Time in Range (TIR) following flash glucose monitoring; relationship with glycaemic control, diabetes-related distress (DRD) and resource utilisation in the Association of British Clinical Diabetologists (ABCD) national audit

Harshal Deshmukh[1,2], Emma Wilmot[3,4], Beatrice Pieri[1,2], Pratik Choudhary[5], Najeeb Shah[1,2], Robert Gregory[5], Anne Kilvert[6], Alistair Lumb[7], Peter Christian[8], Dennis Barnes[9], Jane Patmore[2], Chris Walton[2], R E J Ryder[10], Thozhukat Sathyapalan[1,2]

1) Department of Academic Diabetes and Endocrinology, University of Hull UK.
2) Allam Diabetes centre, Hull University teaching Hospital NHS Trust UK.
3) University Hospitals Derby and Burton NHS Foundation Trust UK.
4) University of Nottingham, Nottingham UK.
5) Leicester Diabetes Centre Leicester General Hospital UK.
6) Northampton General Hospital NHS Trust, Northampton, UK.
7) Oxford University Hospitals NHS Foundation Trust, UK.
8) William Harvey Hospital, UK.
9) Tunbridge Wells Hospital, Tunbridge Wells, UK
10) City Hospital, Birmingham, U.K.

Running Title: Time in Range and Diabetes outcomes

Corresponding Author
Prof Thozhukat Sathyapalan
Hull University Teaching Hospitals NHS Trust
University of Hull
E-mail: thozhukat.sathyapalan@hyms.ac.uk

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Abstract

Introduction

With increasing access to continuous glucose monitoring (CGM), particularly intermittently scanned CGM (isCGM) (FreeStyle Libre), it is essential to understand the relationship between Time in Range (TIR) achieved using the isCGM with changes in glycaemic control, diabetes-related distress (DRD), and resource utilisation in people living with Diabetes.

Methods

Clinicians from 106 NHS UK hospitals submitted isCGM user baseline and follow up data in a web-based tool held within the UK National Health System (NHS) network. Linear regression analysis was used to identify the relationship between follow-up glucose TIR (3.9-10mmol/l) categories (TIR% 50-70 and TIR% >70) with change in HbA1c, DRD and Gold score (measure of hypoglycaemia unawareness, where a score ≥4 suggests impaired awareness of hypoglycaemia).

Results

Of 16,427 participants, 1241 had TIR follow up data available. In this cohort, the mean TIR was 44.8% (±22.5). With the use of isCGM, at 7.9 months mean follow up, improvements were observed in HbA1c (-6.9 (13.5) mmol/mol, P<0.001), Gold score (-0.35(1.5), P<0.001) and DDS (-0.73 (1.23), P<0.001). In the regression analysis restricted to people living with type 1 diabetes, TIR% 50-70 was associated with a -8.9 mmol/mol (±0.6, P<0.001) reduction in HbA1c; TIR% >70 with a -14mmol/mol (±0.8, P<0.001) reduction in HbA1c Incremental improvement in TIR% was also associated with significant improvements in Gold score and DRD. TIR% >70 was associated with no hospital admissions due to hypoglycaemia, hyperglycaemia/DKA, and a 60% reduction in the paramedic call-outs and 77% reduction in the incidence of severe hypoglycaemia.

Conclusion

In a large cohort of UK isCGM users, we demonstrate a significant association of higher TIR% with improvement in HbA1c, hypoglycaemia awareness, DRD and resource utilisation.

Keywords: Time in Range, Time below range, Glycaemic control, Diabetes-related distress, Gold score

Introduction

In the last decade, real-time continuous glucose monitoring (rtCGM) and intermittently scanned CGM (isCGM) have emerged as essential tools to support people living with Diabetes to monitor and manage their glucose levels, leading to improved glycaemic control[1-5]. With the arrival of this new technology, several new matrices for monitoring glucose levels have been recommended for use in clinical practice, such as TIR Time below Range (TBR) and Time above Range (TAR)[5]. TIR is now considered a key measure of therapeutic success[5,6]. The international consensus on TIR recommends[6,7] standardised reporting of the percentage of glucose values, which fall within the target range of 3.9–10 mmol/l range. The target for people living with type 1 and type 2 diabetes is for %TIR >70 (16 h 48 min/day) between 3.9-10mmol/l[7]..

