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Capturing the real-world benefit of residual β-cell function during clinically important time-periods in established Type 1 diabetes

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Abstract

Aims: Many individuals with type 1 diabetes retain residual β-cell function, with increased endogenous insulin secretion associated with reduced hyperglycaemia, hypoglycaemia and glycaemic variability. However, it is unknown when these improvements occur during the day. Dysglycaemia is common in overnight and postprandial periods and associated with diabetes complications. Therefore, this study aimed to determine the influence of residual β-cell function upon nocturnal and postprandial glycaemic control in established type 1 diabetes.

Methods: Under free-living conditions, 66 participants wore a blinded continuous glucose monitor (CGM), kept a food diary, and completed a stimulated urine C-peptide creatinine (UCPCR) test. Nocturnal, and postprandial CGM outcomes (participant means and discrete event analysis) were compared between UCPCR groups: undetectable ($Cpep_{und}$), low ($Cpep_{low}$: 0.001–0.19 nmol/mmol) and high ($Cpep_{high}$: ≥0.2 nmol/mmol).

Results: Greater β-cell function was associated with incremental improvements in glycaemia. $Cpep_{high}$ spent significantly greater time in normoglycaemia than $Cpep_{und}$ overnight (76 ± 20% vs. 58 ± 20%, $p = 0.005$) and 0–300 mins postprandially (68 ± 22% vs. 51 ± 22%, $p = 0.045$), while also having reducing nocturnal variability (SD 1.12 ± 0.41 vs. 1.52 ± 0.43 mmol/L, $p = 0.010$). Analysis of individual events, controlling for diabetes duration, BMI, basal insulin, use of a continuous or flash glucose monitor and (for postprandial) meal type, carbohydrate and bolus insulin intake, replicated the group findings, additionally demonstrating $Cpep_{und}$ had increased hyperglycaemia versus $Cpep_{low}$ overnight and increased postprandial hypoglycaemic events compared with $Cpep_{high}$. For all participants, breakfast had a significantly higher incremental area under the curve than lunch and dinner.

Conclusions: Residual β-cell function is associated with improved nocturnal and postprandial glycaemic control. These data may be of clinical importance

Guy Taylor and Andy Shaw should be considered joint first authors.

for identifying specific periods and individuals where further glycaemic management strategies would be beneficial.

KEYWORDS
continuous glucose monitoring, nocturnal, postprandial, residual β-cell function

1 | INTRODUCTION

It has been recently demonstrated that even in individuals with long-duration established type 1 diabetes, many retain functioning β-cells that secrete endogenous insulin and C-peptide in equimolar amounts.[1,2] Residual β-cell function in type 1 diabetes is associated with improved free-living glycaemic control, with increased C-peptide secretion associated with reduced HbA1c and hypoglycaemic events.[3,4] Continuous glucose monitoring (CGM) measurements over 1–17 week have found that, increased time in normoglycaemia, reduced time spent in hyperglycaemia, reduced time spent or incidence of hypoglycaemia, and reduced glycaemic variability, all associate with increased β-cell function in short- and longer-duration type 1 diabetes.[5–8] However, it is unknown when these improvements occur during the day.

One considerable advantage of using CGM devices over other measure of glycaemic control, such as HbA1c, is the ability to capture free-living daily glucose profiles. Indeed, CGMs have highlighted nocturnal and postprandial glycaemic events as common periods of dysglycaemia in type 1 diabetes.[9,10] These time periods are associated with diabetes complications and often cited as concerns by patients.[11–16] Additionally, individuals with type 1 diabetes tend to have large intraday variation in blood glucose, which may be influenced by circadian rhythms. Similar carbohydrate intake throughout a day can lead to substantially different postprandial events,[17] with early morning increases in circulating growth hormones[18] and reduced insulin sensitivity[19,20] likely contributing to large breakfast postprandial events.[17]

The influence residual β-cell function has on glycaemic control at these clinically important time periods has not previously been explored under free-living or laboratory settings. Therefore, this study examined the real world impact of residual β-cell function upon nocturnal and postprandial glycaemic control, specifically, exploring incremental increases in stimulated C-peptide on individual events, time in range, and responses to different timed meals across the day.

What is already known?

- Many individuals with type 1 diabetes have residual β-cell function secreting micro levels of insulin and C-peptide which is associated with improved glycaemic control. It is unknown when these improvements occur during the day.

What this study has found?

- Greater β-cell function was associated with more time spent in normoglyceamia overnight and postprandially reduced hyperglycaemia and glycaemic variability overnight and reduced postprandial hypoglycaemic events. Even low C-peptide had glycaemic benefits compared with undetectable β-cell function reducing hyperglycaemia overnight.

What are the implications of the study?

- Individuals with no β-cell function may need more support to manage nocturnal and postprandial periods whereas those with C-peptide positivity should pursue more ambitious glycaemic targets.

