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DIABETIC Medicine

RESEARCH: COMPLICATIONS

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

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Abstract

Aims: Evidence suggests that some people with type 1 diabetes mellitus (T1DM) experience temporary instability of blood glucose (BG) levels after COVID-19 vaccination. We aimed to assess this objectively.

Methods: We examined the interstitial glucose profile of 97 consecutive adults (age ≥ 18 years) with T1DM using the FreeStyle Libre® flash glucose monitor in the periods immediately before and after their first COVID-19 vaccination. The primary outcome measure was percentage (%) interstitial glucose readings within the target range 3.9–10 mmol/L for 7 days prior to the vaccination and the 7 days after the vaccination. Data are mean ± standard error.

Results: There was a significant decrease in the % interstitial glucose on target (3.9–10.0) for the 7 days following vaccination (mean 52.2% ± 2.0%) versus pre-COVID-19 vaccination (mean 55.0% ± 2.0%) ($p = 0.030$). 58% of individuals with T1DM showed a reduction in the 'time in target range' in the week after vaccination. 30% showed a decrease of time within the target range of over 10%, and 10% showed a decrease in time within target range of over 20%. The change in interstitial glucose proportion on target in the week following vaccination was most pronounced for people taking metformin/dapagliflozin + basal bolus insulin (change −7.6%) and for people with HbA_{1c} below the median (change −5.7%).

Conclusion: In T1DM, we have shown that initial COVID-19 vaccination can cause temporary perturbation of interstitial glucose, with this effect more pronounced in people talking oral hypoglycaemic medication plus insulin, and when HbA_{1c} is lower.

KEYWORDS

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

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Summary

The COVID-19 vaccination programme is under way in the United Kingdom and worldwide. Flash glucose monitoring has given a new insight into interstitial glucose variability in T1DM. We here describe that COVID-19 vaccination can cause temporary perturbation of interstitial glucose. This effect is more pronounced in in those people with a lower HbA_{1c}. There was no difference between the AstraZeneca and Pfizer vaccines.

1 | INTRODUCTION

Since its appearance in 2019, the SARS-CoV-2, COVID-19, virus has challenged healthcare systems all across the world.[1,2] Furthermore, its impact on morbidity and mortality has been more pronounced in people living with long-term conditions.[3] The focus on mitigating the effects of the virus has led to many routine healthcare services being disrupted and to millions of people with diabetes across the world being fearful regarding the potential for infection with COVID-19 to make them very seriously unwell.[4]

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 type 1 diabetes (T1DM)[5] and may also be adopted in due course in people with insulin-treated type 2 diabetes (T2DM). Flash glucose monitoring allows users retrospectively to review the preceding 8 h of continuous glucose data,[6] along with a contemporary estimated interstitial glucose value and a trend line. Use of CGM has been associated with a significant reduction in HbA_{1c}.[5,7]

Diabetes is associated with poor prognosis after COVID-19 infection. Vaccination is therefore recommended as a priority in people with diabetes. The goal of any vaccination programme is to elicit a sustained and durable immune response in the target population. There is prior evidence, however, that sub-optimal glycaemic control in diabetes has a significant impact on the immune response.[8,9] Thus, it is important to establish if perturbations in glycaemia occur immediately post-vaccination, as this may have potentially important implications regarding the durability/strength of immunity post-COVID-19 vaccination in those with diabetes.

The COVID-19 vaccination programme is now well under way in the United Kingdom (UK) using the Pfizer/Biontech or the Oxford/AstraZeneca vaccine[10] as in many parts of the world with these and other vaccines, with around 90% of the UK population having have been vaccinated with their first dose.

It is known that COVID-19 infection leads to an immune stress response and dysglycaemia. We questioned whether a similar, milder effect might be seen post-vaccination.

We, therefore, collected data from consecutive individuals with diabetes mellitus who routinely use flash glucose monitoring and who have recently received their first dose of vaccine. We here report an analysis of the interstitial glucose profiles of these 97 participants before and after vaccination.

2 | RESEARCH DESIGN AND METHODS

All individuals were under the care of the National Health Service (NHS) specialist diabetes service in Eastern Cheshire, UK. Ours is an adult community diabetes service covering the community served by Macclesfield District General Hospital.

We examined the interstitial glucose profile of 97 consecutive adults (18 years of age or more) with T1DM using the FreeStyle® Libre flash glucose monitor in the period immediately before and after COVID-19 vaccination.

