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Association between recent exposure to continuous glucose monitoring-recorded hypoglycaemia and counterregulatory and symptom responses to subsequent controlled hypoglycaemia in people with type 1 diabetes

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Abstract

Aim: Experimental hypoglycaemia blunts the counterregulatory hormone and symptom responses to a subsequent episode of hypoglycaemia. In this study, we aimed to assess the associations between antecedent exposure and continuous glucose monitoring (CGM)-recorded hypoglycaemia during a 1-week period and the counterregulatory responses to subsequent experimental hypoglycaemia in people with type 1 diabetes.

Materials and Methods: Forty-two people with type 1 diabetes (20 females, mean ± SD glycated haemoglobin 7.8% ± 1.0%, diabetes duration median (interquartile range) 22.0 (10.5-34.9) years, 29 CGM users, and 19 with impaired awareness of hypoglycaemia) wore an open intermittently scanned CGM for 1 week to detect hypoglycaemic exposure before a standardized hyperinsulinaemic-hypoglycaemic [2.8 ± 0.1 mmol/L (50.2 ± 2.3 mg/dl)] glucose clamp. Symptom responses and

counterregulatory hormones were measured during the clamp. The study is part of the HypoRESOLVE project.

Results: CGM-recorded hypoglycaemia in the week before the clamp was negatively associated with adrenaline response [β −0.09, 95% CI (−0.16, −0.02) nmol/L, $p = .014$], after adjusting for CGM use, awareness of hypoglycaemia, glycated haemoglobin and total daily insulin dose. This was driven by level 2 hypoglycaemia [<3.0 mmol/L (54 mg/dl)] [β −0.21, 95% CI (−0.41, −0.01) nmol/L, $p = .034$]. CGM-recorded hypoglycaemia was negatively associated with total, autonomic, and neuroglycopenic symptom responses, but these associations were lost after adjusting for potential confounders.

Conclusions: Recent exposure to CGM-detected hypoglycaemia was independently associated with an attenuated adrenaline response to experimental hypoglycaemia in people with type 1 diabetes.

KEYWORDS

continuous glucose monitoring, counterregulation, counterregulatory hormone and symptom responses, diabetes, hyperinsulinaemic-hypoglycaemic clamp, hypoglycaemia, hypoglycaemia awareness, type 1 diabetes

1 | INTRODUCTION

Despite over a century of experience with insulin treatment, people with type 1 diabetes remain at high risk of hypoglycaemia. It has been well established that recurrent exposure to hypoglycaemia can result in the development of impaired awareness of hypoglycaemia (IAH) and defective glucose counter regulation in people with type 1 diabetes.[1–6] The clinical consequence is that people with IAH have a more than six-fold higher risk of severe hypoglycaemia, defined by the need for assistance from other people to restore blood glucose.[7,8]

In the last decade, continuous glucose monitoring (CGM) with many benefits (e.g. easier readings, alarms for glucose values out of range, and trend information) has been widely implemented in type 1 diabetes care. The use of CGM in people with diabetes has been associated with beneficial effects on glycaemic control.[9–11] By extension, CGM has improved the ability to capture hypoglycaemia in real-time settings in the everyday lives of people with type 1 diabetes compared with finger-prick self-monitoring of blood glucose. CGM has also been widely implemented in clinical research of people with type 1 diabetes, as CGM enables a comprehensive insight into glucose fluctuations, including the exploration of hypoglycaemia frequency, depth and duration. Such research showed that the majority of CGM-recorded hypoglycaemic episodes are asymptomatic, even in people with preserved awareness of hypoglycaemia.[12] The clinical importance of such episodes is debated and is currently under investigation.

Thus, it remains unresolved whether exposure to CGM-recorded hypoglycaemia affects counterregulatory responses to subsequent hypoglycaemia. With the hyperinsulinaemic-hypoglycaemic clamp study performed in the Hypo-RESOLVE project exploring the impact of hypoglycaemia in people with diabetes,[13,14] an insight into this field is offered. Here we aim to assess the associations between antecedent everyday exposure to hypoglycaemia as recorded by intermittently scanned CGM (isCGM) in the week before participating in a clamp experiment and the counterregulatory hormone and symptom responses measured during the clamp in people with type 1 diabetes.

2 | MATERIALS AND METHODS

This exploratory cross-sectional post hoc analysis was performed with data from the two-centre hyperinsulinaemic-hypoglycaemic clamp study performed within the Hypo-RESOLVE project at Nordsjællands Hospital, Hillerød, Denmark, and Radboud University Medical Centre Nijmegen, The Netherlands, from 2019 to 2021.[13,14] Hypo-RESOLVE is an EU-IMI-funded programme that seeks to explore the impact of hypoglycaemia in people with diabetes. The study was registered at clinicaltrials.gov with registration number NCT03976271 and approval from the ethics committees in both countries. Written, informed consent was obtained from all participants.