2 | RESEARCH DESIGN AND METHODS

Participants with a clinical diagnosis of type 1 diabetes (primary osmotic symptoms, weight loss, hyperglycaemia, ketosis, insulin initiation at diagnosis), aged 18–65 years with a diabetes duration ≥1 year, HbA1c <86 mmol/mol (10.0%) and stable multiple daily injections or continuous subcutaneous insulin infusion regimen without changes over the preceding 6 months were recruited from the Newcastle Diabetes Centre. Participants provided written informed consent. This study was a secondary analysis of the participant recruitment phase of an observational exercise study exploring residual β-cell function influence on post-exercise glucose.[21] Given that these findings were exploratory, it wasn't possible to pre-specify the anticipated outcomes at the time of study registration (ISRCTN50072340). The study was approved by the local National Health Service Research Ethics Committee, Newcastle, U.K. (code: 16/NE/0192).

Participants wore a blinded CGM (Enlite® sensor, iProTM2 Professional, Medtronic), continued their standard care (MDI 56% vs. CSII 44%; 15% used CGMs, 9% used flash glucose

monitors) and completed a food and insulin diary at home for 7–8 days. During the CGM collection period, participants completed a home 2 h-postprandial Urine C-peptide creatinine ratio (UCPCR) test, collecting urine in a Boricon container containing boric acid to stabilise C-peptide after their largest meal in a day, before posting to Exeter Clinical Laboratory. Samples were analysed for C-peptide using the routine automated E170 immuno-analyser from Roche Diagnostics, and creatinine was analysed on the Roche P800 modular analyser. UCPCR is highly correlated with post mixed meal tolerance test serum C-peptide,[22] the gold standard, and has inter- and intra-assay coefficients of variation of <4.5% and <3.3%, respectively.[23] Participants were grouped as follows: undetectable ($Cpep_{und}$ 0.000 nmol/mmol), low ($Cpep_{low}$ 0.001–0.19 nmol/mmol) or high ($Cpep_{high}$ ≥0.2 nmol/mmol). The lower limit of detection (0.001 nmol/mol) is the equivalent to serum C-peptide 3 pmol/L, while ≥0.2 nmol/mmol UCPCR is equivalent to >200 pmol/L serum C-peptide, a clinically defined level associated with reduced hypoglycaemia and microvascular complications.[3]

Within the food and insulin diary, participants were asked to collect timings of all meals and snacks eaten during the CGM collection period, a description of the food eaten, estimated carbohydrate content and bolus insulin doses. Food and insulin data were recorded in real time on a paper diary and subsequently analysed after the data collection period.

CGM data were calibrated using capillary blood glucose values recorded in the participants' diaries, and downloaded into Microsoft® Excel. Acceptance criteria for daily (midnight to midnight) CGM data were ≥4 calibrations a day, mean absolute relative difference <28% for a range of >5.6 mmol/L or <18% for a range <5.6 mmol/L,

TABLE 1 Participant demographic data

	$Cpep_{und}$	$Cpep_{low}$	$Cpep_{high}$	*p*
n	34	13	19	
UCPCR (mmol/mol)	0.000 ± 0.000 (0.000, 0.000)	0.034 ± 0.037 (0.002, 0.118)	0.755 ± 0.489 (0.219, 1.881)	
Sex (Male/female)	18/16	7/6	10/9	0.963
Method of control (MDI/CSII)	18/16	6/7	13/6	0.243
Age (Years)	43 ± 12 (25, 68)	41 ± 12 (25, 57)	39 ± 13 (18, 60)	0.567
Age at diagnosis	18 ± 11 (1, 42)	14 ± 8 (8, 32)	28 ± 12[a b] (12, 56)	<0.001
Duration of disease (Years)	25 ± 11 (4, 47)	28 ± 13 (12, 46)	11 ± 8[a b] (1, 30)	<0.001
HbA1c (mmol/L)	61 ± 9 (43, 80)	57 ± 13 (41, 83)	54 ± 9 (34, 73)	0.086
(%)	7.7 ± 0.9 (6.1, 9.5)	7.3 ± 1.1 (5.9, 9.7)	7.1 ± 0.9 (5.3, 8.8)	
BMI	25.4 ± 2.9 (21.5, 33.9)	25.4 ± 4.5 (20.1, 33.9)	25.7 ± 3.5 (21.1, 35.5)	0.924
Glucose monitoring (CGM/Flash/None)	7/4/23	2/0/11	1/2/16	0.561
Total insulin Units/24 hours	43 ± 15 (18, 73)	41 ± 21 (17, 96)	37 ± 24 (13, 122)	0.254
Basal insulin Units/24 hours	22 ± 8	20 ± 14	20 ± 15	0.874
Bolus insulin Units/24 hours	21 ± 10	21 ± 10	17 ± 11	0.487
Bolus insulin (Humalog/Novorapid/Apidra/Fiasp)	8/23/2/1	3/7/1/2	2/17/0/0	0.215
Basal insulin (Degludec/Glargine/Detemir/Humulin I)	0/15/3/0	2/2/1/1	0/12/1/0	0.034

Note: Data presented as mean ± SD with minimum to maximum values in brackets.