The Libre View reporting system[11] provides a number of metrics over the selected time period for each participant that are all dependant on underlying patient interstitial glucose control; these include average glucose, glucose variability and % of glucose results falling within given ranges: 3.9–10 mmol/L, 10.1–13 mmol/L and ≥14 mmol/L—from these one can also calculate the % of blood glucose readings <3.9 mmol/L. To select a primary metric, all the above metrics were evaluated among the 97 participants for 7 days before vaccination and 7 days directly after vaccination. Seven days post-vaccination was chosen pragmatically as the target period, in relation to this being the time that participants anecdotally reported as manifesting perturbed glucose levels.

The primary outcome metric of % of interstitial glucose results falling within the range: 3.9–10 mmol/L was chosen on the basis of practical relevance to day-by-day interstitial glucose control. HbA_{1c} was estimated in Libre View using all interstitial glucose measurements in the 6 weeks prior to COVID-19 vaccination. We took the interstitial glucose analysis from the Libre View system and, therefore, the variability coefficient is derived from that source. The quoted mean absolute relative difference of the sensors used is 11.4%.

Data for that metric were also extracted for the weeks −2 and +2 to evaluate the interstitial glucose stability in the period before and the speed of return to pre vaccination control, after the main measurement period.

Variables that might have an impact on the results were also taken from the patient records. These included age, sex, type of vaccine given, medication, duration with diabetes and body mass index (BMI) and HbA_{1c}. For continuous indicators, the participants were split into two groups across the median value of each variable. These were all first vaccinations and not second vaccinations. Information concerning date of vaccination was obtained

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from the patient's general practice record. We obtained side-effect information by telephoning the participants.

This was a service evaluation registered as (CG 2021/24). Ethics approval was not required for this study, as this mode of monitoring of interstitial glucose is part of standard care for individuals with T1DM, according to National Institute for Health and Clinical Excellence (NICE) guidance[12] and is increasingly being applied in T2DM people treated with insulin. All individual patient data were anonymised prior to statistical analysis.

2.1 | Statistical analysis

Excel 64-bit with Analyse-it add-in was used to perform the analysis. Shapiro–Wilks testing confirmed that the patient proportion of interstitial glucose results in specific ranges fell in a normal distribution. Two-tailed paired t-test for the outcome measures compared results in weeks +1 against −1. The analyses were corrected for multiple comparisons.

The mean and standard deviation of the selected indicators was then calculated for the total cohort and split into two classes for each potential factor. The trend and standard error over the 4 weeks for these variables were plotted graphically. Multiple regression modelling was carried out with change in proportion of interstitial glucose results in the target range 3.9–10.0 mmol/L as the dependent variable. Regression analysis was carried out using Analyse-it add in to EXCEL. Categorical variables, oral adjunctive medication, sex, and vaccination type AZ/PF were coded using 0/1 binary.

3 | RESULTS

The median age of the T1DM cohort was 44 years (overall range 18–70 years); 51 (52.5%) of the participants were female. Baseline demographics are detailed in Table 1, split by sex and by the type of vaccine. There was no difference between the Pfizer/Biontech Oxford/AstraZeneca vaccination groups apart from sex proportion.

COVID-19 vaccination occurred between 5 January and 4 April 2021. A total of $n = 45$ (46.4%) individuals received the Pfizer/Biontech and $n = 52$ (53.6%) individuals the Oxford/AstraZeneca vaccine. Pre-vaccination HbA_{1c} was in the range 40 mmol/mol (5.8% DCCT units) to 92.0 mmol/mol (10.6%) (median 56 mmol/mol [7.6%]) with BMI in the range 17.4–50.9 kg/m^2 (median 26.5 kg/m^2). Median BMI (interquartile range IQR) was 26.5 (23.8–30.4) kg/m^2. Median estimated HbA_{1c} was 56.0 ([IQR] 51.8–63.0) mmol/mol or 7.3 ([IQR] 6.9–7.9)%.

All had received their first vaccination for COVID-19.

All 97 individuals were on a basal bolus regime of long-acting analogue insulin (Insulin Degludec or Glargine) and prandial short-acting analogue insulin (Insulin Aspart or Insulin Lispro). Additional oral hypoglycaemic therapy was used by $n = 26$ individuals, of which $n = 22$ on metformin, $n = 3$ SGLT2-inhibitor Dapagiflozin ($n = 3$) and $n = 2$ on both adjunctive agents.

Mean HbA_{1c} for participants on insulin (as monotherapy) was 58.4 mmol/mol (7.5%) ± standard error (se) 1.2 mmol/mol (0.1%) versus 59.5 mmol/mol (7.6%) ± 1.7mmol/mol (0.1%) for those on insulin plus an oral hypoglycaemic agent. There was no significant difference in HbA_{1c} between these groups. Mean BMI for the insulin alone treated group was 26.2 (standard deviation SD 5.5) kg/m^2. Mean BMI for the metformin-treated group was 32.4 (SD 6.3) kg/m^2. Mean BMI for the SGLT2-inhibitor-treated group was 29.7 (SD 4.4) kg/m^2.

