



# Preserved C-peptide secretion is associated with fewer low-glucose events and lower glucose variability on flash glucose monitoring in adults with type 1 diabetes

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## Abstract

**Aims/hypothesis** We aimed to assess whether persistence of C-peptide secretion is associated with less glucose variability and fewer low-glucose events in adults with type 1 diabetes who use flash monitoring.

**Methods** We performed a cross-sectional study of 290 adults attending a university teaching hospital diabetes clinic, with type 1 diabetes, who use flash monitoring and in whom a random plasma C-peptide was available in the past 2 years. Variables relating to flash monitoring were compared between individuals with low C-peptide (<10 pmol/l) and those with persistent C-peptide (either 10–200 pmol/l or 10–50 pmol/l). In addition, the relationship between self-reported hypoglycaemia and C-peptide was assessed ( $n = 167$ ). Data are median (interquartile range).

**Results** Individuals with preserved C-peptide secretion (10–200 pmol/l) had shorter duration of diabetes (15 [9–24] vs 25 [15–34] years,  $p < 0.001$ ) and older age at diagnosis (23 [14–28] vs 15 [9–25] years,  $p < 0.001$ ), although current age did not differ in this cohort. Preserved C-peptide was associated with lower time with glucose <3.9 mmol/l (3% [2–6%] vs 5% [3–9%],  $p < 0.001$ ), fewer low-glucose events per 2 week period (7 [4–10] vs 10 [5–16],  $p < 0.001$ ), lower SD of glucose (3.8 [3.4–4.2] vs 4.1 [3.5–4.7] mmol/l,  $p = 0.017$ ) and lower CV of glucose (38.0 [35.0–41.6] vs 41.8 [36.5–45.8],  $p < 0.001$ ). These differences were also present in those with C-peptide 10–50 pmol/l and associations were independent of diabetes duration and estimated HbA<sub>1c</sub> in logistic regression analysis. Preserved C-peptide was also associated with lower rates of self-reported asymptomatic hypoglycaemia (8.0% vs 22.8% in the past month,  $p = 0.028$ ).

**Conclusions/interpretation** Preserved C-peptide secretion is associated with fewer low-glucose events and lower glucose variability on flash monitoring. This suggests that individuals with preserved C-peptide may more safely achieve intensive glycaemic targets.

**Keywords** Clinical diabetes · Continuous glucose monitoring · C-peptide · Devices · Hypoglycaemia

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## Abbreviations

CGM Continuous glucose monitoring  
CSII Continuous subcutaneous insulin infusion  
IQR Interquartile range

## Introduction

In recent years the utility of C-peptide measurement in routine clinical diabetes practice has garnered increasing attention [1]. C-peptide measurement in those with a clinician diagnosis of type 1 diabetes is an effective means of identifying individuals who may have monogenic diabetes [2] and of identifying other misclassifications (e.g. type 2 diabetes), with the potential for significant changes in therapy. Even in those with a

## Research in context

### What is already known about this subject?

- Preserved C-peptide secretion is associated with lower frequency of self-reported hypoglycaemia and fewer complications in type 1 diabetes

### What is the key question?

- Does preserved C-peptide secretion result in lower glucose variability and fewer low-glucose events in adults with type 1 diabetes who use flash glucose monitoring?

### What are the new findings?

- Even minimal levels of residual C-peptide are associated with fewer low-glucose events and less glucose variability in adults with type 1 diabetes using flash monitoring
- These associations are independent of duration of diabetes and estimated HbA<sub>1c</sub>