P value from one-way ANOVA, Chi-square test of homogeneity and Fisher's exact test.

[a]Significant difference compared with $Cpep_{und}$.

[b]Significant difference compared with $Cpep_{low}$.

a correlations >0.79 between the calibrating blood glucose value and CGM and no missing data segments of >15 min. Only days that met the CGM data criteria, and the corresponding day's data from the food and insulin diary, were subsequently analysed. If the iPro2 failed to collect four valid days of data, the testing process was repeated. The primary outcome was percentage time spent in normoglycaemia (3.9–10 mmol/L). Secondary outcomes included measures of glycaemic variability ([GV], standard deviation [SD], coefficient of variation [CV]), mean, peak and delta glucose, [incremental] area under the curve ([i] AUC) and percentage time spent in/incidence of hypoglycaemia-1 (<3.9 mmol/L)/-2 (<3.0 mmol/L) and hyperglycaemia-1 (>10 mmol/L)/-2 (>13.9 mmol/L).[24]

CGM data allowed group means and individual event outcomes to be analysed across 24hr (00:00–00:00 h), nocturnal (00:00–06:00 h) and postprandial (**early**: 0–120 mins, **overall**: 0–300 mins) periods. Prandial events started 15 mins prior to reported meal-time allowing for inaccuracy. Events were excluded if CGM values did not rise within 300 mins, or further food or insulin were taken within 120 mins (if taken within 120–300 mins then only 0–120 mins analysed). Values from all identified meals were used to calculate each participant's mean postprandial response, which was subsequently analysed between groups. Meal type was defined as breakfast: first carbohydrate-containing meal (06:00–10:00 h), lunch and dinner: largest carbohydrate-containing meals (11:00–15:00 h and 17:00–21:00 h) and 'other': remaining meals.

Analysis was performed using SPSS-27.0 (IBM CORP) and Rv4.04 using the lmer package. Normality and outliers were assessed, with skewed participants' mean data transformed. Participants' mean variables were compared between UCPCR groups using one-way ANOVA (Tukey post-hoc), or Kruskal–Wallis test, while a mixed-model ANOVA assessed glucose over time. Individual event analysis (continuous outcomes) were assessed by a mixed-effects linear regression, fitted with random effect for individuals and fixed effects for UCPCR category, adjusted for BMI and diabetes duration, basal insulin, use of a continuous or flash glucose monitor and (for postprandial) meal type, carbohydrate and bolus insulin intake. For binary outcomes, a mixed-effects generalised linear model was fitted, with random effects for individuals and fixed effects for UCPCR category, BMI and diabetes duration. Parameter effects and confidence intervals were extracted, with Wald test p-values.