2.1 | Participants

Participants were equally recruited from the diabetes outpatient clinics at both sites. Included participants in the study were adults (18-80 years) diagnosed with type 1 diabetes for >1 year, on basal-bolus insulin therapy, using self-monitoring of blood glucose or CGM for glucose monitoring, and with glycated haemoglobin (HbA1c) of <11.3% (100 mmol/mol). More details about inclusion and exclusion criteria have been reported earlier.[13,14]

2.2 | Procedures in the original clamp study

Participants were invited for a screening visit, during which blood was sampled for measurements of HbA1c and C-peptide levels. At the screening visit, hypoglycaemia awareness status, normal awareness versus IAH, was assessed in accordance with the Gold et al.,[8] Clarke et al.[15] and Pedersen-Bjergaard et al.[16] methods. If a participant was classified as having IAH in two of the methods (scores of ≥4 in Gold et al. or Clarke et al. and either reduced awareness or unawareness in the Pedersen-Bjergaard et al. method), the overall score was IAH. Furthermore, participants were defined as CGM users and non-users according to their current use of CGM in their diabetes care.

2.2.1 | Continuous glucose monitoring

In the week before the hyperinsulinaemic-hypoglycaemic clamp (approximately 7 days), all participants were applied with an open isCGM (Freestyle Libre 1®), providing uniformly collected measurements of the interstitial glucose value every 15 min to identify antecedent hypoglycaemia that might affect the outcomes measured during the clamp. CGM users attending the study were wearing the applied isCGM alongside their usual CGM.

2.2.2 | Hyperinsulinaemic-hypoglycaemic clamp

In preparation for the clamp, participants were asked to reduce their basal insulin treatment as described elsewhere and attend the study site after an overnight fast. Participants were rescheduled if they had a hypoglycaemic event <3.0 mmol/L within 24 h before the experimental day.[13,14]

The clamp procedure was performed using a fixed insulin infusion of 1.5 mU × kg^{-1} × min^{-1} (Insulin Aspart; Novo Nordisk) and a variable 20% glucose infusion. The target glucose levels in the clamp procedure were 30 min of euglycaemia [5.0-5.5 mmol/L (90-99 mg/dl)], followed by 60 min of hypoglycaemia [2.8 ± 0.1 mmol/L (50.4 ± 1.8 mg/dl)]. Thereafter, the insulin was stopped, and the plasma glucose level was normalized.[13,14]

At baseline, just before starting the clamp procedure, and at the end of the hypoglycaemic part of the clamp, plasma levels of counterregulatory hormones (adrenaline, noradrenaline, glucagon, cortisol and growth hormone) and symptom responses, using a modified version of the Edinburgh symptom score,[17,18] were measured. Symptoms were rated on a scale from 1 to 7 and divided into autonomic (hunger, sweating, palpitations, anxiety, tingling of hands and feet, trembling, shivers), neuroglycopenic (blurry and double vision, tiredness, weakness, inability to concentrate, confusion, speech difficulty, dizziness, drowsiness, feeling warm) and non-specific (nausea and headache) symptoms, as described previously.[13,14]

2.2.3 | Laboratory analysis

HbA1c was analysed using TOSOH G8 (Sysmex; Etten-Leur) and G11 HPLC-analyser (Sysmex). Plasma adrenaline and noradrenaline were measured using high-performance liquid chromatography combined with fluorometric detection. The plasma glucagon concentration was measured using radioimmunoassay.[19] Plasma growth hormone and cortisol were measured using a routine analysis method with electrochemiluminescent immunoassay on a Modular Analytics E170 (Roche Diagnostics, GmbH).

2.3 | Procedures in the post hoc analysis

2.3.1 | Continuous glucose monitoring data handling

Only participants with >80% of valid CGM recordings in the monitoring period before the clamp were included, and only data from the applied isCGMs were used in the study analyses. The hypoglycaemic metrics were classified according to international consensus.[20] A hypoglycaemic event was defined as two consecutive measurements (≥15 min) of glucose values <3.9 mmol/L (70 mg/dl). Events were further classified as level 1 [<3.9-3.0 mmol/L (70 mg/dl-54 mg/dl)] and level 2 [<3.0 mmol/L (54 mg/dl)] hypoglycaemia. The calculation of the weekly hypoglycaemic exposure was based on the participants' active CGM sensor time. We assessed the effect of hypoglycaemia appearing within 48 h before the clamp with a categorical covariate [hypoglycaemia (<3.9 mmol/L) within 48 h before the clamp = yes/no].