### How might this impact on clinical practice in the foreseeable future?

- It is likely that tighter glycaemic targets may be more safely realised in people with preserved C-peptide secretion
- Interventions known to preserve C-peptide secretion, such as early intensification of glycaemic control, should be aggressively pursued while trials of other interventions that might preserve C-peptide secretion, such as immunotherapies, should be actively encouraged and funded

clear diagnosis of type 1 diabetes, there is increasing evidence that confirming endogenous insulin secretion has clinical implications. Significant residual C-peptide secretion is more likely in those diagnosed in adulthood, ranging from 36% within the first 5 years to 22% up to 20 years post diagnosis [3], with evidence of stabilisation after an exponential fall in the first 7 years [4]. Even after 50 years of type 1 diabetes, 32.4% of individuals retain detectable C-peptide levels (>16 pmol/l) [5]. Evidence from the DCCT suggests that intensive therapy may prolong the duration of C-peptide persistence [6]. In the DCCT, preserved C-peptide secretion was associated with lower rates of severe hypoglycaemia [7], fewer diabetes complications, lower HbA<sub>1c</sub> and lower insulin doses [8], although these associations were mostly observed in the intensive treatment arm. These associations were not noted in the recent Joslin Medalist Study which assessed individuals with long-standing type 1 diabetes [5]. Preservation of C-peptide has been associated with lower self-reported rates of symptomatic, asymptomatic and severe hypoglycaemia, although not with measures of impaired awareness, in a number of observational studies [9–11]. Many C-peptide assays in current clinical use provide a limit of quantification at around 50 pmol/l; however, C-peptide levels >10 pmol/l have been independently associated with a lower risk of diabetes complications [10]. C-peptide persistence has been associated with improved continuous glucose monitoring (CGM) ‘time in range’ in a largely paediatric cohort of people with recently diagnosed type 1 diabetes [12] and with lower glucose variability and low-glucose events in type 2 diabetes [11]. However, little is known of the effects in adults with type 1 diabetes and beyond

the first few years after diagnosis. Within the past 2 years, our centre has expanded use of flash glucose monitoring to approximately 50% of individuals with type 1 diabetes [13]. Across a similar timescale we have introduced a programme to measure random plasma C-peptide in all individuals with apparent type 1 diabetes of more than 3 years’ duration. The convergence of these two events has provided the opportunity to assess the relationship between C-peptide status and flash glucose monitoring variables in a large cohort of adults with type 1 diabetes in a ‘real-world’ clinical context. We hypothesised that persistence of C-peptide, even at low levels, would be associated with less glucose variability and fewer low-glucose events.

## Methods

**Study design and participants** We conducted a cross-sectional study of adults with type 1 diabetes, using flash glucose monitoring (Freestyle Libre, Abbott, Witney, UK), in whom random plasma C-peptide results were available. Since July 2017, we have routinely measured random C-peptide in all people with type 1 diabetes of greater than 3 years’ duration in our centre (comprising the Royal Infirmary of Edinburgh and Western General Hospital diabetes clinics), to help identify potential misclassifications (e.g. monogenic diabetes or type 2 diabetes). Our centre approved National Health Service-funded flash glucose monitoring for all individuals meeting Scottish Diabetes Group criteria in February 2018 [13]. To date, approximately 50% of our type 1 diabetes population have commenced flash monitoring. All flash

monitoring users are encouraged to link their data to our centre using the LibreView platform (Abbott, Witney, UK). To be included in this study, the following criteria had to be met:

- diabetes duration >3 years;
- concomitant plasma glucose >4 mmol/l at time of C-peptide measurement;
- 2 weeks of flash monitoring data available from LibreView between February and April 2019;
- ≥75% data capture with respect to flash monitoring data within the 2 week period being assessed.

Individuals with C-peptide >200 pmol/l ( $n = 21$ ) were excluded from this analysis to limit the possibility of including people with diagnoses other than type 1 diabetes. All elements of this observational study reflect routine clinical care and therefore ethics approval was not required. These data are presented with the consent of the owner (NHS Lothian).

