Impact of COVID-19 Vaccination on Glycemia in Individuals With Type 1 and Type 2 Diabetes: Substudy of the COVAC-DM Study

Diabetes Care 2022;45:e24–e26 | https://doi.org/10.2337/dc21-1563

*Felix Aberer,[1,2] Othmar Moser,[2,3] Faisal Aziz,[1,2] Caren Sourij,[4] Haris Ziko,[1] Jacqueline Lenz,[1,2] Farah Abbas,[1,2] Anna M. Obermayer,[1,2] Harald Kojzar,[1,2] Peter N. Pferschy,[1,2,5] Alexander Müller,[1,2] Christina Unteregger,[1,2] Marlies Leitner,[1,2] Tamara Banfic,[1,2] Max L. Eckstein,[3] Nadine Wachsmuth,[1,3] Susanne Kaser,[6] Julia K. Mader,[1] Norbert J. Tripolt,[1,2] and Harald Sourij,[1,2] for the COVAC-DM Study Group**

As people with diabetes are considered a high-risk population in the coronavirus disease 2019 (COVID-19) pandemic scenario, they are globally prioritized in COVID-19 vaccine policy. To date, in most industrialized countries, people with diabetes have already been offered the opportunity to receive a vaccine. Nonetheless, concerns exist about vaccine-induced dysglycemia among people living with diabetes, potentially holding them back from getting vaccinated. Immune responses can trigger alterations in insulin sensitivity, potentially increasing insulin requirements due to inflammation, humoral, and cellular immune responses (1). Assuming that natural immunization (infection) triggers (patho)physiological patterns similar to those of pharmacological immunization (vaccination), one can speculate that diabetes management also deteriorates after the vaccination (2), as proinflammatory cytokines increase insulin resistance (3).

Considering this, we aimed to investigate the short-term effects of COVID-19 vaccination on the time spent in different glycemic ranges, assessed by continuous glucose monitoring (CGM) in people with type 1 and type 2 diabetes.

From April to June 2021, a total of 161 individuals were enrolled in the multicenter prospective Immune Response to COVID-19 Vaccination in People with Diabetes Mellitus—COVAC-DM Study (EudraCT2021-001459-15), of whom 74 participants had sufficient CGM data (at least 90%) available around their first COVID-19 vaccination to be included in the present substudy. Fifty-eight individuals had type 1 diabetes (mean age 39.5 ± 14.1 years; mean HbA_{1c} 57 ± 12 mol/mol), and 16 had type 2 diabetes (mean age 60.6 ± 6.2 years; mean HbA_{1c} 63 ± 11 mmol/mol). Of those with type 1 diabetes, 22 (37.9%) were on continuous subcutaneous insulin infusion (total daily bolus insulin, as median [interquartile range], 17 [11]; basal insulin 23 [15] IU) and 36 (62.1%) were on multiple daily insulin injections (MDI) (total daily bolus insulin 19 [12]; basal insulin 19 [12] IU). Fifteen people with type 2 diabetes were on MDI (total daily bolus insulin 18 [30]; basal insulin 28 [20] IU), and one participant was on oral glucose-lowering drugs. The majority of participants received an mRNA-based vaccine (87% BioNTech Pfizer and 6% Moderna vs. 7% AstraZeneca). Data from the CGM were analyzed

[1]Division of Endocrinology and Diabetology, Medical University of Graz, Graz, Austria
[2]Interdisciplinary Metabolic Medicine Trials Unit, Medical University of Graz, Graz, Austria
[3]Department of Exercise Physiology & Metabolism, Institute of Sports Science, University of Bayreuth, Bayreuth, Germany
[4]Division of Cardiology, Medical University of Graz, Graz, Austria
[5]Center for Biomarker Research in Medicine (CBmed), Graz, Austria
[6]Medical University of Innsbruck, Innsbruck, Austria

Corresponding author: Harald Sourij, ha.sourij@medunigraz.at

Received 28 July 2021 and accepted 1 November 2021

Clinical trial reg. no. EudraCT2021-001459-15, https://eudract.ema.europa.eu/

This article contains supplementary material online at https://doi.org/10.2337/figshare.16926577.

F.Abe., O.M., and F.Az. contributed equally to this work.

**A complete list of the COVAC-DM Study Group members can be found in the supplementary material online.*

This article is part of a special article collection available at https://diabetesjournals.org/journals/collection/52/Diabetes-and-COVID-19.

from 2 days prior until 3 days after the first dose of vaccination for time spent in different glycemic ranges (4).

Furthermore, we investigated prospectively whether the presence and severity of self-reported typical side effects and elevated body temperature following the first COVID-19 vaccination alter glycemia and whether bolus insulin dosing behavior and carbohydrate intake were influenced in response to the vaccination.