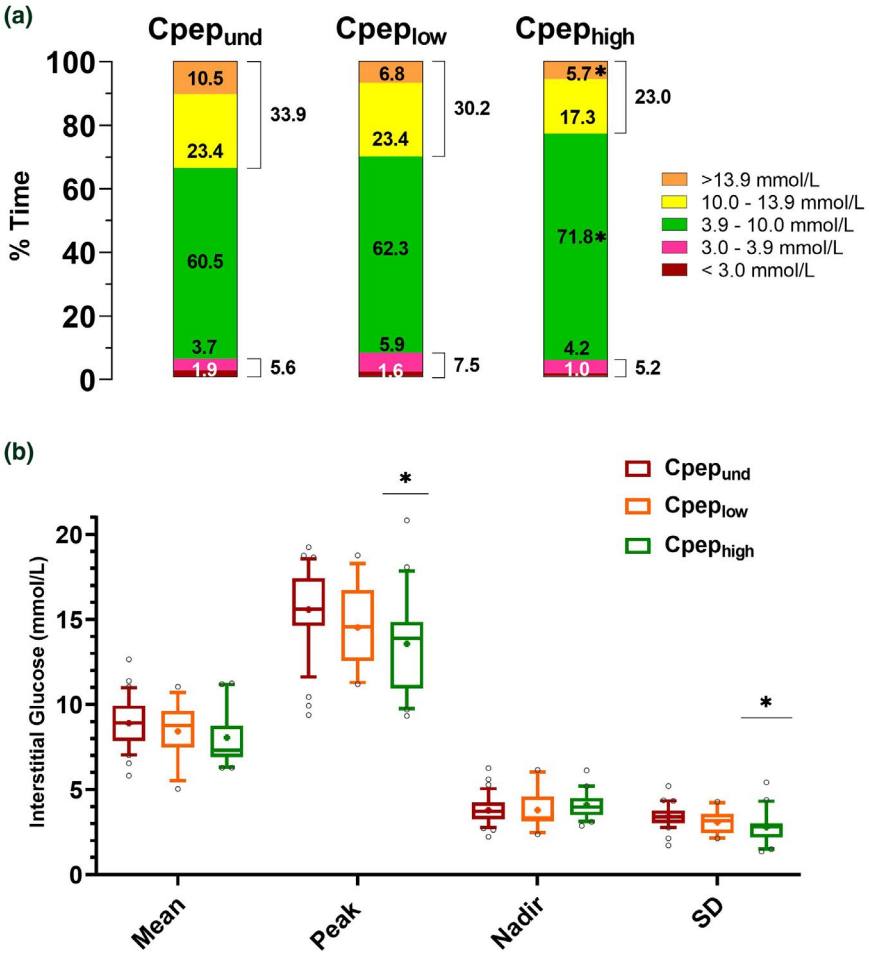

FIGURE 1 Group glycaemic outcomes during 24 h. (A) displays group mean percentage time spent in glycaemic ranges. Orange represents time spent >13.9 mmol/L, yellow represents time spent 10–13.9 mmol/L, green represents time spent 3.9–10 mmol/L, pink represents time spent 3.0–3.9 mmol/L and red represents time spent <3.0 mmol/L. (B) displays group box (representing median and interquartile range) and whiskers (representing 10–90th percentile values), and outlier data as individual participant data points for CGM metrics. $Cpep_{und}$ (red) $n = 32$; $Cpep_{low}$ $n = 13$ (orange); $Cpep_{high}$ $n = 19$ (green). *Significantly different to $Cpep_{und}$

Data are presented as mean ± SD. A p-value <0.05 was considered statistically significant.

3 | RESULTS

Data from 66 participants ($Cpep_{und}$ [$n = 34$], $Cpep_{low}$ [$n = 13$], $Cpep_{high}$ [$n = 19$]) were collected. Age, HbA1c, BMI and use of MDI versus CSII were not statistically different between groups, while $Cpep_{high}$ were older at diagnosis with shorter diabetes duration. The majority of CGM/flash glucose monitoring users were in the $Cpep_{und}$ group, but there were no statistically significant differences between groups (Table 1).

For event analysis, 337 nights were analysed, and 843 postprandial events identified. Following removal of ineligible events (further food or insulin intake), 599 and 252 were analysed for early and overall postprandial periods.

Figure 1 displays participant mean glycaemic outcomes across groups.

3.1 | 24hrs

Higher C-peptide was associated with an increased time in normoglycaemia (Figure 1A, Supplementary Figure S1) and reduced variability (Figure 1B). $Cpep_{high}$ spent more time in normoglycaemia (71.8 ± 17.0%) and less time in hyperglycemia-2 (5.7 ± 9.4%) than $Cpep_{und}$ (60.5 ± 14.6%, $p = 0.028$; 10.5 ± 8.0%, $p = 0.004$) but not $Cpep_{low}$ (62.3 ± 13.2%, $p = 0.204$; 6.8 ± 5.7%, $p = 0.583$). Similarly, $Cpep_{high}$ had significantly lower SD (2.8 ± 0.9 mmol/L)

