Received: 31 December 2022 | Accepted: 18 April 2023

DOI: 10.1111/dme.15119

DIABETIC Medicine

LETTER

The change in glycaemic control immediately after the 3rd COVID-19 vaccination in people with type 1 diabetes

Letter to the Editor,

We previously described how SARS-CoV-2(COVID-19) vaccination could cause temporary perturbation of interstitial glucose in people with type 1 diabetes (T1D). This effect was more pronounced in those people with a lower HbA_{1c}, with no difference between the AstraZeneca and Pfizer vaccines.[1] In the week after their first COVID-19 vaccination, the proportion 'time in target range' (%TIR) 3.9–10 mmol/L median decreased from 55.2% to 52.4% with 58% of people recording a fall. For the 48.5% of people ($n=47$) with $HbA_{1c}<56$ mmol/mol %TIR decreased from 69.3% to 63.5% (−8.3%) and for the 24 (25%) people using insulin+oral treatment 56.7% to 50.7% (−10.1%). We have now repeated the exercise after the most recent COVID-19 vaccination.

We questioned whether a similar effect might be seen following the most recent vaccination. We examined the interstitial glucose profile of 80 out of the previously assessed 97 adults (≥18 years of age) with T1D. Individuals received either the Pfizer/Biontech, Oxford/AstraZeneca vaccine or Moderna vaccine.[2]

Data for that metric were as previously extracted for the weeks −2 and +2 to evaluate the interstitial glucose stability in the period before and after COVID-19 vaccination. Individual patient data were fully anonymised prior to statistical analysis.

In all, 80 people were included. For 17 of the individuals originally followed-up, LIBRE data was not available for analysis.

The median age of the follow-up T1D group was 43.5 years (range 18–70 years); 37 (46.3%) of the patients were female. For the 3rd vaccination, 67% received the Pfizer/Biontech Oxford vaccine, 9% the AstraZeneca vaccination, and 24% the Moderna vaccine. All individuals were previously vaccinated for COVID-19. The interval between the first and subsequent vacation varied between 3 and 9 months. At the last observation date individuals had their 3rd COVID-19 vaccination.

The most recent (after the 1st) COVID-19 vaccination occurred between 17 September 2021 and 17 January 2022. Pre-vaccination median BMI was 27.3 kg/m^2 (IQR 24.0–30.8 kg/m^2). Pre-vaccination median estimated HbA_{1c} was 58 (IQR 54–68) mmol/mol or 7.5% (IQR 7.1–8.4)%. Sensors were active for between 72% and 98% of the observation time.

For the $n=43$ (54%) of T1D individuals who showed a reduction in %TIR in the week after vaccination, 56.4% ± 2.9% of readings were on target pre-vaccination falling to 49.8% ± 3.0% one-week post-vaccination and recovering to 53.3% ± 3.2% 1 week later. 64% of the patients whose %TIR fell previously,[1] fell again after this vaccination.

There was no overall decrease in the %TIR for interstitial glucose on target following the COVID-vaccination in the 7 days following vaccination (range 2 to 96% mean 49.8% ± 2.2%; $p=0.23$; Figure 1a). However, 23% of the 80 individuals showed a decrease in %TIR of ≥10% and 11% individuals showed a decrease in %TIR of ≥20%.