To assess time spent in glycemic ranges in relation to specific side effects, we created a simple score: the presence of any side effect, including headache, body ache, fatigue, and any injection site reaction after vaccination added one point, as did the presence of elevated body temperature of >37°C following the vaccine. If two of the criteria (at least one side effect and elevated body temperature) were met, participants received two points; if none of the criteria were met, participants received zero points. We allocated each day of each participant with available CGM data a side effect score according to the definition described above. Analyses were defined in a statistical analysis plan ahead of study completion.

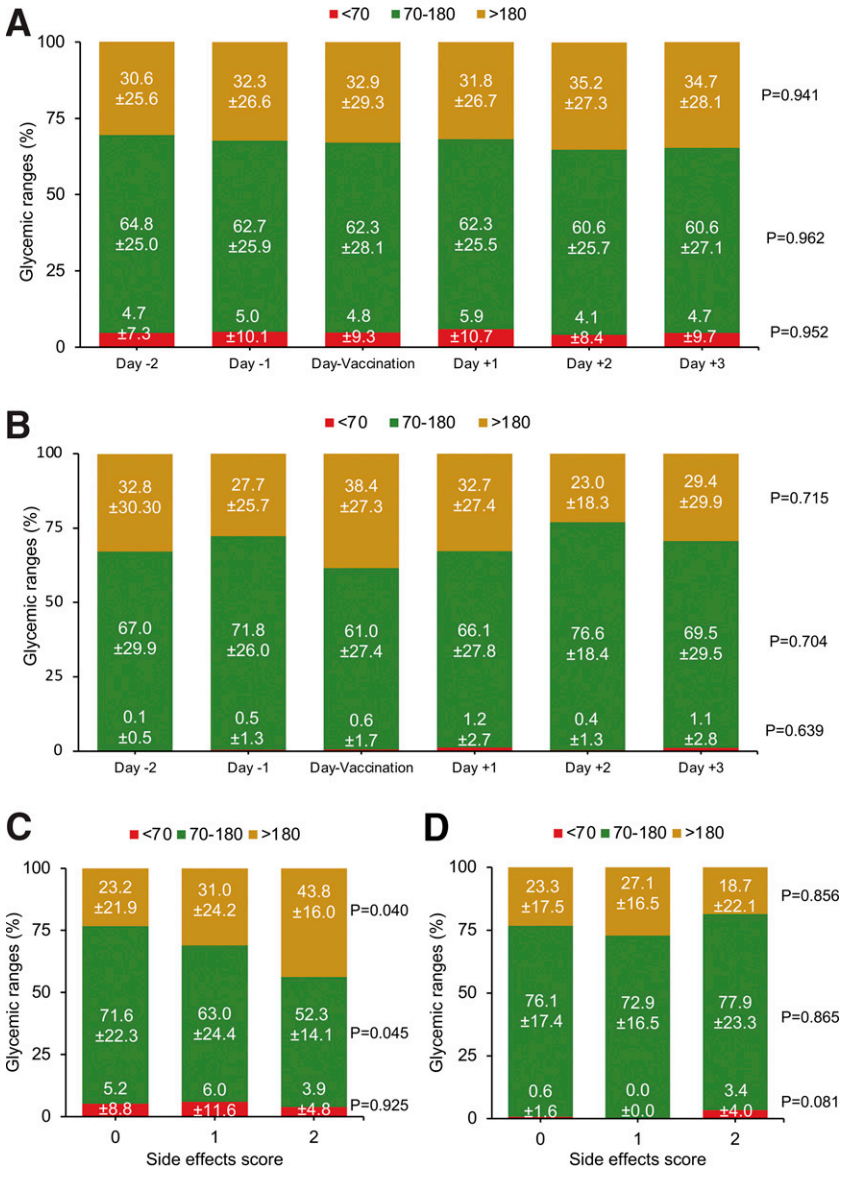

Figure 1–TIR in response to the COVID-19 vaccination in people with type 1 diabetes (*A*) and type 2 diabetes (*B*). Glycemic ranges were based on the side effect score for people with type 1 diabetes (*C*) and type 2 diabetes (*D*). Data were analyzed according to "score-days." Each day for each participant, a side effect score was allocated: symptoms such as headache, body ache, fatigue, and any infection site reaction after vaccination added one point, as did the presence of elevated body temperature >37°C after the vaccine. Glycemic ranges are given in mg/dL.

In total, 49,200 CGM data points were available. For both people with type 1 diabetes (P = 0.962) and type 2 diabetes (P = 0.704), no significant differences were found for the time in range (TIR) (70 – 180 mg/dL) over the course of the vaccination from 2 days prior to receiving the vaccination until 3 days afterward (Fig. 1*A* and *B*). Likewise, the time below range (TBR) (<70 mg/dL; type 1 diabetes, P = 0.952; type 2 diabetes, P = 0.704) and the time above range (TAR) (>180 mg/dL; type 1 diabetes, P = 0.941; type 2 diabetes, P = 0.715) did not change around the COVID-19 vaccination.