The distribution of %interstitial glucose on target was parametrically distributed for the participant group. The range of % interstitial glucose on target (3.9–10 mmol/L) pre-COVID-19 vaccination was 0%–93% (mean

TABLE 1 Baseline characteristics for 97 individuals with T1DM

	Men ($n = 46$)	Women ($n = 51$)
Age (years) (SD)	39.8 (13)	44.9 (12.2)
Mean BMI (kg/m^2) (SD)	27.1 (5.6)	28.4 (6.7)
Duration of diagnosed T1DM (years) (SD)	17.4 (11.6)	20.7 (11.7)
Estimated mean HbA_{1c} (mmol/mol) (SD)	57.3 (9.3) mmol/mol	59.7 (10.0) mmol/mol
Estimated mean HbA_{1c} (% DCCT) (SD)	7.4 (0.8)%	7.6 (0.9)%
% Given Pfizer/Biontech vaccine	41	51
% Given Oxford/AstraZeneca vaccine	59	49

Note: HbA_{1c} + glycosylated haemoglobin.

Data are given as mean ± standard deviation unless otherwise stated.

Abbreviations: BMI, body mass index; T1DM, type 1 diabetes.

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55.0% ± (SE) 2.0%). There was a significant decrease in the % interstitial glucose on target following the COVID vaccination in the 7 days following vaccination (range 0%–93%; mean 52.2% ± 2.0%) ($p = 0.030$) (Figure 2a and Table 2). This equated to a mean 2.8% (95% confidence interval CI 2.4%–3.0%) fall in the % interstitial glucose in the target range 3.9–10 mmol/L ($p = 0.02$). However, a significant number of people experienced major falls in the % interstitial glucose on target. Specifically, Figure 1 shows that 58% of individuals with T1DM showed a reduction in time in target range in the week after vaccination, 30% of individuals showed a decrease of time within range of over 10%, and 1 in 10 individuals showed a decrease in time within range of over 20%.

This phenomenon was mirrored by an increase the proportion of readings in the higher interstitial glucose categories 10.1–13.9 mmol/L and ≥14 mmol/L (Table 2). Interestingly, there was no significant change in interstitial glucose variability in the 7 days post-COVID-19 vaccination (mean 35.7% ± 0.74%) compared with the previous week (mean 36.3% ± 0.75%).

The perturbation of interstitial glucose continued into the second week after vaccination with a mean of 53.6% ± 1.75% of readings on target.

We also looked at the periods −4 to −2 weeks and +2 to +4 weeks for all the individuals with T1DM and found an average change in the proportion of interstitial glucose between 3.9 and 10 mmol/L of up to 1.2% week on week (week −4 to week −2 and week +2 to week +4) compared to the 2.8% change in the proportion of interstitial glucose readings in that range in the week immediately after COVID-19 vaccination.

Split by HbA_{1c} for the periods −4 to −2 weeks and +2 to +4 weeks, there was a 0.3% drop in the proportion of readings on target for those with HbA_{1c} 56 mmmol/mol (7.3%) or less and a 0.5% increase in the proportion of readings on target for those with HbA_{1c} >56mmol/mol (7.3%).

3.1 | Subgroup analysis

When categorised as higher or lower HbA_{1c} (by median HbA_{1c}), the time in range fell by 5.7% in those in lower HbA_{1c} group vs no change for participants in higher HbA_{1c} group ($p = 0.007$) (Figure 2b; data shown for weeks −2 to +2 in relation to vaccine administration). The change in interstitial glucose proportion on target in the week following vaccination was most pronounced for people using oral hypoglycaemic drugs in addition to basal-bolus insulin (Figure 2c). Specifically, the fall in the percentage on target in those using adjunctive oral hypoglycaemics was −7.6% versus 2.9% in those using insulin alone ($p = .009$). Importantly, no participants were started on corticosteroids in the 4-week period analysed here.

There was no significant difference in the change in proportion on target by: type of vaccine, age (split by median age of 44 years), sex, duration of diabetes (split by median duration of 17 years) or BMI (split by median BMI of 26.5 kg/m^2) (Figure 3).

When only the 27 participants on both insulin and oral medication are considered, 19 (70%) showed a reduction in time in range of whom 12 (44%) showed a fall of more than 10% of in the percent of readings on target.

For the 49 participants with better HbA_{1c} control (≤56 mmol/mol [7.3%]), 32 (65%) showed a fall in time in range, of whom 18 (37%) showed a fall of more than 10% in the % of readings on target.

