DIABETICMedicine

DOI: 10.1111/dme.14065

Research: Care Delivery

Associations between HbA_{1c} and continuous glucose monitoring-derived glycaemic variables

I. B. Hirsch[1], J. B. Welsh[2], P. Calhoun[2]*, S. Puhr[2], T. C. Walker[2] and D. A. Price[2]

[1]University of Washington School of Medicine, Seattle, WA, and [2]Dexcom, Inc., San Diego, CA, USA

Accepted 1 July 2019

Abstract

Aims To identify clinically useful associations between HbA_{1c} levels and various continuous glucose monitoring-derived metrics.

Methods We retrospectively analysed end-of-study HbA_{1c} levels and >2 weeks of continuous glucose monitoring data collected from 530 adults with Type 1 diabetes or insulin-requiring Type 2 diabetes during four randomized trials. Each trial lasted ≥24 weeks and provided central laboratory end-of-study HbA_{1c} levels and continuous glucose monitoring data from the preceding 3 months. Participants were assigned to groups based on either HbA_{1c} levels or continuous glucose monitoring-derived glucose values.

Results HbA_{1c} was strongly correlated with mean glucose value (r=0.80), time spent with glucose values in the 3.9–10.0 mmol/l range (time in range; r=–0.75) and percentage of glucose values >13.9 mmol/l (r=0.72), but was weakly correlated with the percentage of glucose values <3.9 mmol/l (r=–0.39) or <3.0 mmol/l (r=–0.21). The median percentage of glucose values <3.0 mmol/l was <1.2% (<20 min/day) for all HbA_{1c}-based groups, but the median percentage of values >13.9 mmol/l varied from 2.5% (0.6 h/day) to 27.8% (6.7 h/day) in the lowest and highest HbA_{1c} groups, respectively. More than 90% of participants with either <2% of glucose values >13.9 mmol/l, mean glucose <7.8 mmol/l, or time in range >80% had HbA_{1c} levels ≤53 mmol/mol (≤7.0%). For participants with HbA_{1c} ≥64 mmol/mol (≥8.0%), the median time in range was 44%, with 90% of participants having a time in range of <59%.

Conclusions The associations shown in the present study suggest that continuous glucose monitoring-derived metrics may help guide diabetes therapy intensification efforts in an HbA_{1c}-independent manner.

Diabet. Med. 36, 1637–1642 (2019)

Introduction

HbA_{1c} is a valuable indirect biomarker of average glycaemia, and informs the relationship between glycaemic control and the chronic vascular complications of diabetes [1]; however, inter-individual variations in the ratio between mean glucose and HbA_{1c} [2], combined with the insensitivity of HbA_{1c} to the timing, amplitude, and frequency of glucose concentration swings [3], limit the precision with which it can be used to guide therapy intensification efforts. By contrast, continuous glucose monitoring (CGM) allows the direct and nearly instantaneous assessment of mean glucose concentrations and the glycaemic responses to interventions; as such, it can empower and motivate people with diabetes [4] and help to improve glycaemic control [5]. The recently described glucose management indicator is a linear function of CGM-derived mean glucose values and is intended to reduce potential confusion by supplanting the earlier 'estimated HbA_{1c}' metric [6]. Other metrics for characterization of short-term glycaemic control with CGM data were proposed by an international consensus conference [7] and include time in range (TIR; usually expressed as the percentage of glucose values from 3.9 to 10.0 mmol/l), as well as the time spent above or below various thresholds indicating clinically significant or immediately actionable hypoglycaemia or hyperglycaemia. In the present study, we report on the relationship between

Correspondence to: John B. Welsh. E-mail: john.welsh@dexcom.com
*Present address: Jaeb Center for Health Research Tampa FL USA
Prior publication: Data in this article were published in abstract form and presented at the 78th Scientific Sessions of the American Diabetes Association (Diabetes 2018;67(S1):A234) and the 54th Annual Meeting of the European Association for the Study of Diabetes (Diabetologia 2018;61 (S1):S393).

What's new?