The bolus insulin dose was not adjusted around the vaccination in people with either type 1 (P = 0.578) or type 2 (P = 0.346) diabetes. Similar results were seen when assessing carbohydrate intake, detailing no significant difference in carbohydrate intake in people with type 1 (P = 0.092) and type 2 (P = 0.958) diabetes around the COVID-19 vaccination.

Thirty-five percent of the available CGM days post-vaccination with complete side effect information were spent with side effect score 0, 58% with side effect score 1, and 7% with side effect score 2. When separating days of people with type 1 and type 2 diabetes based on the side effect score, those with type 1 diabetes spent significantly less TIR on days with an increased side effect score (1 or 2) than on days with a side effect score of 0 (P = 0.033 using Wilcoxon rank sum test). This finding was confirmed, as the TAR was significantly higher on days with a side effect score of >0 (P = 0.043 using Wilcoxon rank sum test). The side effects had no significant impact on the TBR in people with type 1 diabetes (P = 0.925). In people with type 2 diabetes, the side effect score had no influence on the TIR (P = 0.865), TAR (P = 0.856), and TBR (P = 0.081) (Fig. 1*C* and *D*).

Glycemic variability, measured as coefficient of variation, was not significantly different with respect to side effect score for either type 1 (P = 0.206) or type 2 (P = 0.501) diabetes (data not shown).

Our study is not without limitations. In particular, our sample size with CGM

data in people with type 2 diabetes is rather small; hence, our results cannot be transferred to the entire population of people with diabetes. Moreover, all but one participant of the substudy were on continuous subcutaneous insulin infusion or MDI; therefore, we cannot comment on the impact of glycemic excursions in people with type 2 diabetes treated with oral glucose-lowering agents or diet only.

Our data revealed that COVID-19 vaccination per se did not change glycemic control in people with diabetes. Of note, on days on which side effects were present, a deterioration of glycemia was observed in people with type 1 diabetes. While this observation should be further investigated in larger studies, it can be considered when health care professionals inform their patients about potential glycemic aberrations in response to COVID-19 immunization.

Funding. This research project was submitted for funding to the Austrian Science Fund.

Duality of Interest. F.Abe. received speaker honoraria from Amgen, Eli Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, and Novo Nordisk and is an advisory board member of Amgen, Sanofi, and Novo Nordisk. J.K.M. is a member of the advisory boards of Becton-Dickinson, Boehringer Ingelheim, Eli Lilly, Medtronic, Prediktor SA, and Sanofi and received speaker honoraria from Abbott Diabetes Care, AstraZeneca, Eli Lilly, Dexcom, Medtronic, Novo Nordisk, Roche Diabetes Care, Sanofi, Servier, and Takeda. H.S. has received speaker honoraria or serves on advisory boards for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Kapsch BusinessCom, MSD, Novartis, Novo Nordisk, and Sanofi. O.M. has received lecture fees from Medtronic; travel grants from Novo Nordisk A/S, Novo Nordisk AT, Novo Nordisk UK, Medtronic AT, and Sanofi; research grants from Sêr Cymru II COFUND Fellowship/European Union, Novo Nordisk A/S, Dexcom, Sanofi, and Novo Nordisk AT; and material funding from Abbott Diabetes Care. M.L.E. has received a KESS2/European Social Fund scholarship, travel grants from Novo Nordisk A/S and Sanofi, and research grants form Sanofi and Dexcom. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. F.Abe., O.M., C.S., N.J.T., and H.S. designed the study. F.Abe., O.M., F.Az., N.J.T., and H.S. drafted the first version of the manuscript. H.Z., H.K., and N.J.T. performed the data preparation. F.Az. performed statistical analysis and created the figures. C.S., J.L., F.Abb., A.M.O., H.K., P.N.P., A.M., C.U., M.L., T.B., S.K., and J.K.M. performed the patient recruitment, conducted the study visits, and collected research data. S.K. was the local principal investigator of the participating study center in Innsbruck. O.M., M.L.E., and N.W. performed the study in the study center in Bayreuth. All of the authors have revised the manuscript and have agreed to the submission of the latest version and sufficiently contributed to this work. H.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Lewis MR, Tracy RP. The role of the immune system in the insulin resistance syndrome. Curr Diab Rep 2002;2:96–99

2. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol 2021; 17:11–30

3. Koliaki C, Tentolouris A, Eleftheriadou I, Melidonis A, Dimitriadis G, Tentolouris N. Clinical management of diabetes mellitus in the era of COVID-19: practical issues, peculiarities and concerns. J Clin Med 2020; 9:9

4. American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes—2021*. Diabetes Care 2021;44(Suppl. 1):S73–S84