For the 13 participants both on insulin and oral treatment and HbA_{1c} well controlled, 10 (76%) saw a fall in time in range for whom 6 (46%) the fall was more than 10% in the percent of readings on target. The percent of readings on target was lower for women than men for each of the 4 weeks examined as shown in Figure 3e (between 5% and 6% difference across those weeks).

On review of the clinical records, in all the individuals, there was no evidence of any other factor than the

TABLE 2 Outcome results for the 97 individuals with T1DM

Patients	Week before vax		Week after vax		Change in % of readings from week 0 to week 1	*p* value
	Average	Std. dev	Average	Std. dev		
% Results < 3.9 (mmol/L)	4.6	13.2	3.6	16.5	−1.0 (−22%)	0.0001
% Results in control (3.9–10 mmol/L) (target range)	55.0	20.1	52.2	19.6	−2.8 (−5%)	0.030
% Results (10.1–13.9 mmol/L)	25.4	10.5	27.1	9.9	+1.7 (+7.0%)	0.085
% Results (≥14.0 mmol/L)	15.1	16.7	17.2	16.6	+2.1 (+14.0%)	0.038
Average BG mmol/L	9.8	2.4	9.9	2.6	+0.1 (+1.0%)	0.164
Variability	36.3	7.4	35.7	7.2	−0.6 (−2.0%)	0.195

Note: p value is for a paired t-test.

Abbreviations: Avge, Average; Std dev, standard deviation across patients; Vax, vaccination.

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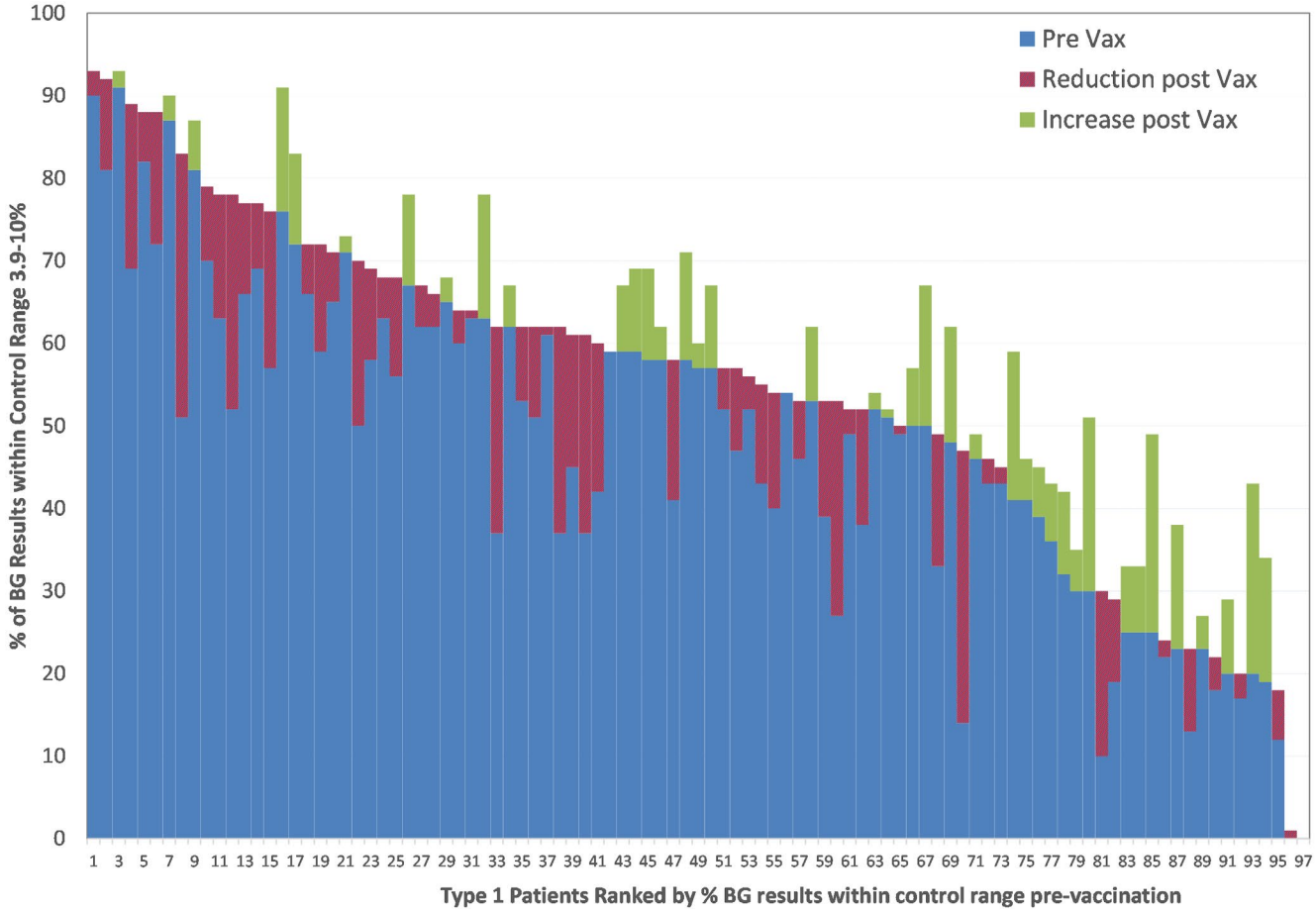