**Outcomes** The principal analyses compared individuals with C-peptide <10 pmol/l (low) and those with C-peptide 10–200 pmol/l (preserved). A further category was created to compare low C-peptide (<10 pmol/l) with ‘micro-secretors’ (10–50 pmol/l). The main outcomes of interest were differences in flash monitoring variables (obtained from the LibreView platform) between those with low and preserved C-peptide. The key flash monitoring variables were average glucose, SD of glucose, CV of glucose, number of low-glucose events (<3.9 mmol/l) per 2 weeks, time below range (glucose <3.9 mmol/l), time in range (glucose 3.9–10.0 mmol/l), time above range (glucose >10 mmol/l), low-glucose event average duration, estimated HbA<sub>1c</sub> and interquartile range (IQR) of glucose. Most recent HbA<sub>1c</sub> measurement, age at diagnosis, diabetes duration, BMI and treatment type (continuous subcutaneous insulin infusion [CSII] or multiple daily injections [MDI]) were obtained from our national clinic database system, SCI-Diabetes (<https://www.sci-diabetes.scot.nhs.uk>). Presence of microvascular complications was derived from SCI-Diabetes and the electronic patient record. Individuals attending the Royal Infirmary of Edinburgh are routinely asked to complete a hypoglycaemia questionnaire at each clinic visit, which includes a modified Clarke questionnaire [14] and Gold score [15] (available in 167/187 [89.3%]).

**Assays** Random plasma C-peptide was measured using an Abbott Architect immunoassay. In-house studies have demonstrated a CV of 7% at 7 pmol/l and of 15% at 4 pmol/l. Based on these data, we report 4 pmol/l as the limit of quantification in this study. HbA<sub>1c</sub> was measured by ion-exchange high performance liquid chromatography using the Arkray Adams A1c automated platform (A. Menarini Diagnostics, Winnersh, UK).

**Statistical analysis** Data were mostly non-normally distributed (as determined by Shapiro–Wilk test) and are presented as median and IQR. Unpaired data were analysed by Mann–Whitney  $U$  test. Categorical data were compared by  $\chi^2$  or by Fisher’s exact test where the conditions for  $\chi^2$  were not met. Correlations were analysed by Spearman’s rank correlation. Logistic regression was performed to identify independent predictors of key flash monitoring variables. Significance was accepted at  $p < 0.05$ . All analyses were performed using RStudio version 1.0.153 (<https://www.rstudio.com>).

## Results

**Participant characteristics** Full characteristics are presented in Table 1, comparing those with low (<10 pmol/l) and preserved (10–200 pmol/l) C-peptide or micro-secretion of C-peptide (10–50 pmol/l). Median C-peptide was <4 pmol/l (<4 to <4) in the low group, 22 pmol/l (16–31) in the micro-secretion group and 32 pmol/l (19–67) in the preserved group. C-peptide concentration was negatively correlated with duration of diabetes ( $r -0.362$ ,  $p < 0.001$ ) (Fig. 1), and although presence of retinopathy (of any severity) was more common in low-C-peptide individuals, this association was not independent of diabetes duration. Neither severe retinopathy (i.e. requiring either retinal photocoagulation or specialist ophthalmology review) nor elevated urinary albumin/creatinine ratio was associated with C-peptide status (Table 1). C-peptide was not significantly correlated with plasma glucose at the time of C-peptide measurement ( $r 0.044$ ,  $p = 0.460$ ) or most recent HbA<sub>1c</sub> ( $r 0.040$ ,  $p = 0.450$ ). In comparison with the other 2597 individuals with type 1 diabetes attending our centre, participants in this study had lower HbA<sub>1c</sub> (58 [52–66] vs 63 [54–74] mmol/mol,  $p < 0.001$ ) (7.5% [6.9%–8.2%] vs 7.9% [7.1%–8.9%]), were more likely to use CSII (28.3% vs 13.4%,  $p < 0.001$ ), were younger (42 [31–53] vs 46 [31–59] years,  $p = 0.016$ ) and had longer duration of diabetes (21 [13–32] vs 19 [10–32] years,  $p = 0.007$ ).