To the best of our knowledge, there are no population-based studies that look at the relationship between follow up TIR% achieved with the isCGM and HbA1c, hypoglycaemia awareness, diabetes-related distress and severe hypoglycaemia (SH). There are also no data on the effect of TIR% on hospital admissions due to hypoglycaemia, hyperglycemia/DKA, and paramedic call-outs in people with diabetes. Therefore, the objective of this study was to assess the relationship between the TIR achieved at follow-up following isCGM initiation, with change in HbA1c, hypoglycaemia unawareness, diabetes related distress, SH and resource utilisation in people living with diabetes.

Methods

This observational study analysed data collated from the nationwide ABCD audit on FreeStyle Libre that started in November 2017. We collected baseline data before isCGM initiation, such as patient demographics, previous completion of structured diabetes education, duration of diabetes, Body Mass Index (BMI), HbA1c values from the previous 12 months. Baseline data also included the Gold score[9], Diabetes Distress Screening scale (DDS2)[10] and severe hypoglycaemia (SH), defined as hypoglycaemia requiring third-party assistance, paramedic callouts, hospital admissions due to hypoglycaemia in the previous 12 months. The follow-up data was collected at the routine follow-up appointment for people living with diabetes in the participating NHS hospitals. Follow-up variables included Gold score[9], HbA1c, DDS2, BMI, SH episodes, paramedic callouts, and hospital admissions due to hypoglycaemia since the previous clinic visit. The Gold score[9] is a validated screening tool used to assess awareness of hypoglycaemia. It is a 7-point Likert scale that asks the question, "do you know when your hypos are commencing?". 1 is "always aware" and seven is "never aware". Diabetes-related distress was measured using the two-item diabetes distress screening tool (DDS2)[10].

All the participants in the audit were prescribed the isCGM (16,427). The NHS physicians who see them in the hospital recruits the patients in the audit, only if they are initiated on the isCGM. Of the 16,427 only a subset of patients had a follow-up (n=6859). Of these 6859, 3250 patients had a recorded TIR in the study. In the 3250 with TIR data, 1,241 (38%) reported data that aligned with the international consensus range of 3.9 to 10 mmol/l. The people who had TIR data had used isCGM more than 70% of the time and this data was downloaded from the isCGM at the first follow-up visit. In February 2019, the Advanced Technologies & Treatments for Diabetes (ATTD) Congress convened an international panel of individuals with diabetes and clinicians and researchers with expertise in CGM . This expert panel reached a consensus on glycemic cut-points -a target range 3.9–10.0 mmol/L for individuals with type 1 diabetes. However, some clinicians decide to modify this range based on clinical presentation

of the patient or simply by patient's choice. When the consensus on glycaemic cut-points for TIR is not used/recommended it is referred to as a personalised TIR

There were also variables specific to isCGM use, and TIR, TBR. Since the international recommendations for TIR were not published at the start of the audit, we had allowed clinicians to report personalised TIR. For the purposes of this paper, TIR data reported which aligns with the international consensus on TIR (3.9-10mmol/l), are reported. The TIR reported in the study is the TIR averaged over the 14-day period obtained from the download at the first follow-up visit.

Statistical methods

All the statistical analyses were done in R version 4.1.2 (https://www.r-project.org/). We labelled the follow-up TIR into three categories TIR%<50, TIR% 50-70 and TIR% >70. We used the non-parametric Kruskal-Wallis test to compare the baseline characteristics of the study population in the three TIR% categories.. The data for this study consisted of people living with T1D who were recommended to use the international consensus on TIR (3.9-10mmol/l range) on their isCGM. We used the TIR data downloaded at the first follow-up visit for analysis. We used regression analysis to estimate the independent effect of TIR% categories on change in HbA1c, DDS and Gold scores. The regression models used the change in HbA1c, DDS and Gold score as dependent variables and TIR% (as a factor variable) and other covariates as independent variables, including the baseline HbA1c. Using TIR% as a continuous variable, we estimated the absolute change in HbA1c with a 10% improvement in TIR%. The baseline data for hospital admissions, paramedic call-outs and severe hypoglycaemia (SH), hyperglycaemia/DKA was available for 12 months preceding the use of isCGM. Since the follow-up data were available for only a mean of 7.9 months, we calculated monthly pro-rata hospital admissions, paramedic call-outs and severe hypoglycaemia before

and after using isCGM. Using the estimates for monthly hospital admissions, paramedic call-outs and SH, we computed a percentage decrease in these parameters with the use of isCGM.