In accordance with the current CGM consensus,[20] we calculated times below range (TBR), times in range and times above range (TAR). TBR, as a percentage of all readings <3.9 mmol/L, was further classified into level 1 (TBRL1, percentage of all readings between 3.8 and 3.0 mmol/L) and level 2 (TBRL2, percentage of all readings <3.0 mmol/L). Analogously, TAR [i.e. readings above 10.0 mmol/L (180 mg/dl)] was divided into level 1 [TARL1, percentage of readings >10.0-13.9 mmol/L (180-250 mg/dl)] and level 2 [TARL2, percentage of readings >13.9 mmol/L (250 mg/dl)]. The coefficient of variation (CV) was calculated as SD/mean glucose and was considered stable if ≤36%.

2.4 | Statistics

For descriptive statistics, means and SDs were used, and medians with interquartile ranges when data were skewed.

Linear regression analyses were performed with the counterregulatory responses to clamped hypoglycaemia as outcome variables. To check for normality, residuals were assessed visually in plots.

For the primary endpoint in this post-hoc analysis, we conducted multiple regression analyses to investigate associations between the

frequency of overall CGM-hypoglycaemia (<3.9 mmol/L)/week in the week before the clamp and the counterregulatory hormone and symptom responses to subsequent hypoglycaemia assessed by the plasma concentration or the symptom score at the end of the hypoglycaemic period. Initially, we used univariate analyses to assess unadjusted associations between the factors: frequency of overall CGM-hypoglycaemia, CGM use, awareness, sex,[21] body mass index (in kg/m^2), diabetes duration in years, total insulin dose per day (units/day), C-peptide status [negative (≤0.047 nmol/L)/positive (>0.047 nmol/L)] and HbA1c (%) and the counterregulatory responses. If an association between a covariate and a counterregulatory response had a $p < .15$, the covariate was included in the multiple regression analysis; CGM use in everyday life and self-assessed hypoglycaemia awareness status were included in the multivariate analyses regardless of the *p*-values, as these factors are associated with exposure to hypoglycaemia.[9,22]

In a subanalysis, we assessed associations between the adrenaline and autonomic symptom responses and other CGM hypoglycaemia metrics measured in the week before the clamp. The CGM metrics included the frequency of overall hypoglycaemic events/week, level 1 events/week, level 2 events/week, TBR, TBRL1, TBRL2, CV (stable/unstable), and appearance of hypoglycaemia in 48 h before the clamp day. Further, in unpaired t-tests, we explored if the adrenaline and autonomic symptom responses (and the other counterregulatory responses) were different when comparing groups (a) with no level 2 hypoglycaemia, and (b) with level 2 hypoglycaemia in the week before the clamp.

SPSS software (version 28.0) was used for statistical analyses, and Microsoft Office 2016 for graphics. Two-sided *p*-values of <.05 were selected as the level of statistical significance. We did not adjust for multiple comparisons in this study. People with missing data within a specific covariate were excluded from the analysis.

3 | RESULTS

In total, 47 people with type 1 diabetes participated in the clamp study, 42 of whom had sufficient CGM data and were included in the present analyses. On average, participants wore the isCGM for 6.9 ± 0.5 days with 93.6% ± 5.2% active CGM wear time, corresponding to 6.4 ± 0.6 days/participant of active CGM sensor time. Baseline characteristics are presented in Table 1.

3.1 | Continuous glucose monitoring data

In total, 255 hypoglycaemic events were registered among 38 participants (four did not have a hypoglycaemic event), corresponding to a median (interquartile range) of 5.8 (3.1-8.8) hypoglycaemic events per participant-week in the week before the clamp. Of these, there were 4.3 (2.3-6.4) level 1 hypoglycaemic events/week and 1.1 (0-2.5) level 2 hypoglycaemic events/week. Participants spent 5.7 (3.0-9.9) % of the recorded time in TBR. The mean CV was 39.6% ± 8.3%, and 29 (69%) had a CV of >36%. Twenty-eight people were exposed to level 2 hypoglycaemia during the monitoring period. Twenty-nine participants (69.0%) experienced a hypoglycaemic event (<3.9 mmol/L) within 2 days before the clamp, and seven experienced a level 2 hypoglycaemic event within 2 days before the clamp. Hypoglycaemic exposure was less in people with versus those without use of CGM in their everyday lives (Table 2).

3.2 | Counterregulatory responses

We observed statistically significant increments in all counterregulatory hormones and symptoms from baseline to hypoglycaemia for the 42 participants included in this analysis (Table 1).

The frequency of CGM-recorded hypoglycaemia in the week before the clamp was negatively associated with the adrenaline, noradrenaline and cortisol responses to clamped hypoglycaemia in univariate analyses (Table S1). Being female was negatively associated with the growth hormone response. The total insulin dose was positively associated with the adrenaline, glucagon and cortisol responses. CGM use was positively associated with the adrenaline response, and HbA1c was positively associated with the adrenaline, noradrenaline and cortisol responses (Table S1).