**Flash glucose data** Average glucose, estimated HbA<sub>1c</sub>, time in range and time above range did not differ significantly between those with C-peptide <10 pmol/l and those with preserved C-peptide secretion (Table 2). However, CV, SD and IQR were all lower in individuals with preserved C-peptide (Table 2 and Fig. 2). Similarly, time below range and number of low-glucose events were lower in individuals with preserved C-peptide (Table 2 and Fig. 2). When limiting the comparison to those with C-peptide levels of 10–50 pmol/l, these associations remained significantly different compared with low-C-peptide individuals (Table 2). C-peptide was significantly correlated with CV ( $r -0.141$ ,  $p = 0.016$ ), time below range ( $r -0.180$ ,  $p = 0.002$ ) and low-glucose events ( $r -0.182$ ,  $p = 0.002$ ) (electronic supplementary material [ESM] Fig. 1a–c).

**Table 1** Comparison of clinical and demographic variables by C-peptide status

Variable	<10 pmol/l n = 201	10–200 pmol/l n = 89	p for <10 pmol/l vs 10–200 pmol/l	10–50 pmol/l n = 58	p for <10 pmol/l vs 10–50 pmol/l
Age at diagnosis (years)	15 (9–25)	23 (14–28)	<0.001	21 (14–30)	<0.001
Duration of diabetes (years)	25 (15–34)	15 (9–24)	<0.001	17 (10–28)	<0.001
Current age (years)	43 (31–53)	39 (31–53)	0.560	41 (31–54)	0.975
BMI (kg/m <sup>2</sup> )	26.6 (23.7–30.0)	27.2 (24–30.6)	0.327	27.2 (24.2–30.7)	0.319
HbA <sub>1c</sub> (mmol/mol)	57 (52–67)	58 (52–65)	0.845	57 (52–64)	0.607
HbA <sub>1c</sub> (%)	7.4 (6.9–8.3)	7.5 (6.9–8.1)		7.4 (6.9–8.0)	
Obese	51/200 (25.5%)	27/89 (30.3%)	0.392	19/58 (32.8%)	0.274
Male	108/201 (53.7%)	53/89 (59.6%)	0.358	34/58 (58.6%)	0.510
CSII	60/201 (29.9%)	22/89 (24.7%)	0.371	16/58 (27.6%)	0.739
Any retinopathy	137/201 (68.2%)	42/89 (47.2%)	<0.001	27/58 (46.6%)	0.039
Any retinal photocoagulation therapy	35/201 (17.4%)	11/89 (12.4%)	0.277	10/58 (17.2%)	0.976
Under specialist ophthalmology review	53/201 (26.4%)	17/89 (19.1%)	0.182	14/58 (24.1%)	0.733
Elevated urinary albumin/creatinine ratio	29/200 (14.5%)	14/88 (15.9%)	0.757	10/58 (17.2%)	0.608

Data are presented as median (IQR) or as n/N (%)

Logistic regression models identified C-peptide status as independently contributing to associations with glucose variability and low-glucose variables (Table 3).

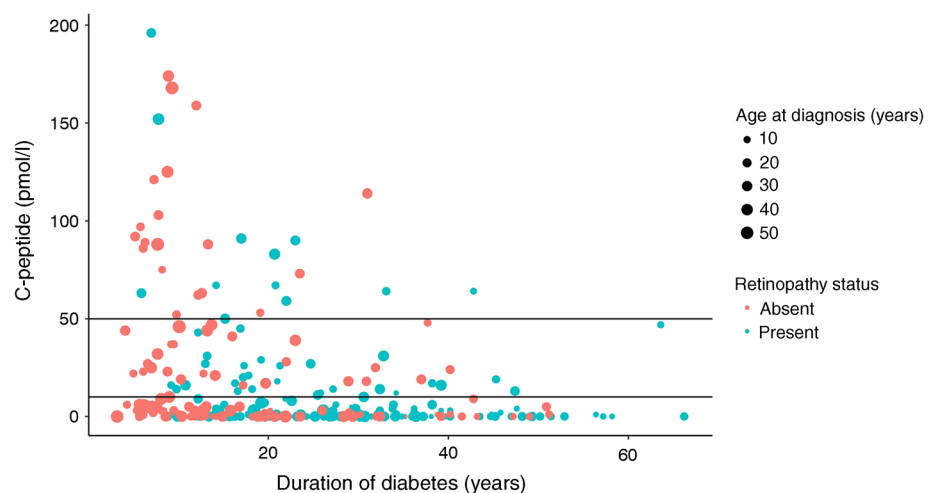
**Hypoglycaemia questionnaire data** Median Gold score (2 [1–2] in low vs 1 [1–2] in preserved,  $p = 0.506$ ) and the percentage of people with impaired awareness of hypoglycaemia, defined as Gold score  $\geq 4$  (9.6% vs 2.4%,  $p = 0.281$ ), did not significantly differ by C-peptide status. Individuals with more than 2–3 episodes of symptomatic hypoglycaemia per week, in the preceding month, did not differ significantly between groups (53.5% vs 40.8%,  $p = 0.137$ ). However, low-C-peptide individuals were more likely to report any asymptomatic hypoglycaemia in the past month (22.8% vs 8.0%,  $p = 0.028$ ) and to report not always being aware of hypoglycaemia (45.6% vs 28.0%,  $p = 0.034$ ).