- Glycaemic control can be assessed with HbA$_{1c}$ or with descriptive statistics from continuous glucose monitoring (CGM) data. HbA$_{1c}$ is highly correlated with the average CGM-derived glucose value.
- Using HbA$_{1c}$ and CGM data from recently completed clinical trials, we found HbA$_{1c}$ to be highly correlated with the percentage of CGM values indicating hyperglycaemia, but poorly correlated with the percentage of CGM values indicating hypoglycaemia.
- Because CGM data revealed hypoglycaemia among participants with HbA$_{1c}$ values ≥69 mmol/mol (≥8.5%), relaxation of HbA$_{1c}$ goals is not an effective strategy for hypoglycaemia prevention.
- CGM-based heuristics to guide therapy intensification efforts independently of HbA$_{1c}$ are also described.

CGM-derived glycaemic variables and the corresponding HbA$_{1c}$ levels by analysing individual-level data from recently completed randomized clinical trials.

Participants and methods

Four recently completed randomized controlled studies of adults with diabetes provided data for the present study. Phase I of the DIAMOND study enrolled participants with Type 1 diabetes [8] or participants with Type 2 diabetes [9] using multiple daily injections of insulin, and compared the effects of CGM to those of usual care based on self-monitoring of blood glucose. Phase II of the DIAMOND study enrolled participants with Type 1 diabetes who had completed the CGM arm in phase I. All continued with CGM; they were randomized to either continue on multiple daily injections or to switch to insulin pump therapy [10]. The REPLACE-BG study [11] enrolled participants with well-controlled Type 1 diabetes and compared the safety and efficacy of CGM used as an adjunct to self-monitoring of blood glucose to that of CGM used non-adjunctively for therapeutic decisions. The HypoDE study [12] enrolled participants with Type 1 diabetes and a history of impaired hypoglycaemia awareness or severe hypoglycaemia, and studied the effectiveness of real-time CGM for reducing the number of hypoglycaemic events. All of these studies lasted at least 24 weeks and used current or recent-generation CGM systems (G4 Platinum or G5 Mobile; Dexcom, Inc., San Diego, CA, USA). The DIAMOND and REPLACE-BG studies excluded participants with evidence of decreased renal function (estimated glomerular filtration rate (GFR) of <45 or <30 ml/min in the respective studies); the DIAMOND study also excluded participants with conditions affecting the reliability of HbA$_{1c}$ measurements. Data from participants for whom <2 weeks of CGM data were available were excluded. Baseline characteristics of participants in the four studies and the number of participants from each study whose data were used in the present analysis are given in Table 1.

End-of-study HbA$_{1c}$ values and corresponding CGM metrics from the last 3 months of study participation were available from 104 completers of the DIAMOND phase I study (29 with Type 1 diabetes who did not continue to phase II and 75 with Type 2 diabetes who were not eligible for phase II), from 69 completers of the DIAMOND phase II study, from 216 completers of the REPLACE-BG study, and from 141 completers of the HypoDE study. For the DIAMOND and REPLACE-BG studies, HbA$_{1c}$ values were determined at Northwest Lipid Research Laboratories, Seattle, with the DCCT standardized analyser (Tosoh Bioscience, South San Francisco, CA, USA). For the HypoDE study, HbA$_{1c}$ values were determined with a certified high-performance liquid chromatography method at MLM Medical Laboratories (Mönchengladbach, Germany).

The variable TIR is expressed as a percentage of glucose values in the range 3.9–10.0 mmol/l. Hyperglycaemic exposure is expressed as the percentage of glucose values > 13.9 mmol/l, while hypoglycaemic exposure is expressed as the

Table 1 Baseline characteristics of participants

Study		DIAMOND phase II		REPLACE-BG		HypoDE	
Subgroup	DIAMOND phase I	Continuous subcutaneous insulin infusion	Multiple daily injections	CGM only	CGM + blood glucose monitoring	Control	Real-time CGM
Assigned to CGM, *n*	105	37	38	149	77	74	75
Age, years	46±14	46±15	45±12	44±14	45±13	47±12	46±12
Diabetes duration, years	19 (9–29)	22 (12–29)	15 (6–29)	23±12	25±12	22±14	21±14
HbA$_{1c}$, mmol/mol	70±7.7	60±7.7	60±9.8	54±7.7	53±7.7	57±10.6	59±10.9
HbA$_{1c}$, %	8.6±0.7	7.6±0.7	7.6±0.9	7.1±0.7	7.0±0.7	7.3±1.0	7.6±1.0
Analysed, *n*	104	69		216		141	

Values are reported as mean ± SD or median (interquartile range).

percentage of glucose values below either 3.9 mmol/l or 3.0 mmol/l. Participants were categorized based on end-of-study HbA_{1c} levels ranging from <48 mmol/mol (<6.5%) to ≥69 mmol/mol (≥8.5%), and separately into categories based on CGM-derived metrics.