Ethical approval

The ABCD nationwide audit program has Caldicott Guardian approval. Guidelines were followed, including that only routine data was collected from centres involved in the audit and data collected was anonymised when submitted to the central database.

Results

Baseline characteristics of the study population

The study consisted of 16,427 people with baseline data, of which 6859 people had paired baseline and follow up data, and a subset (n=3250) with reported TIR. In the 3250 with TIR data, 1,241 (38%) reported data that aligned with the international consensus range of 3.9 to 10 mmol/l. **Table 1** shows the baseline clinical and demographic characteristics of the people living with diabeteswith and without TIR in the study population. Those with TIR data were likely to be older, more likely to be Caucasians and have a significantly higher duration of diabetes and a lower baseline HbA1c.

Table 2 compares the baseline demographics and clinical characteristics of people with diabetes who achieved the TIR%<50, TIR% 50-70 and TIR% >70 at the mean follow-up period of 7.9 months. In this univariate analysis, those who achieved TIR% 50-70, and TIR% >70 were more likely to be older (P<0.001), have a lower baseline HbA1c (P<0.001), and have

lower DRD (P<0.001) at baseline. In addition, the duration of diabetes, baseline Gold score and completion of structured education had a significant but limited absolute effect on the attainment of TIR% 50-70 and TIR% >70 at follow-up.

Relationship between TIR achieved and change in HbA1c, DDS and Gold score

Figure 1a and Fig 1b shows that there was a significant negative correlation between the TIR% and pre-isCGM HbA1c (r^2=-0.45 P-value <0.001) and post-isCGM HbA1c at follow-up (r^2=-0.68 P-value <0.001). With the use of isCGM, at a mean follow-up period of 7.9 months, the improvement in HbA1c was -7 (13) mmol/mol, P<0.001, Gold score -0.35 units (±1.5), P<0.001, and DDS -0.73 (±1.23), P<0.001. In this cohort, the mean TIR was 44.8% (±22.5). The mean follow-up HbA1c in people who achieved TIR%<50 was 71.3 mmol/mol, in TIR% 50-70 was 57.3mmol/mol, and TIR%>70 was 51.2 mmol/mol. The mean reduction in the HbA1c in TIR%<50, TIR% 50-70 and TIR% of >70 on the univariate analysis was -5.2 mmol/mol, -5.5 mmol/mol and -9.8 mmol/mol respectively and significantly different across the three TIR categories(P <0.001).

The mean reduction in DDS in TIR%<50, TIR% 50-70 and TIR% of >70 on the univariate analysis was -0.72 units, -0.75 units and -0.71 units and were not significantly different across the three groups (P=0.94). The reduction in Gold score in TIR%<50, TIR% 50-70 and TIR% of >70 on the univariate analysis was -0.33 units, -0.59 units and -0.51 units and were significantly different (P=0.008) across the three groups.

Relationship between TIR% categories on follow-up HbA1c, DDS and Gold score

Table 3 shows the results of adjusted estimates from the linear regression model for the change (follow-up- baseline) in HbA1c, Gold score and DDS in the TIR% 50-70 and TIR% >70 categories with TIR% <50 as the reference group. A TIR% 50-70 category was associated with -8.9 mmol/mol (±0.6), P<0.001 reduction in HbA1c and TIR% >70 was associated with -14mmol/mol (±0.8), P<0.001 reduction in HbA1c.. In order to estimate the association of 10% increase in TIR with post isCGM HbA1c we divided the TIR by 10% and used it as a continuous dependent variable in the regression model adjusted for baseline variables. In these analysis 10 units (which is 10%) increase in TIR was associated with 3.54 mmol/mol improvement in the HbA1c. The regression analysis also showed that the pre-isCGM HbA1c was also an independent predictor of reduction in HbA1c with the use of isCGM (Beta=-0.57 (±0.01) P<0.001).