## Discussion

As hypothesised, we demonstrated significant associations between residual C-peptide secretion and lower glucose variability and low-glucose events in flash glucose monitoring users. These associations were independent of prevailing HbA<sub>1c</sub> and diabetes duration, suggesting routine evaluation of C-peptide may have clinical utility in the management of type 1 diabetes. These data also highlight the limitations of HbA<sub>1c</sub>, which did not differ between groups, as a means of assessing optimal glycaemic management. In the modern era, it is conceivable that HbA<sub>1c</sub> will be supplanted by CGM metrics to optimise glycaemic management [16], particularly in efforts to minimise glucose variability, which has been posited as an independent risk factor for diabetes complications [17].

Our flash glucose monitoring findings are accompanied by significant differences in self-reported hypoglycaemia, consistent

**Fig. 1** Relationship between diabetes duration and random plasma C-peptide. Blue dots represent individuals with any reported retinopathy and red dots represent those with no retinopathy. Size of dot corresponds to age at diagnosis. Horizontal lines represent 10 pmol/l and 50 pmol/l thresholds





**Table 2** Comparison of data derived from flash monitoring by C-peptide category

Variable	<10 pmol/l <i>n</i> = 201	10–200 pmol/l <i>n</i> = 89	<i>p</i> for <10 pmol/l vs 10–200 pmol/l	10–50 pmol/l <i>n</i> = 58	<i>p</i> for <10 pmol/l vs 10–50 pmol/l
Average glucose (mmol/l)	9.8 (8.7–11.0)	9.8 (8.9–11.0)	0.792	9.5 (8.8–10.4)	0.470
SD (mmol/l)	4.1 (3.5–4.7)	3.8 (3.4–4.2)	0.017	3.8 (3.4–4.2)	0.032
CV (%)	41.8 (36.5–45.8)	38.0 (35.0–41.6)	<0.001	38.5 (35.1–44.4)	0.030
Low events per 2 weeks ( <i>n</i> )	10 (5–16)	7 (4–10)	<0.001	8.0 (4.3–12.8)	0.037
Below 3.9 mmol/l (%)	5 (3–9)	3 (2–6)	<0.001	4 (2–6)	0.034
In range (3.9–10.0 mmol/l) (%)	50 (39–58)	52 (42–61)	0.448	53 (45–62)	0.117
Above 10 mmol/l (%)	44 (32–55)	45 (34–55)	0.637	42 (33–50)	0.565
Low event average duration (min)	100 (76–127)	90 (66–120)	0.138	90 (66–123)	0.302
Estimated HbA <sub>1c</sub> (mmol/mol)	62 (54–69)	62 (55–69)	0.794	59 (55–66)	0.464
Estimated HbA <sub>1c</sub> (%)	7.8 (7.1–8.5)	7.8 (7.2–8.5)		7.6 (7.2–8.2)	
IQR (mmol/l)	5.8 (4.7–6.8)	5.4 (4.6–6.1)	0.028	5.3 (4.6–6.0)	0.032