Results

Among the 530 participants, the median number of reported glucose values was 8567, equivalent to 29.7 complete days of data per participant, assuming that points were collected at 5-min intervals. The mean (±SD; range) HbA_{1c} value was 56 (±9; 33–98) mmol/mol [7.3 (±0.8; 5.2–11.1)%]. The mean (±SD; range) glucose value was 9.3 (±1.5; 5.2–16.2) mmol/l. The average glucose value was highly correlated with both TIR (r=–0.93) and percentage of glucose values >13.9 mmol/l (r=0.92). Higher levels of glycaemic variability (measured as the standard deviation of glucose values) were associated with higher mean glucose values (r=0.66) and lower TIR values (r=–0.76).

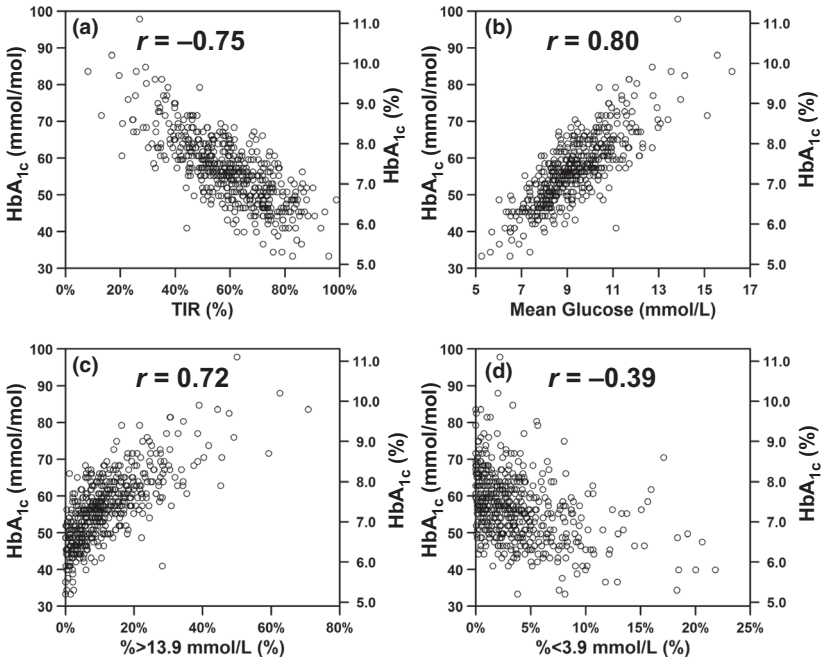

FIGURE 1 Relationships between HbA_{1c} and (a) time in range (TIR), (b) mean glucose, (c) percentage of glucose values >13.9 mmol/l and (d) percentage of glucose values <3.9 mmol/l.