Similarly, the reduction in the DDS was associated with significantly greater in TIR% 50-70 (Beta=-0.29 (±0.07), P<0.001) and TIR% >70 (Beta=-0.40 (±0.09), P<0.001). There was also a borderline significant reduction in the follow-up Gold score in the TIR% 50-70 (Beta=-0.17 (±0.08), P=0.05) and a statistically significant reduction in Gold score in the TIR% >70 categories (Beta=-0.32 (±0.15), P=0.01). The adjusted r-squared for change in HbA1c, DDS, and Gold score models was 0.53, 0.48 and 0.35, respectively, indicating a good model fit for all three models.

Relationship between TIR and resource utilisation

Overall, the use of isCGM with a mean follow-up period of 7.9 months, was associated with a 48% reduction in hypoglycaemia related admissions, a 43% reduction in the hyperglycaemia/DKA related hospital admissions and a 77.2% reduction in the paramedic call-

outs. The study participants who achieved the TIR% 50-70% had no hypoglycaemia related hospital admissions, a 7.8% reduction in hyperglycaemia/DKA related hospital admissions and an 80% reduction in paramedic callouts. The study participants who achieved TIR >70% had no hospital admissions due to hypoglycaemia, hyperglycaemia/DKA and a 60% reduction in paramedic call-outs.

As compared to the pre isCGM there was also a significant reduction in severe hypoglycaemia (SH) associated with the use of isCGM with a 77% overall reduction in the episodes of SH. The study participants with TIR% 50-70 was associated with 87% reduction in SH. In comparison, in the study participants with TIR% >70% was associated with 77% reduction in the incidence of SH during the follow-up period.

Discussion

In a large cohort of UK isCGM users, we demonstrate a significant improvement in HbA1c, hypoglycaemia awareness, DRD, and resource utilisation associated with the achieved follow up TIR% category.

With the increasing uptake of rtCGM and isCGM, TIR has emerged as a crucial parameter to monitor and optimise glucose levels in people with diabetes[3,5-7]. TIR%, , is destined to become central to the diabetes consultation given the ease of interpretation for both health care workers and people living with diabetes. However, the effect of HbA1c on microvascular and macrovascular complications of diabetes has been extensively studied[11-13], firmly cementing its role as a routinely measured outcome in diabetes care. Nonetheless, early studies

investigating the association between TIR and complications in diabetes have shown promising results. For example, recent studies have shown a positive correlation between improved TIR and better outcomes for diabetic retinopathy[14], diabetic peripheral neuropathy[15] and reduction in albuminuria[16] with improved TIR. Another study[17] looked at the association between TIR and carotid intima-media thickness (CIMT) and showed that those with normal CMIT maintained a higher TIR as compared to those with lower TIR. Beck et al[18]. explored the TIR% with microvascular outcomes in the DCCT cohort and demonstrated a relationship between TIR% and both retinopathy and microalbuminuria[18]. Given these promising results, there is a need to investigate the relationship between TIR% and long-term micro and macro-vascular outcomes.

The ABCD audit studies [19,20] and others studies[21-24] have previously shown a significant beneficial effect of isCGM on glycaemic control, DRD, hypoglycaemia unawareness and resource consumption in people living with diabetes. Here, we have extended our analysis to explore the relationship between TIR% and the changes seen in HbA1c, hypo awareness and acute events in people started on the ISCGM. This study has shown that TIR%<50, TIR% 50-70 and TIR% >70 corresponds to an average HbA1c of 71.3 mmol/mol 57.3 mmol/mol and 51.2 mmol/mol, respectively. This agrees with previous studies, which show a comparable association between HbA1c and TIR%[5]. Furthermore, the use of regression analysis, adjusted for baseline covariates, shows that, if the TIR% 50-70 is achieved, we can expect up to -8.7mmol/mol reduction in HbA1c following ISCGM initiation. TIR% of >70 is associated with a -14.1 mmol/mol reduction in HbA1c.

Using the data from the ABCD audit we have previously shown that the use of isCGM is associated with a significant reduction in diabetes-related distress when measured by the DDS2 scale[20]. We now show that the beneficial effect of isCGM on DRD- is associated by TIR% with an additional reduction in DRD with incremental improvements in TIR%. The use of isCGM

was associated with improvement in Gold score and hypoglycaemia awareness in the study population and is also associated with TIR% with a higher TIR% associated with a more significant reduction in the Gold score.