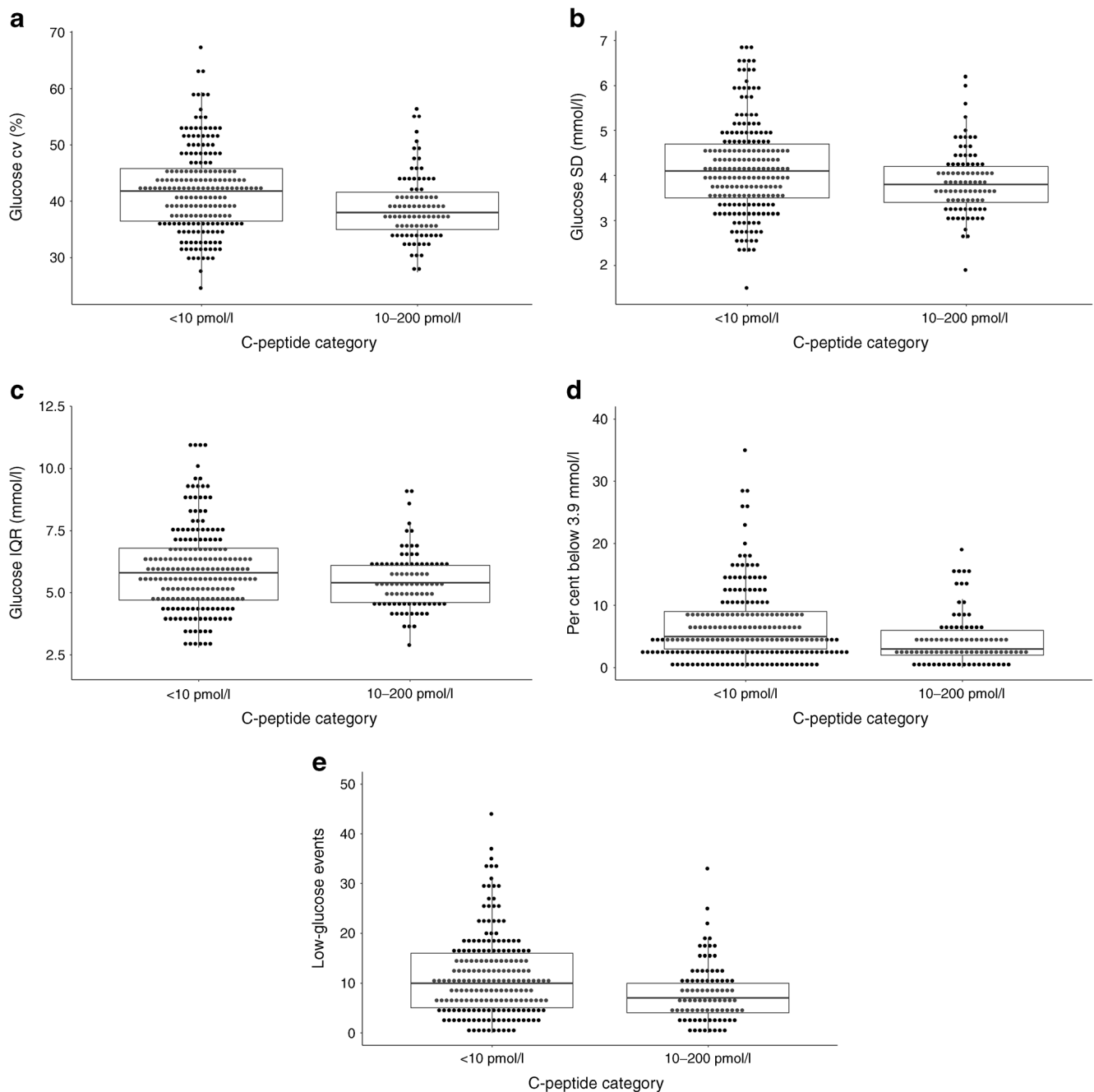
Data are presented as median (IQR)