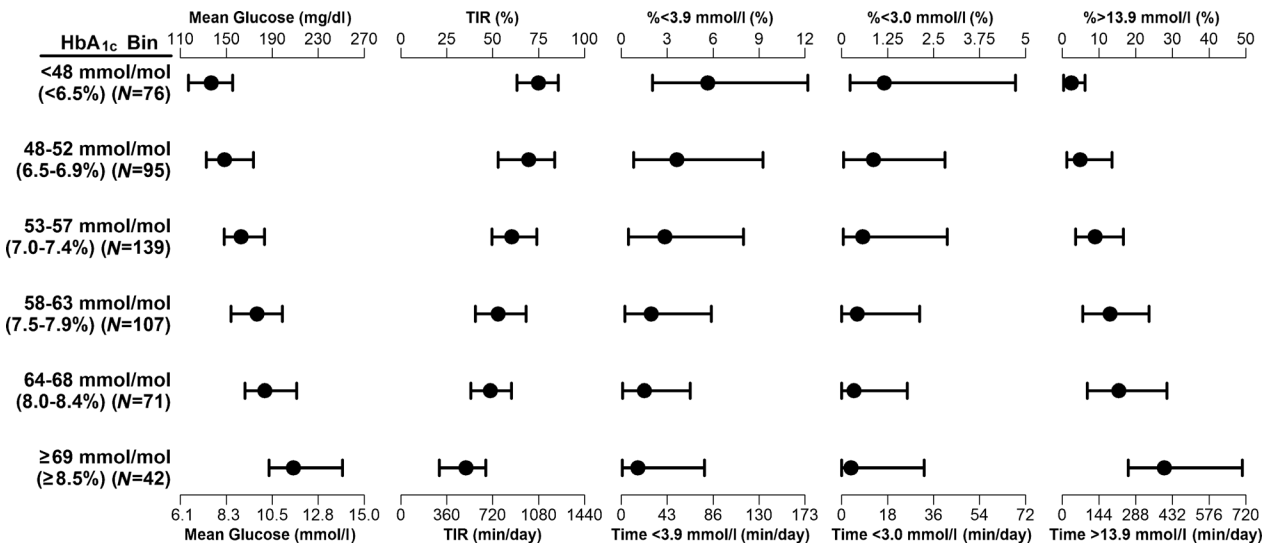

FIGURE 2 Median and interdecile ranges of various continuous glucose monitoring (CGM)-derived variables for participants with HbA_{1c} values in different bins.

Relationships between HbA$_{1c}$ and four CGM-based glycaemic variables are shown in Fig. 1. There was a strong inverse correlation between HbA$_{1c}$ and TIR, such that every 10% change in TIR was associated with a 7mmol/mol (0.7%) change in HbA$_{1c}$. There were strong positive correlations between HbA$_{1c}$ and both mean glucose and the percentage of glucose values >13.9 mmol/l, and a weak inverse correlation between HbA$_{1c}$ and the percentage of glucose values <3.9 mmol/l. Of the 139 individuals with a TIR of ≥70%, 130 had a glucose management indicator of ≤7% and 111 had an HbA$_{1c}$ of ≤53 mmol/mol (7%).

The median and interdecile (10th to 90th percentile) ranges of CGM-derived variables for participants in six different HbA$_{1c}$-based groups are shown in Fig. 2. For the 76 participants with HbA$_{1c}$ values <48 mmol/mol (<6.5%), the median TIR was 74.9%. In this group, the median frequency of glucose values <3.9 mmol/l was 5.6% and the median frequency of glucose values >13.9 mmol/l was 2.5%. For the 188 participants with HbA$_{1c}$ values ≤53 mmol/mol (≤7.0%), the median TIR was 72.1%, with 90% of participants having a TIR of >57%. This group of participants with relatively good glycaemic control had a mean glucose level of 8.0 mmol/l, median percentage of glucose values <3.9 mmol/l of 4.4%, and a median percentage of glucose values >13.9 mmol/l of 3.7%. For the 42 participants with HbA$_{1c}$ values ≥69 mmol/mol (≥8.5%), the median TIR was 35.5%. In this group, the median frequency of glucose values <3.9 mmol/l was 1.1%, and the median frequency of glucose values >13.9 mmol/l was 27.8%. Overall, the median percentage of glucose values <3.0 mmol/l was <1.2% (<20 min/day), but the median percentage of glucose values >13.9 mmol/l ranged from 2.5% (0.6 h/day) to 27.8% (6.7 h/day) in groups with the lowest to the highest HbA$_{1c}$ values, respectively. For participants with HbA$_{1c}$ values ≥64 mmol/mol (≥8.0%), the median TIR was 43.8%, with 90% of participants having a TIR of <59%.

