress reaction. The physiological response to stress has the capacity to elevate levels of counter-regulatory hormones within the human body. Adrenaline, growth hormone, cortisol, and/or glucagon are particularly noteworthy in individuals possessing alpha cell reserves. These reactions have the potential to negatively impact glucose management in individuals with T1DM. Individuals diagnosed with T1DM may exhibit diminished capacity to promptly mitigate heightened levels of blood glucose, resulting in occurrence of hyperglycaemia[20].

Most of the studies show no significant change in glucose parameters before and after the COVID-19 vaccination. However, in a study by Heald and colleagues, a significant reduction in TIR post-vaccination was observed that was more prominent in patients also receiving oral medications. Their initial observation identified age as a predisposing factor for glucose variability after vaccination[24]. Some studies show a significant increment in blood glucose level after vaccination, and no studies till date have shown a significant decrease in blood glucose level after vaccination. Shoelson *et al.*[28] described that the extent of activation of inflammatory pathways by vaccination is generally insufficient to produce tangible effects on mean blood glucose levels or glucose variability. Even though Heald has reported that the COVID-19 vaccination can cause temporary relative hyperglycaemia in people with T1DM, the need for insulin dose adjustment in these patients is almost non-existent. This has been supported by the evidence gathered by Piccini and colleagues with the use of AHCLs. In subjects treated by AHCLs, the technological algorithm has the capacity to mitigate a temporary elevation in glucose levels induced by the vaccine uptake. However, no discernible alterations were observed in the total daily dose or bolus proportion of insulin in the users[23].

There have been concerns raised regarding the ability of people with T1DM to build an adequate immune response following vaccination. The presence of immunological dysregulation in both T-cell and B-cell compartments is a prominent characteristic observed in T1DM from the very beginning of the disease. This dysregulation may serve as an indication of aberrations in the immune response. The immune dysregulation caused by DM may be the root cause of the occurrence of severe COVID-19 disease, as well as a dampened immune response to vaccination[26]. Recent studies have provided evidence that indicates a defective ability to inactivate the virus in T1DM. The patients failed to generate an increase in granzyme A and perforin, which are T-cell-specific SARS-CoV-2 cytotoxic factors. The cytotoxic

factors detected after vaccination have been found to be increased in subjects without diabetes in response to the SARS-CoV-2 in-vitro challenge, while no effect was observed in the majority of patients with T1DM[27,29]. This suggests a possibility of reduced cytotoxic effector function in T1DM and a less immunogenic or efficient vaccination in these individuals. Nevertheless, there were no notable disparities in the levels of neutralizing antibodies specific to the SARS-CoV-2 spike protein between T1DM patients and healthy controls.

Our study has its strengths and limitations. We performed a meticulous search across multiple databases, guaranteeing the thorough inclusion of pertinent studies. Next, through the aggregation of data from several trials, we conducted the first meta-analysis (as per our knowledge) to determine the precise effect of COVID-19 immunization on glycemic control. However, our study also has a few limitations. Despite the inclusion of seven studies, the availability of data from an increased number of studies could enhance the statistical power and generalizability of the findings. We were unable to assess additional safety-related factors such as the occurrence of severe hypoglycaemia or hyperglycemic events, diabetic ketoacidosis, or complications related to COVID-19 in T1DM patients in a meta-analytic approach due to limited availability of data on these parameters in selected studies. CGM is a relatively novel technology with limited usage among patients around the globe, and hence adequate studies are still not available.

It is crucial to acknowledge that the studies included in this analysis had variations in study design, sample population characteristics, and types of COVID-19 vaccination administered, leading to heterogeneity in the findings. Finally, all of the studies specifically examined the immediate impact of the COVID-19 vaccine on glycemic control, and there is a research gap on the long-term impacts of the vaccines on T1DM patients. Additionally, most of the studies have a monocentric study design with sample sizes that are quite small, which may not represent the true data of the population. However, the result produced by our study can act as a preliminary for further studies with a larger sample size. The studies included in our meta-analysis had significant publication bias, which may be due to the fact that these are pioneer studies looking for the impact of COVID-19 vaccination on glucose control parameters. Nevertheless, the results produced by our study can be useful for further vaccination and its continuation in T1DM patients, as well as for planning accordingly.

Conclusion

Overall, the COVID-19 vaccination has shown an excellent safety profile in terms of glycemic control in T1DM patients. The uptake of vaccination should be encouraged among patients to mitigate the risks of severe COVID-19 infections in the future.

Ethical approval

No ethical approval was obtained because of the nature of the systematic review article.

Consent

Informed consent was not obtained for this systematic review.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution

Conceptualization: P.L., H.K., M.P., A.A.; Methodology: P.L., H.K., S.Z., K.K.,; Software: P.L., K.K.; Validation: P.L. and K.M.P.; Formal analysis: P.L. and K.K.; Investigation: P.L., M.P., K.K.; Resources: P.L.; Data curation: P.L., H.K.K.K.; Writing—original draft preparation: P.L., H.K., S.Z., K.K., C.K.S., M.P., L.K.J., A.A.; Writing—review and editing: P.L., C.K.S., L.K.J.; Visualization: P.L., K.K. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest disclosure

The authors have no conflict of interest to declare.

Research registration unique identifying number (UIN)

UIN: CRD42023423467 Research registry: PROSPERO Link: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=423467.

Guarantor

Dr Pratik Lamichhane.

Data availability statement

The data will be made available upon reasonable request to the readers.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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