In multivariate analyses, the frequency of CGM-recorded hypoglycaemia was negatively associated with the adrenaline response to experimentally induced hypoglycaemia during the clamp (β −0.09, 95% CI (−0.16, −0.02), $p = .014$), when adjusting for CGM use, awareness status, HbA1c and total dose of insulin per day. No associations were found between the frequency of CGM-recorded hypoglycaemia and any other counterregulatory hormone responses after adjusting for other relevant factors. The associations between total insulin dose and glucagon and cortisol responses to hypoglycaemia were maintained in multivariate analyses (Table 3).

In univariate analyses of the symptom responses, the frequency of CGM-recorded hypoglycaemia was negatively associated with total, autonomic and neuroglycopenic symptoms during the hypoglycaemic clamp (Table S2). These associations were lost after adjustment in the multivariate analyses (Table 4).

In univariate analyses, being female was positively associated with total, autonomic and non-specific symptom scores, while normal awareness was positively associated with only total and autonomic symptom scores (Table S2). In multivariate analyses, these associations were lost except for the positive association between being female and the non-specific symptom score (Table 4).

3.3 | Other continuous glucose monitoring-recorded hypoglycaemia metrics and counterregulatory responses

As illustrated in Table 5, multiple CGM hypoglycaemia metrics (overall, level 1 and 2 hypoglycaemia/week, TBR, TBR1) were negatively associated with the adrenaline response in univariate analyses. However,

TABLE 1 Baseline characteristics of participants and CGM metrics in the week before the clamp.

Characteristics	Type 1 diabetes
No. of participants	42
Female, n (%)	20 (48)
Age, years	51.0 (30.5-63.3)
Diabetes duration, years	22.0 (10.5-34.9)
BMI, kg/m^2	26.8 ± 3.6
HbA1c, %	7.8 ± 1.0
HbA1c, mmol/mol	61.9 ± 10.3
C-peptide negative, n (%)[a]	34 (83)
Total insulin units per day, IU/day[a]	43.0 (36.0-65.7)
Insulin administration, pen/pump	24/18 (57/43)
Awareness, NAH/IAH; n (%)	23/19 (55/45)
Gold, aware/impaired awareness	27/15 (64/36)
Clarke, aware/reduced awareness	28/14 (67/33)
Pedersen-Bjergaard, aware/impaired awareness/unawareness	16/18/8 (38/43/19)
CGM users	29 (69)
isCGM	18
rtCGM	11
Self-reported no. of episodes of mild hypoglycaemia in 1 week	4.0 (2.0-7.0)
No of participants with ≥1 severe hypoglycaemia event within the last year, n (%)	11 (26)
CGM metrics in the week before the clamp	
Active sensor time, days	6.4 ± 0.6
Active wear time, %	93.6 ± 5.2
CGM-recorded hypoglycaemia/week	5.8 (3.1-8.8)
Level 1/week, <3.9-3.0 mmol/L	4.3 (2.3-6.4)
Level 2/week, <3.0 mmol/L	1.1 (0-2.5)
Most recent exposure to hypoglycaemia before the clamp, days	2.0 ± 1.2
Mean glucose, mmol/L	9.3 ± 1.9
Standard deviation, mmol/L	3.8 ± 1.2
Coefficient of variability, %	39.6 ± 8.3
≤36/>36%, n (%)	13/29 (31/69)
Time below 3.9 mmol/L, %	5.7 (3.0-9.9)
Time below 3.9-3.0 mmol/L, %	4.0 (2.4-6.0)
Time below 3.0 mmol/L, %	0.9 (0.2-3.6)
Time in range, %	52.3 (44.2-69.1)
Time above range, %	40.3 (22.3-52.1)
Counterregulatory delta-responses	
Adrenaline, nmol/L	1.3 (0.7-2.2)
Noradrenaline, nmol/L	0.7 (0.3-1.2)
Glucagon, pmol/L	1.0 (0-3.0)
Cortisol, nmol/L	0.2 (0-0.3)
Growth hormone, mE/L	48.5 (21.4-80.7)
Total symptom score	15.0 (4.8-33.0)
Autonomic symptom score	5.0 (1.0-12.0)
Neuroglycopenic symptom score	10.5 (2.8-20.0)
Non-specific symptom score	0 (0-2.0)

Note: Autonomic symptoms: hunger, sweating, palpitations, anxiety, tingling of hands and feet, trembling, shivers. Neuroglycopenic symptoms: blurry and double vision, tiredness, weakness, inability to concentrate, confusion, speech difficulty, dizziness, drowsiness and feeling warm. Non-specific symptoms: nausea and headache.

Abbreviations: BMI, body mass index; CGM, continuous glucose monitoring; HbA1c, glycated haemoglobin; IAH, impaired awareness of hypoglycaemia; isCGM, intermittently scanned continuous glucose monitoring; NAH, normal awareness of hypoglycaemia.