Several studies [19,18] [23,25] have shown the significant benefit of isCGM on resource utilisation in people living with diabetes. For example, A. Jeyam et.al[23] analysed data from the Scottish diabetes registry and showed a 41% reduction in DKA using isCGM in the Scottish diabetes registry. In the present study, we show similar estimates with 43% reductions in hospital admissions due to hyperglycaemia/DKA. Here we show that participants who achieved a TIR >50% showed no hypoglycaemia related hospital admissions in the mean 7.9 month follow-up period and significant reductions in episodes of admissions related to DKA, SH and paramedic call-outs. These results show the importance of TIR% in improving resource utilisation in people living with diabetes.

The international consensus on TIR published their recommendation in 2019, and our data, collected up to December 2021, suggest that these recommendations have still to become embedded in routine clinical practice, with only 38% of the health care professionals reporting data which aligned to the recommended 3.9 to 10 mmol/l range. This highlights the need to increase awareness and encourage wider adoption of international consensus TIR for people living with diabetes and the health care professionals supporting them. We have shown that a %TIR of >70% was associated with a more significant improvement in glycaemic control, diabetes-related distress and resource consumption following isCGM initiation. However, it is not always feasible to achieve a TIR% of >70 in some people. It is therefore reassuring that those who achieved a TIR% of 50-70% also experienced benefits from the isCGM, including improvement in HbA1c, reduced diabetes-related distress and resource utilisation.

Our study has several limitations. Firstly, this was an observational study with no randomisation arm. Secondly, hospital admissions and SH data may be subject to recall bias. Next, the follow-up period of this study is 7.9 months, and it remains to be seen if the people living with diabetes can maintain a stable TIR% with the use of isCGM over long periods and if the benefits associated with this persist on a more extended follow-up period. A further limitation was the low reporting of TIR data which aligned with the recommended 3.9-10mmol/l range. We also see differences in the baseline characsteric in participants who had follow-up TIR data and those who did not. It is unclear how these differences can affect the study outcome. Nevertheless, despite the limitations, this is the first real-world study looking at a comprehensive list of short-term diabetes-related outcomes and provides valuable insights into the correlation between these outcomes and TIR.

In summary, our study supports the use of international consensus TIR of 3.9–10 mmol/L and TIR% >70 for optimal glycaemic control, reduction in diabetes-related distress and resource consumption following isCGM initiation. To realise the potential benefits, awareness of the international TIR recommendations will need to be promoted amongst health care professionals.

Table 1: Baseline clinical and demographic characteristics of the people with and without time in range data

	People with no TIR data (N=13,177)	**People with TIR data (N=3,250)**	**P-value**
Age (years) median (IQR)	39 (25-54)	42(27-56)	<0.001
Sex, % female	6509 (49.4%)	1745 (53.6%)	0.64
Ethnicity			
Caucasians	9814 (74%)	2909 (89%)	<0.001
All other ethnicities and no reported ethnicity	3363(24%)	341 (11%)	
Baseline BMI (kg/m^2) median (IQR)	25.3(22.2-29.0)	25.5(22.2-29.1)	0.38
Duration of diabetes (years) median (IQR)	16 (7-19.9)	18 (7-31)	<0.001
Type 1 diabetes	12139 (92%)	2990 (92%)	0.5
Type 2 diabetes	117 (0.1%)	19 (0.1%)	
Other types of diabetes	921(8%)	241(8%)	
Completion of structured education	3462 (26%)	980 (30%)	0.01
Average pre-isCGM HbA1c (mmol/mol) (%) median (IQR)	68(58-80.6)	66.0(57.0 -76.3)	<0.001
Baseline DDS2	3.03(±1.4)	2.89(±1.4)	0.3
Gold score	2.72(±1.75)	2.65(±1.71)	0.08
≥4 Gold score(IAH)	3928 (29%)	825 (25%)	0.4

Table 2: Baseline characteristics of study participants who achieved TIR% of 50-70 (n=439) and TIR% of >70

	TIR<50 (n=594)	TIR 50-70 (n=439)	TIR>70 (n=208)	P-value*
Age (years)	38.2(±18.2)	44.3 (±17.3)	46.3 (±17.7)	<0.001
Gender (Female %)	49%	40%	45%	0.59
Baseline BMI (kg/m^2)	25.5(±5.9)	26.4(±6.1)	25.9(±5.1)	0.02
Duration of diabetes (years)	15 (7-27)	22 (10-35)	16 (13-33)	<0.001
Pre-isCGM HbA1c (mmol/mol)	76.6 (±17.5)	62.8 (±11.8)	61 (±19.6)	<0.001
Baseline DDS2	3.1 (±1.3)	2.7 (±1.3)	2.5 (±1.1)	<0.001
Baseline Gold score	2.7 (±1.7)	2.9 (±1.6)	2.5 (±1.5)	0.01