FIGURE 1 Individual patient results, % of results in control range (3.9–10 mmol/L) over 7 days before vaccination and change to 7 days after vaccination. A total of 55 (57%) participants showed an increase, whereas 39 (41%) participants showed a decrease, and 2 participants had no change

vaccination to account for the changes in interstitial glucose profile–that is there was no evidence of intercurrent illness, minor operation or other events that would significantly influence interstitial glucose levels.

3.2 | Multiple regression analysis

Multivariate linear regression analysis indicated that estimated HbA_{1c} (standardised beta 0.23, $p = 0.02$) and mode of treatment (insulin + oral hypoglycaemic agents (standardised beta −0.23, $p = 0.036$) were independently associated with a reduction in the proportion of interstitial glucose readings in the target range ($r^2 = 0.10$). The model included the independent variables of age ($p = 0.80$), BMI ($p = 0.76$) and type of vaccine ($p = 0.56$), which had no significant effect on this outcome.

On review of the clinical records, in all the individuals, there was no evidence of any other factor than the vaccination to account for the changes in interstitial glucose profile—that is there is no evidence of inter-current illness, minor operation or other events that would significantly influence interstitial glucose levels. No participant tested positive for COVID-19 in the 4-week period that we examined. There were no clinically reported inflammatory reactions at injection sites. 15% of participants reported myalgia post-COVID-19 vaccination and 22% reported malaise with 14% reporting headache.

4 | DISCUSSION

In a group of people with T1DM, we found that COVID-19 vaccination was associated with a temporary incremental change in interstitial glucose levels for many people. 58% of individuals with T1DM showed a reduction in time in target range in the week after vaccination. The effect was more pronounced in individuals with better blood glucose control on the basis of estimated HbA_{1c} (Figure 2b). Importantly, there was no difference between the Pfizer/Biontech Oxford/AstraZeneca vaccines in relation to their metabolic effect in the days after vaccination (Figure 3a).

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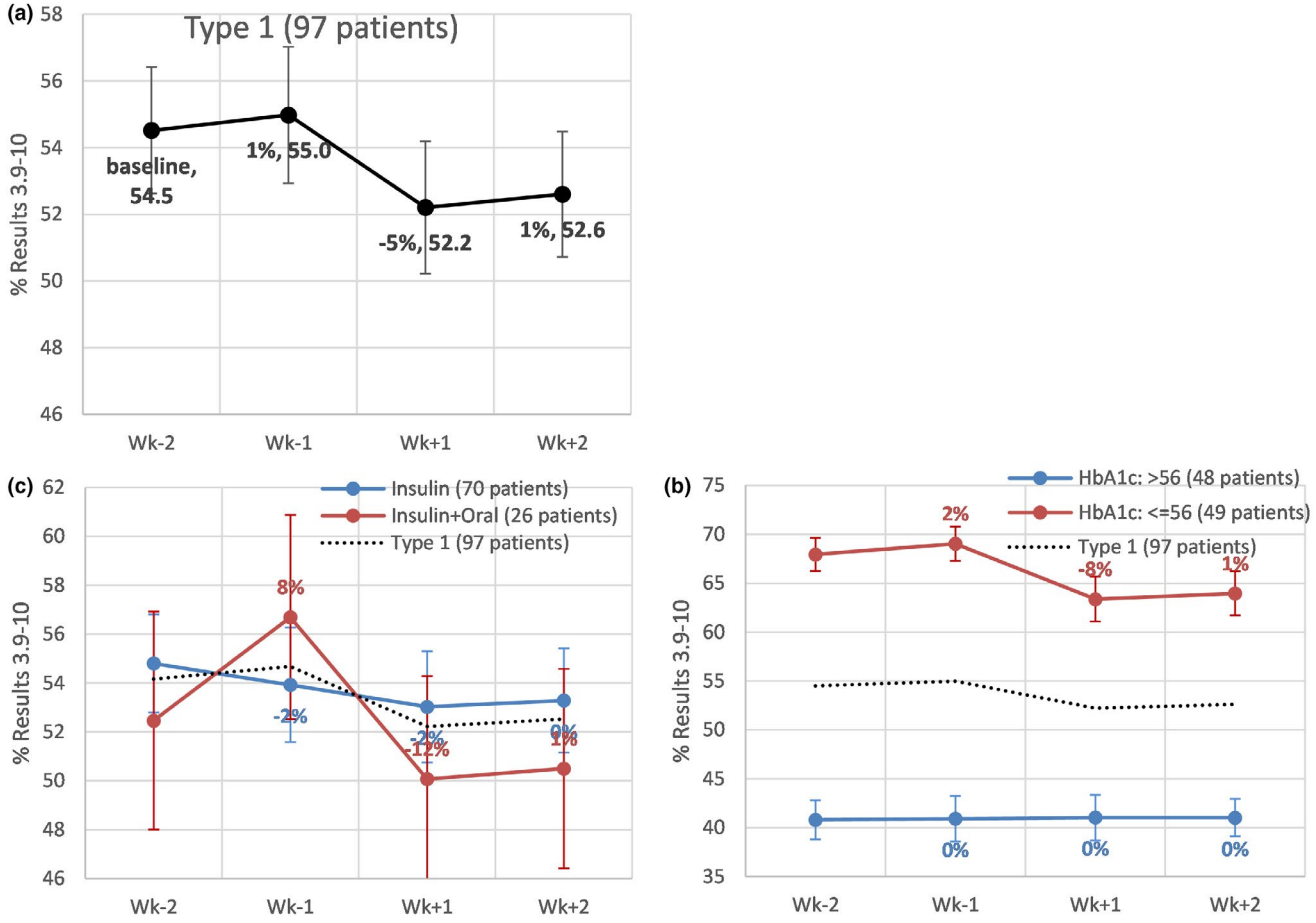