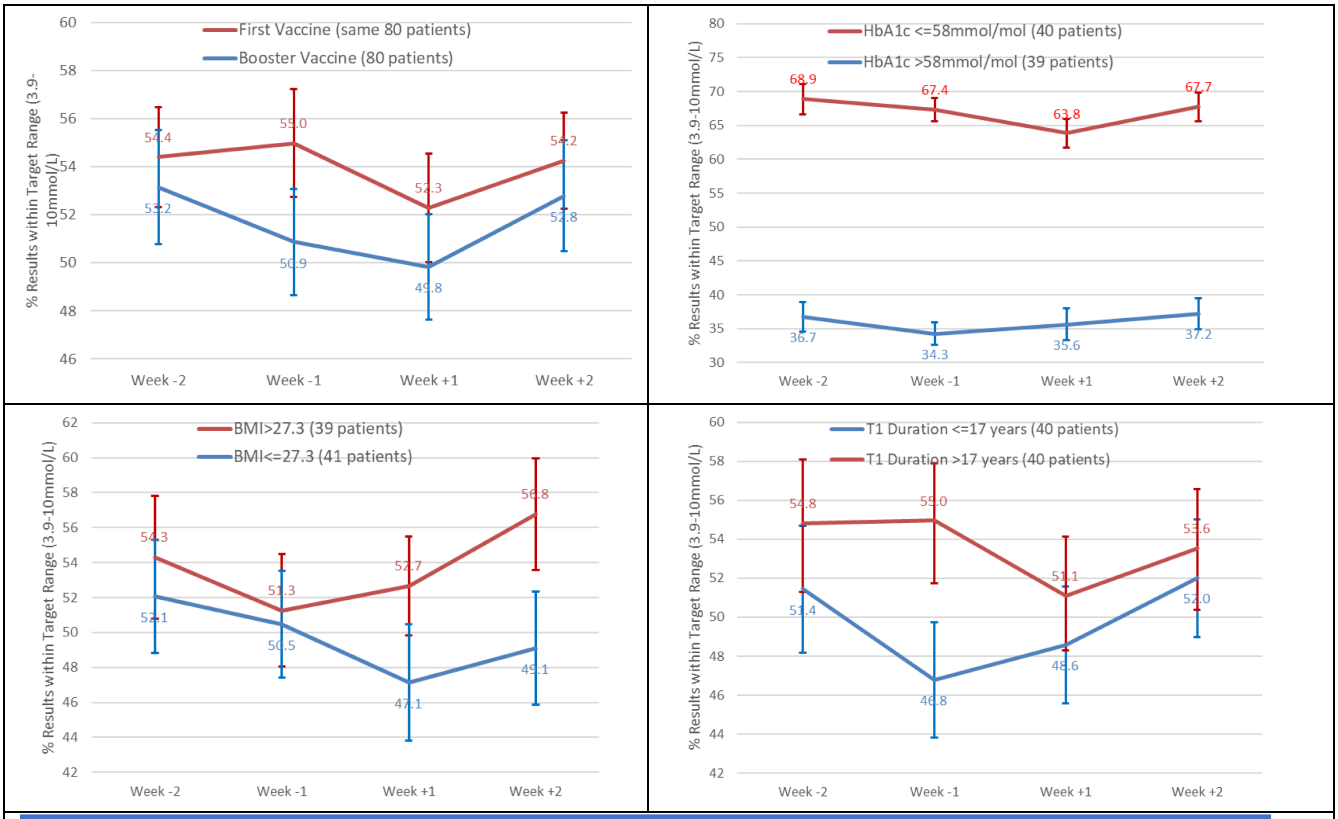
There was no significant change in interstitial glucose variability in the 7 days post COVID-19 vaccination (mean 35.6% ± 0.8%), compared with the previous week (mean 35.9% ± 0.7%).

When categorised as 'high' or 'low' HbA_{1c} (by median HbA_{1c} 58 mmol/mol), the %TIR fell by 3.6% in those in low HbA_{1c} group versus no change for patients in high HbA_{1c} group ($p=0.04$; Figure 1b; data shown for weeks −2 to +2 in relation to vaccine administration).

There was a significant change in %TIR in the week following vaccination for people with BMI at or below the median of 27.3 kg/m^2 (Figure 1c). The fall in %TIR for this group was 3.4% ($p=0.02$). For duration of diabetes (split by median duration of 17 years) for patients with duration >17 years the fall in %TIR was 3.9% ($p=0.04$; Figure 1d).

There was no significant difference between the Pfizer/Biontech, Oxford/AstraZeneca and Moderna vaccines in relation to their association with change in %TIR in the week after vaccination.