[a]Analysis of 41 participants, data are shown as number (%), mean ± SD or median (interquartile range). Wilcoxon signed ranks test was used to evaluate the counterregulatory responses from baseline to hypoglycaemia.

in multivariate analysis, only the frequency of level 2 hypoglycaemia remained significantly associated with the adrenaline response [β −0.21, 95% CI (−0.41, −0.019), $p = .036$]. In addition, adrenaline responses to hypoglycaemia were significantly smaller in people with level 2 hypoglycaemia in the week before the clamp than in people with no level 2 hypoglycaemic exposure at all (1.4 ± 0.2 nmol/L vs. 2.4 ± 0.4 nmol/L, $p = .037$) (Figure 1A). In addition, the cortisol response to clamped hypoglycaemia was significantly smaller in people with compared with people without level 2 hypoglycaemia in the week before the clamp (delta-responses: +0.1 ± 0.03 vs. +0.2 ± 0.03 nmol/L, $p = .005$). No significant differences were observed between the people with and without level 2 hypoglycaemia with respect to the noradrenaline, glucagon, or growth hormone responses.

Several CGM hypoglycaemia metrics were negatively associated with the autonomic symptom response in univariate analyses (overall and level 1 hypoglycaemia/week, TBR, TBRL1), yet no associations were maintained in multivariate analyses. The change in autonomic symptoms in response to hypoglycaemia was numerically lower in people with level 2 hypoglycaemia as compared with those without level 2 hypoglycaemia, but this failed to reach statistical significance (delta-responses: 6.1 ± 1.3 vs. 9.9 ± 2.2, $p = .123$) (Figure 1B). There were also no differences between these groups with respect to total or neuroglycopenic responses.

4 | DISCUSSION

In this study of people with type 1 diabetes, we show that recent episodes of CGM-recorded hypoglycaemia, particularly at level 2, over an

TABLE 2 CGM-recorded hypoglycaemic exposure in the week before the clamp in everyday CGM users and non-users with normal and impaired awareness.

	CGM users			CGM non-users			All CGM users versus non-users
	All (n = 29)	NAH (n = 14)	IAH (n = 15)	All (n = 13)	NAH (n = 9)	IAH (n = 4)	*p*-Values
CGM-recorded hypoglycaemia/week (<3.9 mmol/L)	5.5 (2.9-7.4)	5.4 (2.1-7.3)	5.9 (2.9-7.8)	7.4 (4.4-11.0)	7.2 (4.4-10.6)	10.7 (5.7-11.1)	.060
Level 1/week (<3.9-3.0 mmol/L)	4.4 (1.9-6.2)	4.5 (1.8-6.1)	4.1 (1.9-6.6)	4.2 (3.5-6.7)	4.1 (3.0-5.6)	7.4 (4.8-8.3)	.346
Level 2/week (<3.0 mmol/L)	1.0 (0-1.9)	0.5 (0-1.4)	1.0 (0-2.3)	2.2 (1.3-3.9)	2.2 (1.3-4.4)	2.7 (0.5-3.9)	.002*
Time below 3.9 mmol/L	3.7 (1.8-7.9)	3.8 (1.3-7.8)	3.7 (2.3-8.2)	8.8 (6.6-10.6)	8.8 (6.6-10.0)	9.5 (5.4-12.2)	.012*
Time below 3.9-3.0 mmol/L	3.2 (1.6-5.9)	3.4 (1.3-5.6)	3.1 (2.1-6.5)	5.2 (4.0-6.4)	5.2 (3.2-6.0)	5.7 (4.5-7.8)	.082
Time below 3.0 mmol/L	0.4 (0-2.1)	0.4 (0-1.9)	.7 (.2-2.4)	3.6 (2.5-5.0)	3.6 (2.5-5.0)	3.1 (0.9-5.1)	<.001*

Note: Data are shown as median (interquartile range). Mann-Whitney U-test is used for unadjusted comparison of hypoglycaemic exposure in the week before the clamp in the groups of CGM users versus non-users.
Abbreviations: CGM, continuous glucose monitoring; IAH, impaired awareness of hypoglycaemia; NAH, normal awareness of hypoglycaemia.
*$p < .05$ between all CGM users versus all non-users.

TABLE 3 Factors associated with the counterregulatory hormone responses to hypoglycaemia in 42 people with type 1 diabetes participating in a hyperinsulinaemic-hypoglycaemic clamp after 1 week of CGM recording.