FIGURE 2 Development of indicator values over 4 weeks around the day of vaccination. The vaccination takes place on the transition between Week −1 and Week +1. The % shown change reflects the change to the previous week. The bar reflects the standard error (SE). The panels shown in (a)—all patients; (b)—split by median HbA_{1c} and (c)—split by insulin treated alone versus insulin + metformin or dapagliflozin

The reduction in the proportion of interstitial glucose readings in the target range of 3.9–10 mmol/L persisted into the second week after vaccination, although to a lesser degree (Figure 2a).

The percentage decrease in time in range interstitial glucose readings is transient, but the percentage reduction in below range interstitial glucose readings is of clinical relevance to those individuals in whom it is seen. The effect on interstitial blood glucose levels for many of the people with T1DM was more pronounced in those on adjunctive dapagliflozin or metformin than those on insulin alone.

There was a significant variation in the change in the proportion of interstitial glucose readings in the target range as shown in Figure 1 with some individuals showing improved control on this measure, likely due to natural variation.

The 2-week post-COVID-19 vaccination period was taken based on patient reports of the period of time in which they were seeing perturbation of blood glucose. We, therefore, wanted to take a comparable period before the COVID-19 vaccination, that is, 2 weeks, hence, the period for which we looked at interstitial glucose levels.

The fact that although the proportion of interstitial glucose readings on target decreased for many individuals, but variability of interstitial glucose did not change suggests that for these people there was an overall shift upwards in interstitial glucose levels, rather than any significant change in variability.

The finding that there was a greater reduction in the proportion of interstitial glucose readings on target for people with a lower HbA_{1c} (Figure 2b) may indicate that these individuals were more sensitive to the effects of vaccination on interstitial glucose levels. In essence they had 'more to lose' in terms of what in some individuals, was already a high proportion of interstitial glucose readings on target.

Clinical data support a robust neutralizing antibody response in patients with COVID-19 with diabetes[13] and that vaccination should be advocated. Our findings do indicate, however, that patients with T1DM should be counselled and prepared for possible transient hyperglycaemia following the COVID-19 vaccine.[14]

We are also not in a position as yet to appreciate whether such effects on interstitial glucose readings are seen in