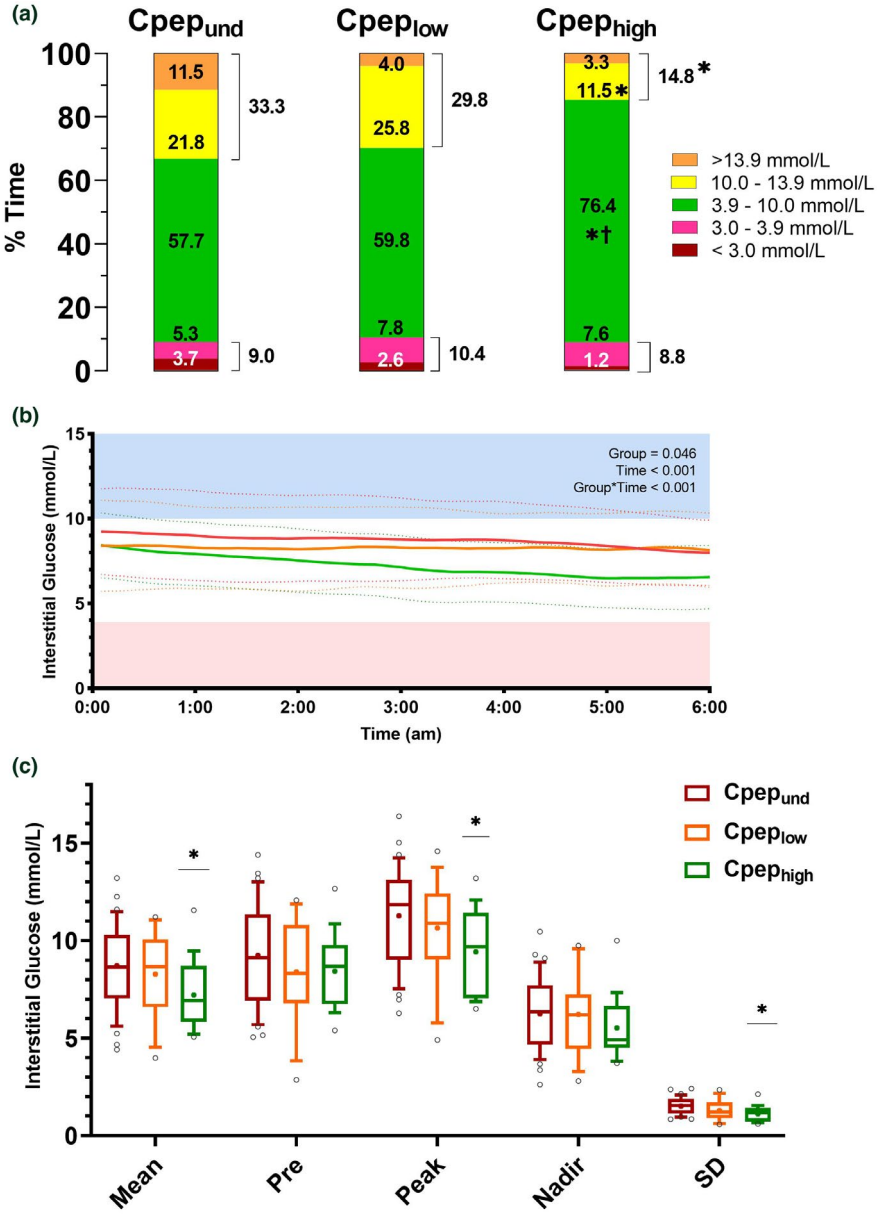

FIGURE 2 Group glycaemic outcomes during nocturnal periods. (A) displays group mean percentage time spent in glycaemic ranges. Orange represents time spent >13.9 mmol/L, yellow represents time spent 10–13.9 mmol/L, green represents time spent 3.9–10 mmol/L, pink represents time spent 3.0–3.9 mmol/L, and red represents time spent <3.0 mmol/L. (B) displays group mean (±SD) glucose time course from midnight to 6am. (C) displays group box (representing median and interquartile range) and whiskers (representing 10–90th percentile values), and outlier data as individual participant data points for CGM metrics. Pre represents mean glucose concentration at midnight, peak represents mean highest glucose concentration, nadir represents lowest $Cpep_{und}$ (red lines) $n = 32$; $Cpep_{low}$ $n = 13$ (orange lines); $Cpep_{high}$ $n = 19$ (green lines). *Significantly different to $Cpep_{und}$. †Significantly different to $Cpep_{low}$

and peak glucose, than $Cpep_{und}$ (SD 3.4 ± 0.7 mmol/L, $p = 0.003$; *peak glucose* 15.6 ± 2.4 mmol/L, $p = 0.007$) but not $Cpep_{low}$ (SD 3.1 ± 0.7 mmol/L, $p = 0.231$, *peak glucose* 14.5 ± 2.4 mmol/L, $p = 0.270$). CV was not significantly different ($Cpep_{und}$ 38.9 ± 7.1%, $Cpep_{low}$ 37.2 ± 8.6%, $Cpep_{high}$ 34.2 ± 7.4%, $p = 0.097$).

3.2 | Nocturnal

Increased β-cell function was associated with reduced nocturnal variability and mean glucose (Figure 2A–C), with $Cpep_{high}$ spending significantly more time in normoglycaemia (76.4 ± 19.9%) than $Cpep_{low}$ (59.8 ± 20.2%, $p = 0.025$ and $Cpep_{und}$ (57.7 ± 20.3%, $p = 0.005$), and less in hyperglycaemia than $Cpep_{und}$ (Figure 2A, Supplementary Figure S1B). $Cpep_{und}$ had a threefold increase in %time hypoglycemia-2 compared with $Cpep_{high,}$ albeit without significant group differences ($p = 0.508$).

$Cpep_{high}$ had significantly lower SD (1.1 ± 0.4 mmol/L) than $Cpep_{und}$ (1.5 ± 0.4 mmol/L, $p < 0.01$), with no significant differences in CV ($Cpep_{und}$ 18.8 ± 5.2%, $Cpep_{low}$ 16.5 ± 5.8%, $Cpep_{high}$ 16.4 ± 5.7%, $p = 0.220$).