The relation between the change in %TIR following the 1st and most recent COVID-19 vaccination is shown in Figure 1 lower panel. The same response (decrease or



	Total	BMI		HbA1c (mmol/mol)		T1D Duration (years)	
		<=27.3	>27.3	<=58	>58	<=17	>17
V1Decrease: V3Decrease	**27**	**15**	**12**	**18**	**9**	**13**	**14**
V1Increase: V3Decrease	18	9	9	6	11	9	9
V1Decrease: V3Increase	16	9	7	9	7	4	12
V1Increase: V3Increase	19	8	11	7	12	14	5
TOTAL	80	41	39	40	39	40	40
Decreased both rounds	**34%**	**37%**	**31%**	**45%**	**23%**	**33%**	**35%**

FIGURE 1 Upper panel: The development of indicator values over 4 weeks around the day of vaccination. The vaccination takes place on the transition between Week −1 and Week +1. The % change shown reflects the change to the previous week. The bar reflects the standard error (SE). The panels show (a)—patients after most recent and 1st vaccination (for those with data for both periods); (b)—split by median HbA_{1c}; (c)—split by median BMI: (d). Lower panel: The difference in response between V1 (=initial) and V3 (=Booster) rounds by number of individual patients who decrease or increased/stayed the same in % of time in Target in reach round. Patient who did not change are excluded.

increase in %TIR) was seen in 50% of individuals. The only major difference in terms of the consistency of change in %TIR was (1) for estimated HbA_{1c}: for those individuals with an above median HbA_{1c} less individuals showed decreased %TIR after the 3rd COVID-19 vaccine versus the 1st vaccine; and (2) for duration of T1D for which those with an above median duration of T2D > 17 years, for which less individuals showed an increase in %TIR after the 3rd versus the 1st COVID-19 vaccination.

Multivariate linear regression analysis linking factors to the change indicated that estimated HbA_{1c} pre vaccination (standardised beta −0.4, $p < 0.01$) and for BMI pre vaccination (standardised beta −0.6, $p < 0.01$) were independently associated with a reduction in the proportion of interstitial glucose readings in %TIR ($r^2 = 0.2$). The model also included the independent variables of sex, age, duration of T1D, insulin/insulin+oral treatment and type of vaccine, which were stepwise excluded as their *p*-values were >0.05.

In conclusion, in a group of people with T1D, following the most recent COVID-19 vaccination, we have again found that COVID-19 vaccination is associated with a

temporary incremental change in interstitial glucose levels for many people. 54% of T1D individuals showed a reduction in the %TIR in the week after their 3rd COVID-19 vaccination. This compares with 58% after the 1st COVID-19 vaccination. However, the average change in %TIR of the whole group was no longer statistically significant and the proportion of individuals who showed a decrease in TIR was less. These implies some degree of habituation to the COVID-19 vaccine.

As previously, the effect was more pronounced in individuals with better blood glucose control on the basis of estimated HbA_{1c}. We also saw a reduction in the %TIR in the week following COVID-19 vaccination for people with an $HbA_{1c} \leq 58$ mmmol/mol and duration of T2D > 17 years and for those with a BMI below the median.

Our findings do indicate that patients with T1D should be advised and prepared for possible transient hyperglycaemia following subsequent COVID-19 vaccinations.[3] This is supported by a recent report of two young individuals with T1D who presented with severe diabetic ketoacidosis (DKA) after receiving second doses of COVISHIELD (ChAdOx1 nCoV-19) and COVAXIN (BBV152- inactivated whole virion) vaccines.[4]

The findings in this study relating to the 3rd COVID-19 vaccination and in our previous study relating to the 1st COVID-19 vaccination[1] contrast with those of who found no difference in %TIR or in insulin dose.[5] However, their report related to children and adolescents, whereas our report relates to people over the aged of 18 years.

Individual patient knowledge and involvement remain the cornerstones of diabetes management. Therefore, it is important to inform individuals with T1D may experience a temporary perturbation in their glucose levels.