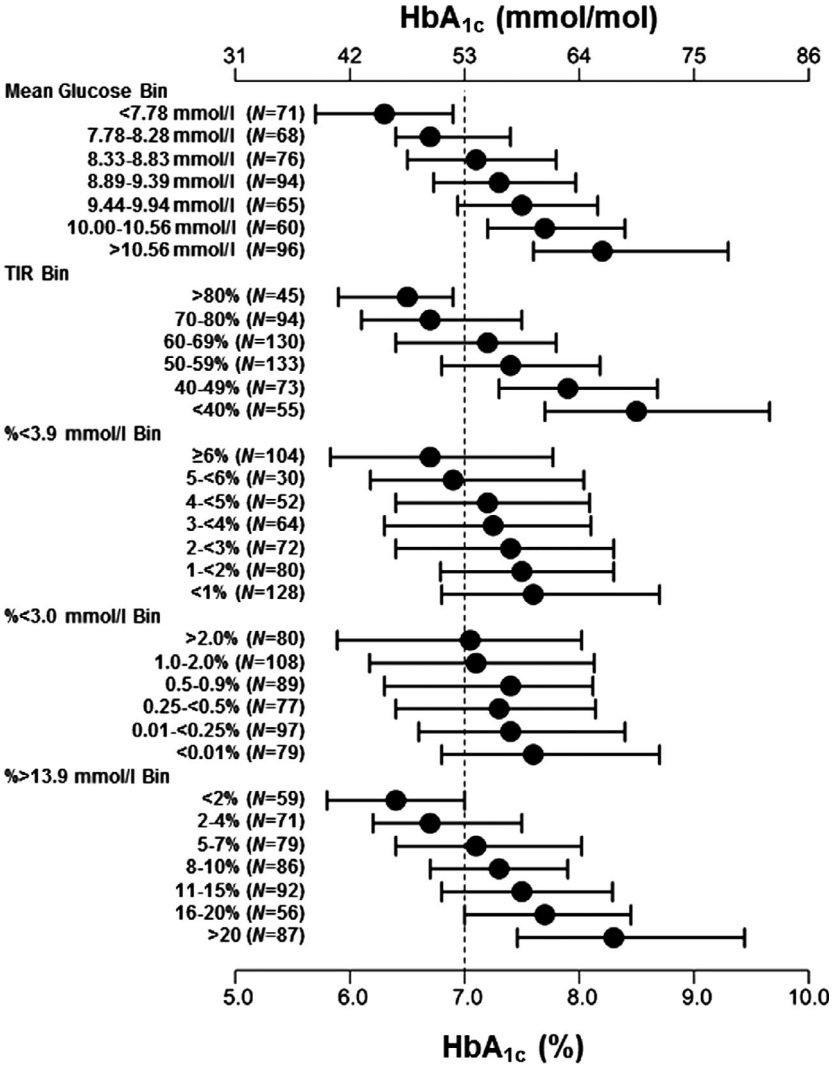

FIGURE 3 Median and interdecile ranges of HbA$_{1c}$ values for participants with various continuous glucose monitoring (CGM)-derived variables in different bins.

Median and interdecile ranges of HbA_{1c} values for participants grouped according to various CGM-derived metrics are shown in Fig. 3. At least 90% of the individuals in several CGM-based groups had HbA_{1c} values ≤53 mmol/mol (≤7.0%), including groups with mean glucose values <7.8 mmol/l, with TIR values of > 80%, and <2% of glucose values >13.9 mmol/l. By contrast, >90% of the individuals in other CGM-based groups had HbA_{1c} values >53 mmol/mol (>7.0%), including groups with mean glucose values >10.0 mmol/l, with TIR values of <50%, and with ≥16% of glucose values >13.9 mmol/l. Of the 113 individuals with HbA_{1c} values ≥64 mmol/mol (≥8.0%), only nine (8%) had TIR values of ≥60%, and 57 (50%) had 20% or more of their glucose values >13.9 mmol/l. By contrast, of the 188 individuals with HbA_{1c} values ≤53 mmol/mol (≤7.0%), 159 (85%) had TIR values of ≥60%, and only two (1%) had ≥20% of their glucose values >13.9 mmol/l.

These relationships were considered separately for individuals with Type 1 diabetes and those with Type 2 diabetes (n=455 and n=75, respectively). Although all participants with Type 2 diabetes were on intensive insulin therapy, they experienced less hypoglycaemia than participants with Type 1 diabetes at both the 3.9 mmol/l threshold (1.2% vs 4.1%) and the 3.0 mmol/l threshold (0.3% vs 1.3%).