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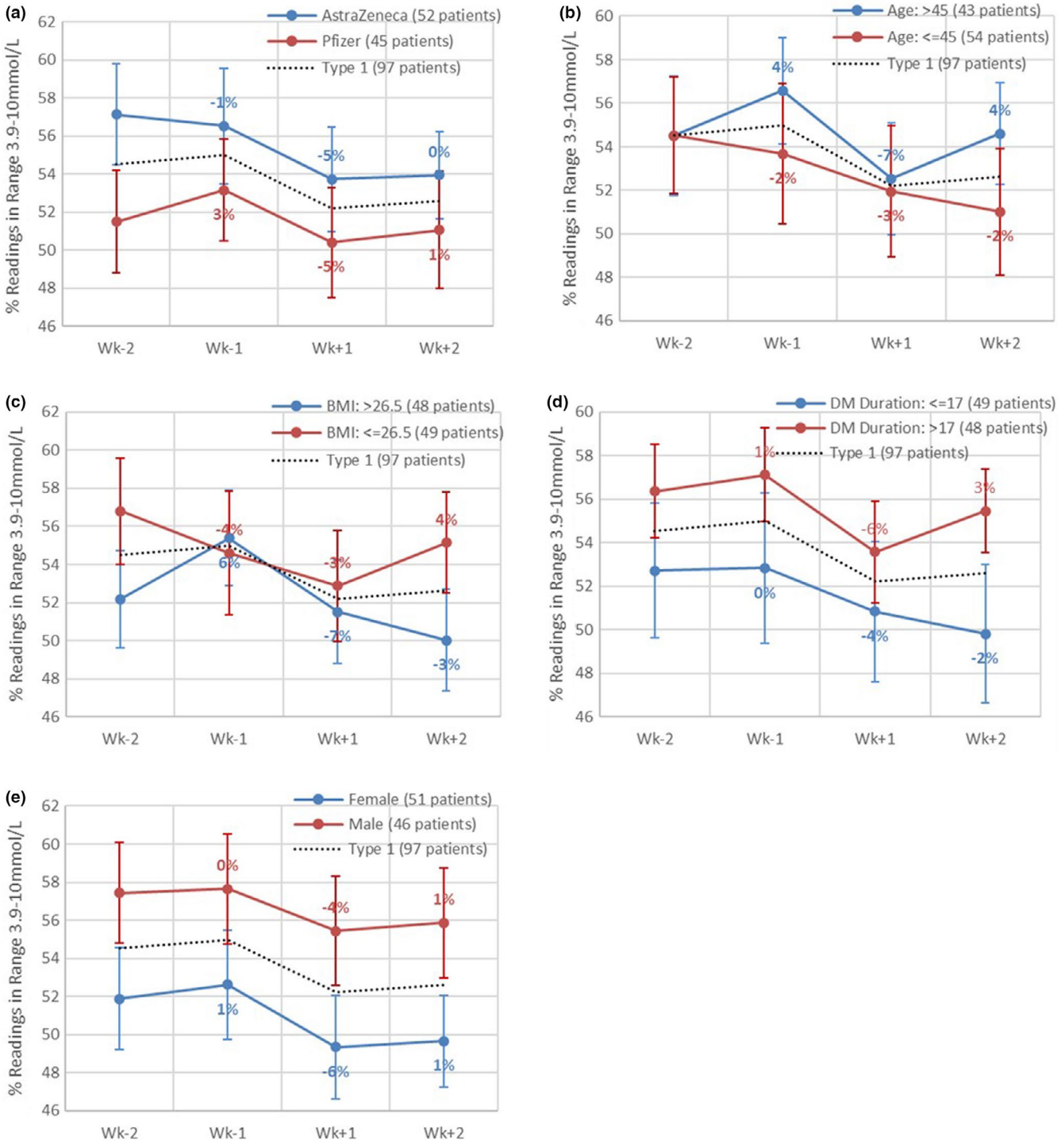

FIGURE 3 Percentage of time in range over the 4 weeks around the day of vaccination, stratified by patient characteristics. The vaccination takes place on the transition between Week −1 and Week +1. The percentages on the figures reflect the change in percentage time in range from the previous week. The bars reflect the standard error (SE). The separate panels show the population stratified according to: (a)—type of vaccine administered; (b)—median age; (c)—BMI; (d)—duration of T1DM and (e)—gender

patients with T1DM following their second vaccination. The planning for these studies is underway. Furthermore, a question remains as to whether altered/reduced immunity to COVID-19 vaccination in those with diabetes.

In relation to the rates of prescribing of dapagliflozin and metformin with insulin, the East Cheshire diabetes nurse (DSN) team have been very proactive about the use of adjunctive metformin and dapagliflozin in individuals with T1DM, with blood glucose levels consistently above target, and we have in fact reported the success of carefully considered dapagliflozin addition recently.[15]

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Both the Pfizer/Biontech and Oxford/AstraZeneca COVID-19 vaccines exert their effect by stimulating an antibody response to the spike protein of the virus.[16,17] The vaccines have different efficacy rates and slightly different side-effect profiles as described through the Joint Committee on Vaccination and Immunisation (JCVI) Independent report in April 2021.[18]