with findings from several previous investigations [9–11], although significant differences were limited to asymptomatic hypoglycaemia in our study. Marren et al [9] describe significant differences in self-reported symptomatic and asymptomatic hypoglycaemia in those with preserved C-peptide, although the median C-peptide concentration in this group (114 pmol/l) was substantially higher than in our study (32 pmol/l). While we report random plasma C-peptide and Marren et al [9] used values after a standard mixed-meal tolerance test, the correlation between random and post-mixed-meal C-peptide is known to be very strong ( $R=0.91$ ) and is unlikely to substantially limit the comparability of these studies [18]. Other important contrasts with this study are the higher HbA<sub>1c</sub> (67–69 mmol/mol [8.3–8.5%] vs 57–58 mmol/mol [7.4–7.5%] in our cohort) and significant difference in age between C-peptide groups, which was not different in our study (which was limited to adults) despite differences in diabetes duration and age at diagnosis. Kuhlreiber et al [10] demonstrated similar associations between hypoglycaemia and fasting C-peptide, although the median concentration of C-peptide associated with mild and moderate hypoglycaemia (42.4 pmol/l) was higher than the median in both our preserved and micro-secretor categories. The novelty of our self-reported hypoglycaemia data is the demonstration of lower rates of asymptomatic hypoglycaemia at an even lower C-peptide threshold than previously demonstrated [9–11].

The fact that C-peptide status is strongly associated with reduced low-glucose events and glucose variability, but not average glucose, time in range or time above range, offers a mechanistic insight into the consequences of preserved C-peptide. If this were simply a ‘buffering’ effect of ongoing endogenous insulin secretion, smoothing out the peaks and troughs in glucose in individuals receiving exogenous insulin, we might expect to see this reflected in a lower HbA<sub>1c</sub>. However, this was not the case in either our cohort or that of Marren et al [9]. Loss of the glucagon counter-regulatory

response to hypoglycaemia occurs in many individuals with type 1 diabetes within 5 years of diagnosis and is linked, in part, to the loss of a paracrine effect of endogenous insulin on alpha cells in pancreatic islets [19]. Adults with type 1 diabetes and preserved C-peptide (>99 pmol/l after a mixed-meal tolerance test) have relative preservation of the glucagon response to hypoglycaemia [20]. Therefore, the role of intra-islet insulin signalling offers a compelling mechanism to explain the association of preserved C-peptide with reduced low-glucose events [21, 22], although this phenomenon was not observed in young individuals within 1 year of diagnosis [23]. The only cohorts where preserved C-peptide was associated with lower HbA<sub>1c</sub> were the intensive arm of DCCT [8] and the study by Kuhlreiber et al [10], both of which had comparatively low HbA<sub>1c</sub> levels. Cohorts with no difference in HbA<sub>1c</sub>, in relation to C-peptide status (including this study), may reflect a failure to intensify glycaemic management in individuals who would be at lower risk of hypoglycaemia [9].

The key strength of this study is its novelty in assessing the relationship between C-peptide and flash glucose monitoring variables in a ‘real-world’ clinical context. Where associations of CGM with C-peptide were reported previously, this was in a largely paediatric population, within 2 years of diagnosis and with relatively higher levels of C-peptide [12]. Our cohort also benefits from being balanced in terms of current age and HbA<sub>1c</sub> between low and preserved C-peptide groups. As a ‘real-world’ assessment, the various measures obtained in this study (questionnaire data, HbA<sub>1c</sub>, C-peptide and flash monitoring data) were not captured simultaneously, although we would envisage this increasing the likelihood of a type II error rather than producing false positive associations with C-peptide. Random C-peptide appears to be as robust a measure of C-peptide status as values obtained after a mixed-meal tolerance test [18], and indeed we found no significant correlation between C-peptide and concomitant plasma glucose. It would have been