Mixed-effects analysis of individual events replicated overall group findings (Supplementary Table S1). Additionally, $Cpep_{und}$ had significantly higher nocturnal CV than $Cpep_{high}$ and greater %time hyperglycemia-2 versus $Cpep_{low}$. Increased BMI was associated with higher mean, pre-bed, peak, AUC and nadir glucose, increasing %time in hyperglycemia-1 and decreasing %time in normoglycaemia. Use of a CGM or a flash glucose monitor did not statistically change time spent in normoglycaemia,

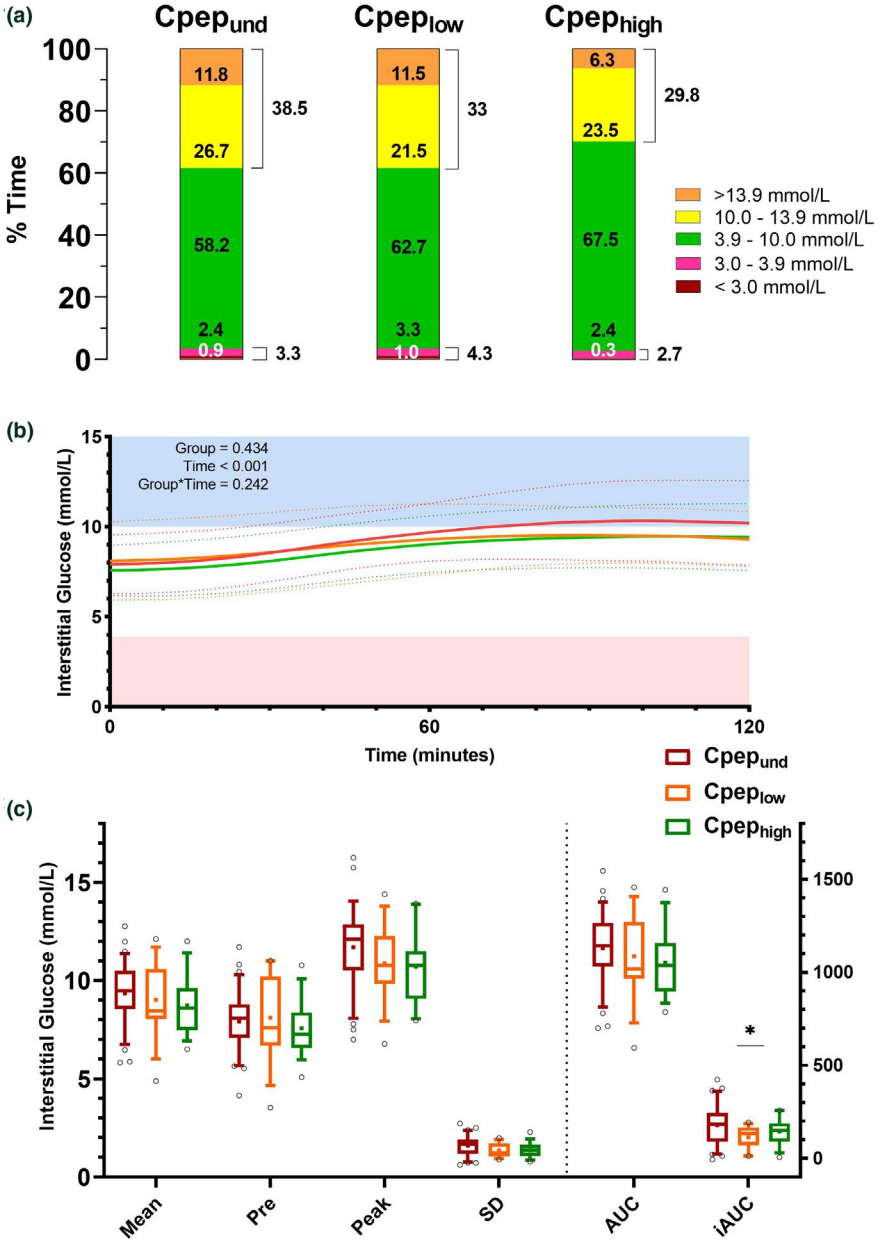

FIGURE 3 Group glycaemic outcomes during the early postprandial periods (0-120 mins). (A) displays group mean percentage time spent in glycaemic ranges. Orange represents time spent >13.9 mmol/L, yellow represents time spent 10–13.9 mmol/L, green represents time spent 3.9–10 mmol/L, pink represents time spent 3.0–3.9 mmol/L, and red represents time spent <3.0 mmol/L. (B) displays group mean (±SD) glucose time course post-prandially. (C) displays group box (representing median and interquartile range) and whiskers (representing 10–90th percentile values), and outlier data as individual participant data points for CGM metrics. Values from all identified meals were used to calculate each participant's mean postprandial response, which was subsequently analysed between the groups $Cpep_{und}$ (red lines) $n = 32$; $Cpep_{low}$ $n = 13$ (orange lines); $Cpep_{high}$ $n = 19$ (green lines). *Significantly different to $Cpep_{und}$

hyperglycaemia-1 or 2, or hypoglycaemia-1 or 2, despite CGM use reducing % time spent <3.9 mmol/L by a mean 6.3% (95% confidence intervals 15.5 to −2.9%, $p = 0.205$) compared with not using a glucose monitor.