*P-value from Kruskal-Wallis test

TIR: Time in Range

Table 3: Regression analysis showing independent effects of TIR% categories on follow-up HbA1c, Gold score and DDS in people with Type 1 diabetes

	HbA1c*		Gold Score**		DDS***	
	Beta(SE)	P-value	Beta(SE)	P-value	Beta(SE)	P-value
TIR 50-70	-8.9(±0.6)	<0.001	-0.17(±0.12)	0.082	0.29 (±0.07)	<0.001
TIR >70	-13.9 (±0.8)	<0.001	-0.32(±0.15)	0.013	0.40 (±0.09)	<0.001

*Adjusted for age, gender, BMI, baseline HbA1c and duration of diabetes and duration of follow-up

** Adjusted for age, gender, BMI, baseline Gold score and duration of diabetes and duration of follow-up

** *Adjusted for age, gender, BMI, baseline DDS and duration of diabetes and duration of follow-up

Figure 1a and Figure 1b: Correlation between TIR with baseline HbA1c and Post-isCGM HbA1c

Legend Figure 1a and Figure 1b: Figure 1 and Figure 1b show the correlation plots of the TIR with pre isCGM HbA1c and post isCGM HbA1c

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Conflicts of interest

The ABCD nationwide FSL audit is supported by a grant from Abbott Laboratories. EGW serves on the advisory panel for Abbott Diabetes Care, Dexcom, and Eli Lilly and Company; has received research support from Diabetes UK; and is on the speakers bureau for Abbott Diabetes Care, Dexcom, Eli Lilly and Company, Insulet Corporation, Novo Nordisk, and Sanofi. CW has a spouse/partner serving on the advisory panel for Celgene and on the speakers bureau for LEO Pharma and Novartis. REJR serves on the advisory panel for Novo Nordisk A/S and on the speakers bureau for BioQuest. TS is on the speakers bureau for NovoNordisk Foundation and reports a relationship with Bristol-Myers Squibb, Eli Lilly and Company, and Sanofi. HD is partly funded through the NIHR academic programme. No other potential conflicts of interest relevant to this article were reported. The FSL audit was independently initiated and performed by ABCD, and the authors remain independent in the analysis and preparation of this report.

Novelty Statement

What is already known?

- Time in range (TIR) is now considered a key measure of therapeutic success in people living with diabetes, especially, those on insulin treatment.

What this study has found?

- Our study supports the use of international consensus TIR of 3.9–10 mmol/L and TIR% >70 for optimal glycaemic control, reduction in hypoglycaemia unawareness and diabetes-related distress and resource consumption following isCGM initiation.

What are the implications of the study?

- To realise the potential benefits of TIR, awareness of the international TIR recommendations will need to be promoted amongst health care professionals.

Author Contributions

HD, EW, CW, REJR and TS conceived the paper. HD and BP did the statistical analysis and HD wrote the first draft. EW, CW, REJR, BP, PC, NS, RG, AK, AL, PC, JP, and TS critically reviewed the manuscript, made changes, and provided comments for the discussion. TS provided overall supervision for the project.