	Adrenaline, nmol/L	Noradrenaline, nmol/L	Glucagon, pmol/L	Cortisol, nmol/L	Growth hormone, mE/L
Covariates	β (95% CI) *p*-Value	β (95% CI) *p*-Value	β (95% CI) *p*-Value	β (95% CI) *p*-Value	β (95% CI) *p*-Value
Intercept	−0.31 (−3.58, 2.96)	−0.11 (−2.97, 2.76)	0.09 (−3.81, 3.98)	−0.03 (−0.56, 0.50)	48.72 (7.17, 90.26)
CGM-Hypoglycaemia/week	−0.09 (−0.16, −0.02) .014*	−0.05 (−0.12, 0.01) .109	0.04 (−0.16, 0.25) .672	−0.01 (−0.02, 0.003) .147	−0.05 (−2.65, 2.50) .969
CGM use, yes	0.58 (−0.16, 1.31) .119	−0.09 (−0.76, 0.57) .776	0.62 (−1.63, 2.87) .579	0.01 (−0.10, 0.11) .910	13.88 (−13.42, 41.19) .309
Awareness, normal	0.001 (−0.68, 0.69) .997	0.05 (−0.56, 0.65) .871	0.09 (−2.02, 2.19) .934	−0.02 (−0.11, 0.08) .736	15.62 (−9.36, 40.60) .213
Baseline value before hypoglycaemia was induced	2.86 (−0.28, 6.00) .073	1.12 (0.84, 1.40) <.001*	0.85 (0.47, 1.24) <.001*	0.71 (0.33, 1.09) <.001*	0.33 (−1.41, 2.08) .701
HbA1c, %	0.17 (−0.21, 0.54) .375	0.14 (−0.19, 0.48) .390	[a]	0.03 (−0.02, 0.09) .235	[a]
Total insulin dose per day, IU/day	0.01 (−0.001, 0.02) .086	[a]	0.04 (0.01, 0.07) .018*	0.001 (0.00, 0.003) .049*	[a]
Sex, female	[a]	[a]	[a]	[a]	−19.85 (−45.37, 6.58) .124

Note: Data are analysed in multiple regression analyses for each counterregulatory hormone.
Abbreviation: CGM, continuous glucose monitoring; CI, confidence interval; HbA1c, glycated haemoglobin.
[a]Covariate not included in the analysis.
*$p < .05$.

approximate 7-day period, are associated with attenuated sympathoadrenal responses to subsequent experimental hypoglycaemia. The negative association between CGM-recorded hypoglycaemia and the adrenaline response was present when we adjusted for previous CGM use, hypoglycaemia awareness status, HbA1c and total insulin use per day. In the adjusted analyses, we did not find any associations

TABLE 4 Factors associated with the symptom responses to hypoglycaemia in 42 people with type 1 diabetes participating in a hyperinsulinaemic-hypoglycaemic clamp after 1 week of CGM recording.

	Total symptom score	Autonomic symptom score	Neuroglycopenic symptom score	Non-specific symptom score
Covariates	β (95% CI) *p*-Value	β (95% CI) *p*-Value	β (95% CI) *p*-Value	β (95% CI) *p*-Value
Intercept	32.80 (10.15, 55.44)	1.25 (−24.01, 26.52)	22.48 (9.20, 35.77)	0.76 (−0.97, 2.49)
CGM-Hypoglycaemia/week	−0.98 (−2.18, 0.22) .105	−0.33 (−0.83, 0.17) .184	−0.71 (−1.42, 0.01) .052	0.03 (−0.08, 0.13) .592
CGM use, yes	−1.64 (−14.22, 10.94) .793	−0.05 (−5.05, 4.95) .984	−1.33 (−9.10, 6.44) .730	−0.27 (−1.37, 0.84) .592
Awareness, normal	7.88 (−3.68, 19.45) .175	3.57 (−1.07, 8.21) .127	3.44 (−3.65, 10.54) .332	0.35 (−0.67, 1.37) .493
Baseline value	0.49 (−0.17, 1.15) .143	0.72 (−0.09, 1.53) .081	0.46 (−0.19, 1.11) .158	0.77 (0.41, 1.14) <.001*
HbA1c, %	[a]	1.00 (−1.61, 3.60) .444	[a]	[a]
Sex, female	7.28 (−4.60, 19.16) .222	2.79 (−1.79, 7.37) .224	[a]	1.19 (0.15, 2.22) .026*

Note: Data are analysed in multiple regression analyses for each symptom score.
Abbreviation: CGM, continuous glucose monitoring; CI, confidence interval; HbA1c, glycated haemoglobin.
[a]Covariate not included in the analysis.
*$p < .05$.

between CGM-recorded hypoglycaemia and noradrenaline, cortisol, growth hormone, glucagon, and total, autonomic and neuroglycopenic symptom scores.

The association between real-life CGM-recorded hypoglycaemia and the reduced adrenaline response is consistent with the human experimental literature[2,3] and a recent epidemiological study[23] and suggests that frequent sensor-detected hypoglycaemia may help identify people with reduced adrenaline responses to experimental hypoglycaemia who are potentially at greater risk of severe hypoglycaemia.[2,3] It is notable that the association between CGM-hypoglycaemia and the blunted adrenaline response was mainly driven by level 2 CGM-hypoglycaemic exposure. In extension, the adrenaline response of people with no level 2 hypoglycaemic exposure was comparable with that in people without diabetes in the original clamp study (2.7 ± 0.4 nmol/L), as reported by Fabricius et al.[14] These findings support the recommended hypoglycaemia level classification from the International Hypoglycaemia Study group[24] and that of the Advanced Technologies & Treatments for Diabetes for CGM[20] with respect to the clinical relevance of level 2 hypoglycaemia as detected by CGM.