3.3 | Postprandial

Increasing C-peptide was associated with incremental improvements in post-prandial normoglycaemia and hyperglycaemia (Figure 3A, Supplementary Figure S1C), with $Cpep_{high}$ having significantly greater time in normoglycaemia (68.1 ± 21.9%) than $Cpep_{und}$ (51.4 ± 21.7%, $p = 0.045$) over 0–300 min.

In the early postprandial period, residual β-cell function reduced glycaemic excursions. Mean and peak glucose were less in $Cpep_{high}$ (mean: 8.7 mmol/L peak: 10.7 mmol/L) and $Cpep_{low}$ (mean: 9.0 mmol/L, peak: 10.9 mmol/L), than $Cpep_{und}$ (mean: 9.4 mmol/L, peak: 11.7 mmol/L), but not significantly so. $Cpep_{low}$ had a significantly lower iAUC than $Cpep_{und}$ (Figure 3C).

Mixed-effects analysis (Supplementary Table S1) also found reduced time spent in hyperglycaemia-2 for $Cpep_{high}$ compared with $Cpep_{und}$ in the early postprandial period, while $Cpep_{low}$ had reduced post-prandial CV compared with $Cpep_{und}$. Over 0–300 min, $Cpep_{high}$ were significantly less likely to have a hypoglycaemic-1 event than $Cpep_{und}$. Increased BMI and meal insulin bolus were associated with higher postprandial glucose. Compared with breakfast, dinner had a significantly higher pre-meal glucose, while lunch, dinner and other meals had a significantly reduced iAUC. Use of flash glucose monitoring significantly reduced peak glucose, SD and CV in the early postprandial period and iAUC in both the early and overall postprandial period compared with not using a glucose monitor. CGM use did not significantly change any postprandial variable measured.

4 | CONCLUSIONS

Through analysis of clinically meaningful time periods during free-living, we have demonstrated for the first time that increasing β-cell function in type 1 diabetes is associated with improved glycaemia overnight and postprandially. This builds upon previous work demonstrating that individuals with residual β-cell function spend less overall free-living time in hyperglycaemia or hypoglycaemia compared with those with undetectable β-cell function.[5–7] Specifically, we show that $Cpep_{high}$ spent the most time in normoglycaemia overnight and had the lowest nocturnal variability. We also demonstrated $Cpep_{und}$ spent less time in normoglycaemia in postprandial periods (0–300 min). In a mixed-effect model, accounting for covariates, higher C-peptide was still associated with improved glycaemic outcomes. Additionally, a very low level of C-peptide was also significantly associated with meaningful reductions in overnight hyperglycaemia, whereas a high C-peptide was associated with less postprandial hypoglycaemic events, in comparison with individuals with no β-cell function.

Increased β-cell function likely improves nocturnal glycaemia due to endogenous responsivity to changing blood glucose. Rickels et al.[6] found that those with superior β-cell function have greater C-peptide response to hyperglycaemic clamps, and greater glucagon response to hyperinsulinemic-hypoglycaemic clamps. Continued secretion of insulin into the portal vein, even the small amount seen in type 1 diabetes, likely attenuates highs through reduction of hepatic glucose production, with increased glucagon response lessening hypoglycaemia. The mechanisms explaining the enhanced glucagon response observed in those with high C-peptide is unclear, with theories including the suppression of functional β-cells activating neighbouring α-cells within intact islets[25] or the presence of C-peptide itself enhancing the counter regularity responses to hypoglycaemia.[26] This may lower GV and protect against nocturnal dysglycaemia, potentially giving individuals confidence to adhere to more intensive insulin regimens, lowering nocturnal mean glucose.

Despite $Cpep_{high}$ spending greater time in normoglycaemia postprandially (0–300 min), improvements in postprandial glucose with increasing β-cell function were less marked. When analysed by mixed-model, $Cpep_{low}$ group had limited improvements in glycaemia compared with $Cpep_{und}$, with $Cpep_{high}$ only having reduced likelihood of hypoglycaemic events. Paradoxical postprandial glucagon rises, caused partly by dysfunctional β-cells unable to suppress α-cells,[6,25] and unaffected by C-peptide level,[6] may partly explain the limited group differences.