References

1. Olczuk D, Priefer R. A history of continuous glucose monitors (CGMs) in self-monitoring of Diabetes mellitus. *Diabetes Metab Syndr.* 2018;12(2):181-187.
2. Heinemann L. Continuous Glucose Monitoring (CGM) or Blood Glucose Monitoring (BGM): Interactions and Implications. *J Diabetes Sci Technol.* 2018;12(4):873-879.
3. Beck RW, Bergenstal RM, Laffel LM, Pickup JC. Advances in technology for management of type 1 diabetes. *Lancet.* 2019;394(10205):1265-1273.
4. Moser O, Riddell MC, Eckstein ML, et al. Glucose management for exercise using continuous glucose monitoring (CGM) and intermittently scanned CGM (isCGM) systems in type 1 diabetes: position statement of the European Association for the Study of Diabetes (EASD) and of the International Society for Pediatric and Adolescent Diabetes (ISPAD) endorsed by JDRF and supported by the American Diabetes Association (ADA). *Diabetologia.* 2020;63(12):2501-2520.
5. Wilmot EG, Lumb A, Hammond P, et al. Time in range: A best practice guide for UK diabetes healthcare professionals in the context of the COVID-19 global pandemic. *Diabet Med.* 2021;38(1):e14433.
6. Wright LA, Hirsch IB. Metrics Beyond Hemoglobin A1C in Diabetes Management: Time in Range, Hypoglycemia, and Other Parameters. *Diabetes Technol Ther.* 2017;19(S2):S16-S26.
7. Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. *Diabetes Care.* 2019;42(8):1593-1603.
8. Saboo B, Kesavadev J, Shankar A, et al. Time-in-range as a target in type 2 diabetes: An urgent need. *Heliyon.* 2021;7(1):e05967.
9. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I Diabetes with impaired awareness of hypoglycemia. *Diabetes Care.* 1994;17(7):697-703.
10. Fisher L, Glasgow RE, Mullan JT, Skaff MM, Polonsky WH. Development of a brief diabetes distress screening instrument. *Ann Fam Med.* 2008;6(3):246-252.
11. Diabetes Control and Complications Trial (DCCT): results of feasibility study. The DCCT Research Group. *Diabetes Care.* 1987;10(1):1-19.
12. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes.* 1995;44(8):968-983.
13. Diabetes C, Complications Trial /Epidemiology of Diabetes I, Complications Study Research G. Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30-Year Follow-up. *Diabetes Care.* 2016;39(5):686-693.
14. Lu J, Ma X, Zhou J, et al. Association of Time in Range, as Assessed by Continuous Glucose Monitoring, With Diabetic Retinopathy in Type 2 Diabetes. *Diabetes Care.* 2018;41(11):2370-2376.
15. Ahmad I, Noohu MM, Verma S, Singla D, Hussain ME. Effect of sensorimotor training on balance measures and proprioception among middle and older age adults with diabetic peripheral neuropathy. *Gait Posture.* 2019;74:114-120.
16. Ranjan AG, Rosenlund SV, Hansen TW, Rossing P, Andersen S, Norgaard K. Improved Time in Range Over 1 Year Is Associated With Reduced Albuminuria in Individuals With Sensor-Augmented Insulin Pump-Treated Type 1 Diabetes. *Diabetes Care.* 2020;43(11):2882-2885.
17. Lu J, Ma X, Shen Y, et al. Time in Range Is Associated with Carotid Intima-Media Thickness in Type 2 Diabetes. *Diabetes Technol Ther.* 2020;22(2):72-78.

18. Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. *Diabetes Care.* 2019;42(3):400-405.
19. Deshmukh H, Wilmot EG, Gregory R, et al. Effect of Flash Glucose Monitoring on Glycemic Control, Hypoglycemia, Diabetes-Related Distress, and Resource Utilization in the Association of British Clinical Diabetologists (ABCD) Nationwide Audit. *Diabetes Care.* 2020;43(9):2153-2160.
20. Deshmukh H, Wilmot EG, Gregory R, et al. Predictors of diabetes-related distress before and after FreeStyle Libre-1 use: Lessons from the Association of British Clinical Diabetologists nationwide study. *Diabetes Obes Metab.* 2021;23(10):2261-2268.
21. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kroger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *Lancet.* 2016;388(10057):2254-2263.
22. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes: a Multicenter, Open-Label Randomized Controlled Trial. *Diabetes Ther.* 2017;8(1):55-73.
23. Jeyam A, Gibb FW, McKnight JA, et al. Flash monitor initiation is associated with improvements in HbA1c levels and DKA rates among people with type 1 diabetes in Scotland: a retrospective nationwide observational study. *Diabetologia.* 2022;65(1):159-172.
24. Tyndall V, Stimson RH, Zammitt NN, et al. Marked improvement in HbA1c following commencement of flash glucose monitoring in people with type 1 diabetes. *Diabetologia.* 2019;62(8):1349-1356.
25. Roussel R, Riveline JP, Vicaut E, et al. Important Drop in Rate of Acute Diabetes Complications in People With Type 1 or Type 2 Diabetes After Initiation of Flash Glucose Monitoring in France: The RELIEF Study. *Diabetes Care.* 2021;44(6):1368-1376.