In addition to the lower response of adrenaline, we also found the cortisol response[1,25] to be smaller in people with level 2 hypoglycaemic exposure in the week before the clamp as compared with those without such exposure, whereas this was not the case for growth hormone and noradrenaline responses. This is in line with other studies investigating the effect of antecedent hypoglycaemia on counterregulatory responses to hypoglycaemia,[2,3,6] and the role of cortisol in the defence against prolonged hypoglycaemia.[1,25]

In contrast, the association between CGM-hypoglycaemic exposure and the autonomic symptom response to subsequent hypoglycaemia found in the univariate analysis could no longer be detected after adjusting for potential confounders. This may be attributed to the experimental settings, which potentially influenced the subjectively measured symptom responses by participants having specific expectations for the clamp study[26] as well as other factors interfering with the symptom perception, including sleep quality, stress level and mood on the day of the clamp experiment. More importantly, this discrepancy in findings further underscores that autonomic symptoms are not the result of the adrenaline response but are generated separately. Indeed, previous studies have already shown that autonomic symptoms are generated from sympathetic neural stimulation in the central nervous system rather than as a consequence of adrenomedullary stimulation by hypoglycaemia.[18,27,28]

In this study, observations of less exposure to hypoglycaemia, particularly at level 2, in the week before the clamp in CGM users versus non-users, regardless of awareness status, are in line with

TABLE 5 Univariate and multivariate associations of the CGM-recorded hypoglycaemic metrics in the week before the clamp and the counterregulatory adrenaline and autonomic responses to hypoglycaemia of the hyperinsulinaemic-hypoglycaemic clamp (all adjusted for baseline values).

	Adrenaline response (nmol/l)		Autonomic symptom score	
	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value
Univariate analyses hypoglycaemic metrics				
Overall frequency of hypoglycaemic events/week (<3.9 mmol/L)	−0.12 (−0.18, −0.05)	.002*	−0.50 (−0.94, −0.06)	.026*
Level 1 events/week (<3.9-3.0 mmol/L)	−0.11 (−0.20, −0.02)	.015*	−0.58 (−1.13, −0.04)	.036*
Level 2 events/week (<3.0 mmol/L)	−0.20 (−0.35, −0.05)	.010*	−0.54 (−1.52, 0.45)	.277
TBR (<3.9 mmol/L)	−0.09 (−0.16, −0.02)	.015*	−0.52 (−0.96, −0.07)	.024*
TBRL1 (<3.9-3.0 mmol/L)	−0.11 (−0.21, −0.02)	.021*	−0.74 (−1.32, −0.15)	.015*
TBRL2 (<3.0 mmol/L)	−0.14 (−0.31, 0.04)	.120	−0.52 (−1.60, 0.56)	.335
CV (stable)	0.39 (−0.42, 1.21)	.335	1.54 (−3.49, 6.56)	.539
Hypoglycaemia (all) within 48 h before the clamp (yes)	−0.64 (−1.44, 0.15)	.109	−0.38 (−5.25, 4.49)	.876
Multivariate analyses hypoglycaemic metrics				
Intercept	1.98 (1.10, 2.85)		13.92 (4.83, 23.00)	
Level 1 events/week	−0.12 (−0.26, 0.01)	.075	−0.27 (−1.18, 0.64)	.549
Level 2 events/week	−0.21 (−0.41, −0.01)	.036*	−0.03 (−1.36, 1.29)	.962
TBR (<3.9 mmol/L)	0.04 (−0.90, 0.17)	.521	−0.32 (−1.19, 0.55)	.463
Hypoglycaemia (all) within 48 h before the clamp (yes)	−0.06 (−0.90, 0.77)	.877	−0.75 (−6.41, 4.91)	.789
Baseline value	2.94 (−0.33, 6.21)	.076	0.73 (−0.08, 1.54)	.074

Abbreviations: CGM, continuous glucose monitoring; CI, confidence interval; TBR, times below range; TAR, times above range.
*$p < .05$.