Glycaemic improvements appear to be incremental with increasing β-cell function. In our mixed-effects regression, $Cpep_{low}$ spent significantly less time in hyperglycemia-2 than $Cpep_{und}$ overnight. Combined with research demonstrating that residual β-cell function reduces time spent in hypoglycaemia,[5] it appears that minimal C-peptide secretion may offer glycaemic benefits. However, unlike Gibb et al.,[5] no significant differences in %time in hypoglycaemia existed, despite $Cpep_{high}$ appearing to have clinically significant improvements nocturnally. This is likely due to the extremely skewed nature of time spent in hypoglycaemia data, making statistical analysis difficult, and our study being underpowered to detect these small, but important differences, if indeed genuine.

Irrespective of UCPCR, an increased BMI and larger meal bolus insulin were associated with higher postprandial and nocturnal glucose, potentially due to relative insulin resistance,[27] further highlighting the importance of

maintaining a healthy weight in type 1 diabetes.[28] Despite increased mean glucose and %time spent in hyperglycaemia, a higher BMI was not protective against hypoglycaemia, with no association with %time spent in or incidence of hypoglycaemia level 1 or 2.

The association between postprandial glucose and bolus insulin is likely to be influenced by the timing of the insulin in comparison with the food intake, which was not recorded in this study and is, therefore, a limitation. Previous studies have demonstrated that bolus administration 20 min before a meal leads to reduced postprandial excursions in comparison with immediately before a meal.[29] Newer ultra-fast bolus insulins (Fiasp) also reduce postprandial excursions compared with more commonly used rapid acting bolus insulin (Humalog and Novorapid).[30] Fiasp was only used by 3 participants in the current study (1 with $Cpep_{und}$ and 2 with $Cpep_{low}$) and was, thus, not considered as a parameter in our mixed-effects models.

As standard care was maintained throughout the study, some participants were using real time CGM or flash glucose monitoring. Surprisingly, use of a CGM or flash monitor was not associated with improved time spent in normoglycaemia during nocturnal or postprandial periods, unlike previous studies that have found improvements over 24 h and nocturnally.[31,32] Use of a flash monitor, but not a CGM, was associated with improved post-prandial glucose, reducing peak glucose and glycaemic variability measures. It is possible that the proactive nature of the flash glucose monitoring system helps individuals' inform meal time bolus insulin dosage decisions,[33] with cumulative usage teaching individuals their "normal" postprandial responses improving future events. At the time of data collection, CGMs were prescribed using NICE Guidelines (NG17)[34] and only offered to individuals with episodes of severe hypoglycaemia or complete hypoglycaemia unawareness. It was therefore used as a safety net to prevent severe hypoglycaemic events in individuals' at risk rather than for proactive management of postprandial glucose control. Despite only being prescribed to individuals who are more likely to spend time in hypoglycaemia, mean time spent <3.9 mmol/L overnight was reduced by CGM, although this did not reach statistical significance.

The improvements in glycaemic control in overnight and postprandial period are similar to our previous findings demonstrating that individuals with a higher residual β-cell function display a substantially greater amount of time spent in normoglycaemia in the hours following a bout of moderate-intensity exercise.[21] It is likely that residual β-cell function offers some partial protection against dysglycaemia at all time periods throughout a day. This further demonstrates the importance of interventions aiming to preserve β-cell function in the recently diagnosed and why they should target maintaining a high C-peptide (>0.2 mmol/mol) secretion,[6] albeit preserving a smaller amount of function likely confers clinical benefits compared with absolute loss.[5]

In conclusion, we demonstrate association of residual β-cell function with improved free-living glycaemic control in type 1 diabetes overnight and postprandially. The amount of support needed to manage these time periods may be divergent between those with detectable and undetectable levels of C-peptide. In situations with limited resources, the increased difficulties those with no C-peptide face overnight and after meals could be a way of helping allocate diabetes technology and support. In addition, the assistance of residual β-cell function in managing blood glucose may allow tighter more ambitious glucose targets for C-peptide positive type 1 diabetes individuals.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

G.S.T. designed study, recruited participants, researched data, wrote the manuscript. A.S processed data, wrote the manuscript. D.J.W. designed study, researched data, wrote the manuscript. J.A.S. recruited participants, designed study, provided clinical cover and reviewed/edited the manuscript. J.W. undertook statistical analysis and reviewed/edited the manuscript. T.J.M. analysed samples and reviewed/edited the manuscript. R.O. was involved in study design and reviewed/edited the manuscript. K.S. contributed to data collection and reviewed/edited the manuscript.

DATA AVAILABILITY STATEMENT

The datasets used during the current study are available from the corresponding author (Daniel J West; Email: daniel.west@newcastle.ac.uk, telephone: +44 (0)191 20 87076) on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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