Discussion

The present analysis adds detail to the close relationship that has been observed between several CGM-derived glycaemic variables and HbA_{1c}, with an especially strong correlation between HbA_{1c} and mean glucose (and the glucose management indicator, which is derived from the mean glucose). HbA_{1c} was strongly related to hyperglycaemic exposure and inversely related to TIR. The correlations between HbA_{1c} and hypoglycaemic exposure were inverse and relatively weak, consistent with the insensitivity of HbA_{1c} to hypoglycaemic events. The present analysis also provides clinicians with heuristics for guiding therapy intensification efforts, such as the value of minimizing the percentage of glucose values >13.9 mmol/l and helping define optimal TIR goals. Consistent with earlier observations from the T1D Exchange registry regarding severe hypoglycaemia in people with poor glycaemic control [13,14], glucose values <3.0 mmol/l were recorded in individuals with HbA_{1c} levels ≥69 mmol/mol (≥8.5%), showing that relaxing HbA_{1c} goals is an ineffective strategy for hypoglycaemia prevention. The range of mean glucose values for specific HbA_{1c} values, and the range of HbA_{1c} values for specific mean glucose values, confirm and extend earlier observations of individual variation in glycation ratios [2,3] and justify incorporating CGM-derived metrics into routine care discussions.

Strengths of the present study include the fact that the four clinical trials providing data for this analysis addressed different questions, enrolled adults with either Type 1 or Type 2 diabetes, and observed a wide range of end-of-study HbA_{1c} values. The comparability of CGM systems and the central laboratory measurements of HbA_{1c} levels were additional strengths of the present study. The choice to analyse participants with at least 14 days of CGM data was justified by separate studies [15,16] showing that this amount of data provides a good estimate of glucose metrics for a 3-month period; however, most participants evaluated in the present study provided more than twice this amount.

Our results are consistent with those reported in the study by Vigersky and McMahon [17] regarding the relationship between HbA_{1c} and TIR, in which the two were highly correlated (r=0.84) and each 10% change in TIR was associated with a 9mmol/mol (0.8%) change in HbA_{1c}. A recent report on children and adolescents in Sweden [18] noted similar relationships between HbA_{1c} and CGM-derived metrics such as TIR and time spent in the narrower target range of 3.9–7.8 mmol/l, and suggested that participants aged 6–18 years should aim to keep their time in this range at or above 50%.

These results confirm prior studies showing that people with similar HbA_{1c} levels may have widely disparate exposure to hypoglycaemia and hyperglycaemia, and emphasize the value of CGM studies when evaluating people with diabetes. CGM-derived outcomes such as TIR are increasingly recognized as drivers of improved diabetes management and mindset [19], and CGM-based estimates of hypoglycaemia and hyperglycaemia can be very meaningful and feasible outcome measures for clinical trials [20]. CGM data can also help manage people with impaired renal function, haemoglobinopathies, or other conditions in which HbA_{1c} levels might be misleading. When using CGM reports to inform therapy intensification strategies in people with suboptimally controlled diabetes, clinicians may wish to focus on strategies to increase TIR and limit the duration of hyperglycaemic excursions.

Funding sources

None.

Competing interests

I.B.H. has served as a consultant to Abbott Diabetes Care, Adocia, Bigfoot Biomedical and Roche. His institution has received research grant support from Medtronic. J.B.W., P.C., S.P., T.C.W. and D.A.P. are current or former employees of Dexcom, Inc.

Ethical approval

Ethics approvals were obtained separately for the DIAMOND, HypoDE, and REPLACE-BG studies, and informed consents were obtained from all participants. Because all participants consented to re-analysis of their de-identified data such as those reported here, no additional ethics

approval was required. [Correction added on 8 September 2019, after first online publication: Ethical approval text has been corrected].

References

1 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329**: 977–986.

2 Argento NB, Nakamura K, Sala RD, Simpson P. Hemoglobin A1C, mean glucose, and persistence of glycation ratios in insulin-treated diabetes. *Endocr Pract* 2014; **20**: 252–260.

3 Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM. The Fallacy of Average: How Using HbA1c Alone to Assess Glycemic Control Can Be Misleading. *Diabetes Care* 2017; **40**: 994–999.