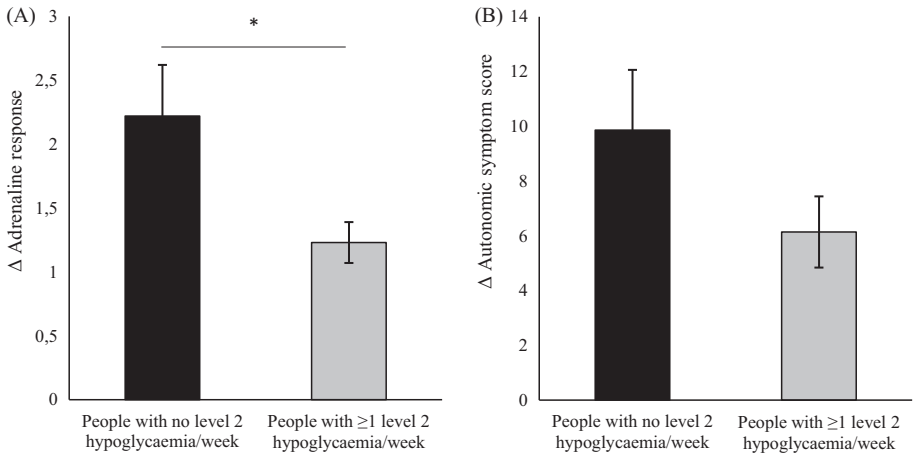

FIGURE 1 (A) Δ Adrenaline and (B) autonomic symptom responses from baseline to hypoglycaemia in a hyperinsulinaemic-hypoglycaemic clamp procedure in people with type 1 diabetes with no level 2 hypoglycaemia (n = 14), and with level 2 hypoglycaemia (n = 28) in the week before the clamp. Data are shown as mean ± SEM. An unpaired t-test was performed to compare the delta responses in the groups. *$p < .05$.

previous findings showing the beneficial effect of isCGM on exposure to hypoglycaemia.[9–11]

While it is still uncertain whether the hypoglycaemia detected using CGM versus plasma glucose measurement has similar consequences, our results suggest that at least for level 2 hypoglycaemia, CGM may identify those individuals who have attenuated adrenaline responses to subsequent hypoglycaemia. In a clinical context, this knowledge may help clinicians point out hypoglycaemic high-risk individuals with attenuated adrenaline responses by applying a short period of CGM monitoring as a supplement to the awareness classification already used. However, future clamp studies are needed to confirm the degree of CGM-hypoglycaemia avoidance (including depth and duration) that is needed to reduce the development of defective glucose counterregulation and/or restore normal responsiveness.

The strengths of this analysis relate in part to those of the clamp study this analysis was used for, including its large sample size[29] and the thorough phenotyping of the participants, particularly in terms of hypoglycaemia exposure and awareness status. However, the study has some limitations to consider in the interpretation of the results. Methodically, the one-stepped design did not allow comparison of glycaemic thresholds for symptom and hormonal counterregulatory responses. In addition, as the original study was not designed to

determine whether previous CGM-detected hypoglycaemia leads to the suppression of counterregulatory hormone and symptom responses to subsequent hypoglycaemia, we can only report associations, and not provide causality. In accordance, as participants were instructed to avoid hypoglycaemia 24 h before the clamp, we could not examine associations between very recent hypoglycaemia and the endpoints. Finally, the short period of CGM recording is a limitation. It is possible that the CGM-detected hypoglycaemia over the 7-day period may be a biomarker of those individuals who have experienced recurrent hypoglycaemia over much longer periods of time or people with short-term behavioural changes in the recording period. Longer periods of CGM monitoring before the clamp study would achieve a more robust impression of the average glucose profile of the participants and limit the effect of potential behavioural changes and measurement insecurities in the first days of wearing a CGM sensor.[30]

5 | CONCLUSION

In conclusion, in this cross-sectional post-hoc analysis, recent hypoglycaemia recorded by isCGM during approximately 1 week, particularly <3.0 mmol/L, captured in real-time daily life settings, is associated with attenuated adrenaline responses to subsequent (controlled) hypoglycaemia in people with type 1 diabetes.

AUTHOR CONTRIBUTIONS

The original study was designed by TWF, CV, BG and UPB. TWF and CV performed the clamp experiment. CHS and UPB designed this post hoc analysis. JJH generated data. CHS analysed the data and wrote the first draft of the manuscript. All authors contributed to the discussion of the results, provided feedback for the further development of the manuscript, and approved the final version. CHS is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

CHS, CV and PLK have no conflicts of interest to declare. TWF has been employed by Novo Nordisk after the completion of the study. CT has received research support from AstraZeneca, received lecture fees from AstraZeneca and Novo Nordisk, and served on advisory boards for Bayer, MSD, Boehringer-Ingelheim and Novo Nordisk. BG has received research support from Novo Nordisk. UPB has served on advisory boards for Sanofi, Novo Nordisk and Vertex, and has received lecture fees from Novo Nordisk and Sanofi. MLE has been a member of advisory panels and/or received speakers fees and/or research support from Novo Nordisk, Eli Lilly, Abbott Diabetes Care, Medtronic, Dexcom, Astra Zeneca, Ypsomed, Pila Pharma and Zucara. JJH is supported by the Novo Nordisk Foundation. SAA has served on advisory boards for Medtronic and Novo Nordisk and spoken at educational events sponsored by Sanofi and Novo Nordisk.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The datasets generated and analysed in the present study are available from the corresponding author upon reasonable request.

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