**Fig. 2** Influence of C-peptide category upon the following flash glucose data: **(a)** CV, **(b)** SD, **(c)** IQR, **(d)** percentage of time below 3.9 mmol/l and **(e)** low-glucose events per 14 days. The boxes represent median and IQR and whiskers represent  $1.5 \times$  IQR

preferable to have access to different low-glucose thresholds (e.g.  $<3$  mmol/l); however, the nature of the data capture process did not permit this. It would also have been useful to have reported insulin dose data, but unfortunately these were not consistently available. The decision to exclude individuals with C-peptide  $>200$  pmol/l was pragmatic, to limit the likelihood of including misclassified cases, but also because the specific research question related to the effect of relatively low levels of C-peptide secretion. We did not measure diabetes antibodies

as a matter of routine and so it is possible that our cohort contained a very small proportion of individuals with a cause of insulin deficiency other than type 1 diabetes, e.g. hepatocyte nuclear factor 1- $\beta$  monogenic diabetes. However, this does not affect the central tenet of our study regarding the relationship between C-peptide and low-glucose events. While the ‘real-world’ design is a strength in terms of generalisability, our cohort is skewed towards people with lower HbA<sub>1c</sub> and greater CSII usage than our centre’s total type 1 population.

**Table 3** Logistic regression analysis results assessing factors associated with a flash monitoring data result above the median for this cohort

Variable	SD above median (4.0 mmol/l)		CV glucose above median (40.3%)		IQR glucose above median (5.6 mmol/l)		Low events per 2 weeks above median (nine events)		Percentage of time below 3.9 mmol/l above median (4%)	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
C-peptide 10–200 pmol/l	0.32 (0.16–0.63)	0.001	0.30 (0.17–0.52)	<0.001	0.40 (0.21–0.75)	0.005	0.29 (0.15–0.54)	<0.001	0.32 (0.17–0.60)	<0.001
Duration of diabetes (per year)	1.00 (0.98–1.03)	0.841	0.99 (0.96–1.00)	0.194	1.00 (0.98–1.03)	0.776	0.97 (0.95–1.00)	0.021	0.98 (0.96–1.00)	0.074
Estimated HbA <sub>1c</sub> (per mmol/mol)	1.16 (1.12–1.21)	<0.001	0.98 (0.96–1.00)	0.019	1.37 (1.10–1.18)	<0.001	0.89 (0.86–0.91)	<0.001	0.88 (0.84–0.91)	<0.001
Male	1.34 (0.72–2.50)	0.355	1.70 (1.03–2.84)	0.040	1.32 (0.73–2.38)	0.359	1.18 (0.67–2.10)	0.567	1.19 (0.67–2.15)	0.552
CSII	0.82 (0.42–1.61)	0.573	1.00 (0.57–1.77)	0.976	0.94 (0.50–1.80)	0.862	0.68 (0.36–1.29)	0.245	1.05 (0.55–2.00)	0.888

These findings suggest that routine clinical measurement of C-peptide in type 1 diabetes may be important not only in confirming the correct diagnosis of diabetes, but also in informing the risk of low glucose and glycaemic instability. Given that we have shown an effect in the C-peptide range 10–50 pmol/l, we suggest that wider availability of higher-sensitivity C-peptide assays may be of value, as many currently available clinical assays report 50 pmol/l as their lower limit of quantification. Our findings support previous conclusions, drawn from self-reported hypoglycaemia [9], that there appears to be a failure of intensification in glucose-lowering therapy in people who are at lower risk of hypoglycaemia and glucose variability. These data also raise the possibility of stratified glycaemic targets which acknowledge the influence of residual C-peptide secretion. Given the apparent importance of persistent C-peptide secretion, every effort should be made to ensure early intensification of glycaemic control at diagnosis, as this is currently the only available intervention shown to preserve C-peptide secretion [6]. Moreover, studies of novel strategies to preserve C-peptide secretion, such as immunotherapies, should be supported and funded [24].

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**Data availability** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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