KEYWORDS

3rd COVID-19 vaccination, flash glucose monitoring, Glycaemic stability, HbA_{1c}, type 1 diabetes

AUTHOR CONTRIBUTIONS

A. H. Heald prepared all drafts of the paper. Extraction and validation of patient data was undertaken by L. Horne. Data analysis was performed by MS with contributions from S. G. Anderson. R. Rea, J. M. Gibson, M. B. Whyte, A. A. Syed and A. Paisley. S. G. Anderson and W. Ollier provided ongoing input to the manuscript with senior review by S. G. Anderson and W. Ollier.

ACKNOWLEDGMENTS

The authors would like to acknowledge Robert Moore for his observation that led to this paper.

CONFLICT OF INTEREST STATEMENT

No author has any conflict of interest.

FUNDING INFORMATION

There was no external funding for this study.

DATA AVAILABILITY STATEMENT

Any reasonable requests for data extracts will be considered by Dr.Adrian Heald as corresponding author.

A. H. Heald[1,2]
M. Stedman[3]
L. Horne[4]
R. Rea[5]
M. B. Whyte[6]
A. A. Syed[1,2]
A. Paisley[1,2]
J. M. Gibson[1,2]
S. G. Anderson[7,8]
W. Ollier[9]

[1]*The School of Medicine and Manchester Academic Health Science Centre, University of Manchester, Manchester, UK*
[2]*Department of Diabetes and Endocrinology, Salford Royal Hospital, Salford, UK*
[3]*Res Consortium, Andover, Hampshire, UK*
[4]*Vernova Healthcare, Watersgreen Medical Centre, Macclesfield, UK*
[5]*Oxford Centre for Diabetes, Endocrinology and Metabolism and NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS FT, Oxford, UK*
[6]*Department of Clinical & Experimental Medicine, University of Surrey, Guildford, UK*
[7]*Glasgow-Caribbean Centre for Development Research and The George Alleyne Chronic Disease Research Centre, University of the West Indies, Bridgetown, Barbados*
[8]*Division of Cardiovascular Sciences, Faculty of Biology Medicine and Health, University of Manchester, Manchester, UK*
[9]*Faculty of Science and Engineering, Manchester Metropolitan University, Manchester, UK*

Correspondence
A. H. Heald, Salford Royal Hospital, Stott Lane, Salford M6 8HD, UK.
Email: adrian.heald@manchester.ac.uk

ORCID

A. H. Heald https://orcid.org/0000-0002-9537-4050
M. Stedman https://orcid.org/0000-0002-0491-7823
R. Rea https://orcid.org/0000-0001-6515-8325
M. B. Whyte https://orcid.org/0000-0002-2897-2026
A. A. Syed https://orcid.org/0000-0001-8696-7121

REFERENCES

1. Heald AH, Stedman M, Horne L, et al. The change in glycaemic control immediately after COVID-19 vaccination in people with type 1 diabetes. *Diabet Med*. 2022;39(4):e14774.
2. UK Health Security Agency. Guidance for healthcare practitioners about the coronavirus (COVID-19) vaccination programme. 2020. Accessed December 19, 2022. https://www.gov.uk/government/publications/covid-19-vaccination-programme-guidance-for-healthcare-practitioners.
3. Ganakumar V, Jethwani P, Roy A, Shukla R, Mittal M, Garg MK. Diabetic ketoacidosis (DKA) in type 1 diabetes mellitus (T1D) temporally related to COVID-19 vaccination. *Diabetes Metab Syndr*. 2022;16:102371.
4. Voysey M, Clemens SAC, Madhi SA, et al. Oxford COVID vaccine trial group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397(10269):99-111.
5. Gouda N, Dimitriadou M, Sotiriou G, Christoforidis A. The impact of COVID-19 vaccination on glycaemic control in children and adolescents with type 1 diabetes mellitus on continuous glucose monitoring. *Acta Diabetol*. 2022;59:1609-1614.