Vaccination for influenza has also been noted to cause blood glucose levels to become unstable for a time, perhaps related not only to a reaction to the virus but also to the excipients within the administered vaccine.[19] The UK Government previously published data of all UK spontaneous reports (received between 9/12/20 and 07/03/21) for mRNA Pfizer/BioNTech vaccine in which there were 27 cases of hyperglycaemia (not restricted to type 1 diabetes).[20] Similar reporting found 54 cases of hyperglycaemia (between 4/01/21 and 07/03/21) for COVID-19 vaccine Oxford University/AstraZeneca.[21] Furthermore, in a case series from India, in all three cases described there was historical exceptionally good compliance to diet and exercise before administration of the vaccine with a significant increase in blood glucose levels following vaccination with the Covishield™ vaccine.[22]

Our use of flash glucose monitoring allows identification of subclinical trends in dysglycaemia that may escape other forms of monitoring.[5–7]

Transient fluctuations in blood glucose have many causes. With our analysis of the cases revealing no other contributory factors such as infection or hypersensitivity to the excipients, it seems likely that the observed relative hyperglycaemia was associated with the COVID-19 vaccination.

One possible mechanism for the hyperglycaemia described here, is stimulation of the immune system resulting in a transient stress response, to a milder degree than would typically occur with a COVID-19 infection. Physiologic stress has the potential to increase counter regulatory hormone levels.[23] Most notable among these are adrenaline, growth hormone and cortisol and/or glucagon in those with alpha cell reserve. People with T1DM may be less able to rapidly counteract such elevations in blood glucose.[24] The series that we report comprises individuals having their first COVID vaccine. It has been reported that people with prior COVID-19 infection reported side effects from the vaccine more frequently after the first dose.[25]

Vaccinations, by nature of their intended purpose, elicit an immune response, often to varying degrees within and between individuals determined by a wide range of factors some of which reside within the vaccine, for example, the type of adjuvant or within the host, for example, immune response genes. Sestan et al.[26] reported in 2018 that viral-induced inflammation leads to insulin resistance in the skeletal muscle, followed by compensatory hyperinsulinemia, which promotes the anti-viral effector response of CD8+ T cells.

It is not surprising that such immune responses have complex down-stream effects on metabolism including regulation of blood glucose levels. A range of cytokines produced through immune-driven inflammation are known to impact on blood glucose levels and insulin resistance within tissues.[23,27] Such actions are likely to have complex and further biological interplay with factors including adipokines, hormones and cortisol. In individuals with existing impaired glucose control, this is likely to be more pronounced.

Individual patient knowledge and involvement remain the cornerstones of diabetes management. Therefore, it is important to inform individuals with T1DM about the phenomenon reported here, whereas future research may shed more light on the underlying mechanisms.

4.1 | Strengths and limitations

While we report these results in a group of 97 people with T1DM at once centre, this is based on day to day flash glucose monitoring over a period of 4 weeks.

A limitation is that we have not quantified what (if any) changes were made in the insulin doses during the week following the COVID-19 vaccine. The change in % interstitial glucose on target post-COVID-19 vaccination could have been larger than we have seen, with subsequent mitigation by measures that were taken by the participants studied, such as increased dose of prandial insulin. There was no measurement of inflammatory markers such as baseline/pre-vaccination C-reactive protein (CRP) versus CRP post-vaccination, as this was a real-world study conducted in real time in light of patient reports of blood glucose perturbation post-COVID-19 vaccination. Furthermore, we accept that a proportion of participants did not experience any deterioration in interstitial glucose control following COVID-19 vaccination. We are also not yet in a position to compare first and second vaccination effects on interstitial glucose regulation. Finally, we did not have serological data in our participant group for prior infection.

5 | CONCLUSIONS

In a group of individuals with T1DM, we have shown that COVID-19 vaccination can cause temporary perturbation of interstitial glucose in people with T1DM with this effect more pronounced in those people with better pre-vaccination blood glucose control (as measured by HbA_{1c}) but no difference in effect between the Pfizer/Biontech Oxford/AstraZeneca COIVD-19 vaccines. This finding is of relevance to people with T1DM and to clinicians.

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A larger, multi-site patient series is necessary to investigate this further. However, the results here raise the question of whether people with T1DM should be given specific advice in advance of COVID-19 booster vaccination in relation to potential temporary effects on their glycaemic control.

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CONFLICT OF INTEREST

No author has any conflict of interest.

AUTHOR CONTRIBUTIONS

AHH prepared all drafts of the paper. Extraction and validation of patient data were undertaken by LH. Data analysis was performed by MS with contributions from SGA. RR, JMG, MW, SGA and WO provided ongoing input to the manuscript with senior review by WO.

DATA AVAILABILITY STATEMENT

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

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