4 Lawton J, Blackburn M, Allen J, Campbell F, Elleri D, Leelarathna L *et al*. Patients' and caregivers' experiences of using continuous glucose monitoring to support diabetes self-management: qualitative study. *BMC Endocr Disord* 2018; **18**(1): 12.

5 Fonseca VA, Grunberger G, Anhalt H, Bailey TS, Blevins T, Garg SK *et al*. Continuous Glucose Monitoring: A Consensus Conference of the American Association of Clinical Endocrinologists and American College of Endocrinology. *Endocr Pract* 2016; **22**: 1008–1021.

6 Bergenstal RM, Beck RW, Close KL, Grunberger G, Sacks DB, Kowalski A *et al*. Glucose Management Indicator (GMI): A New Term for Estimating A1C From Continuous Glucose Monitoring. *Diabetes Care* 2018; **41**: 2275–2280.

7 Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH *et al*. International Consensus on Use of Continuous Glucose Monitoring. *Diabetes Care* 2017; **40**: 1631–1640.

8 Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S *et al*. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: The DIAMOND randomized clinical trial. *JAMA* 2017; **317**: 371–378.

9 Beck RW, Riddlesworth TD, Ruedy K, Ahmann A, Haller S, Kruger D *et al*. Continuous Glucose Monitoring Versus Usual Care in Patients With Type 2 Diabetes Receiving Multiple Daily Insulin Injections: A Randomized Trial. *Ann Intern Med* 2017; **167**: 365–374.

10 Beck RW, Riddlesworth TD, Ruedy KJ, Kollman C, Ahmann AJ, Bergenstal RM *et al*. Effect of initiating use of an insulin pump in adults with type 1 diabetes using multiple daily insulin injections and continuous glucose monitoring (DIAMOND): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol* 2017; **5**: 700–708.

11 Aleppo G, Ruedy K, Riddlesworth T, Kruger D, Peters A, Hirsch I *et al*. REPLACE-BG: A Randomized Trial Comparing Continuous Glucose Monitoring With and Without Routine Blood Glucose Monitoring in Well-Controlled Adults with Type 1 Diabetes. *Diabetes Care* 2017; **40**: 538–545.

12 Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D *et al*. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. *Lancet* 2018; **391**: 1367–1377.

13 Weinstock RS, Xing D, Maahs DM, Michels A, Rickels MR, Peters AL *et al*. Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. *J Clin Endocrinol Metab* 2013; **98**: 3411–3419.

14 Cengiz E, Xing D, Wong JC, Wolfsdorf JI, Haymond MW, Rewers A *et al*. Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. *Pediatr Diabetes* 2013; **14**: 447–454.

15 Riddlesworth TD, Beck RW, Gal RL, Connor CG, Bergenstal RM, Lee S *et al*. Optimal Sampling Duration for Continuous Glucose Monitoring to Determine Long-Term Glycemic Control. *Diabetes Technol Ther* 2018; **20**: 314–316.

16 Xing D, Kollman C, Beck RW, Tamborlane WV, Laffel L, Buckingham BA *et al*. Optimal sampling intervals to assess long-term glycemic control using continuous glucose monitoring. *Diabetes Technol Ther* 2011; **13**: 351–358.

17 Vigersky RA, McMahon C. The Relationship of Hemoglobin A1C to Time-in-Range in Patients with Diabetes. *Diabetes Technol Ther* 2019; **21**: 81–85.

18 Petersson J, Åkesson K, Sundberg F, Särnblad S. Translating Glycated Hemoglobin A1c into Time Spent in Glucose Target Range: a Multicenter Study. *Pediatr Diabetes* 2019; **20**: 339–344.

19 Runge AS, Kennedy L, Brown AS, Dove AE, Levine BJ, Koontz SP *et al*. Does Time-in-Range Matter? Perspectives From People With Diabetes on the Success of Current Therapies and the Drivers of Improved Outcomes. *Clin Diabetes* 2018; **36**: 112–119.

20 Beck RW, Calhoun P, Kollman C. Use of continuous glucose monitoring as an outcome measure in clinical trials. *Diabetes Technol Ther* 2012; **14**: 877–882.