Cardiovascular Autonomic Neuropathy Is Associated With Increased Glucose Variability in People With Type 1 Diabetes

Sara H. Naaman,[1] Hatice I. Mizrak,[1] Nanna Lind,[1] Jens C. Laursen,[1] Huda Kufaishi,[1] Marie M.B. Christensen,[1] Ajenthen G. Ranjan,[1,2] Kirsten Nørgaard,[1,3] and Christian S. Hansen[1]

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OBJECTIVE

We investigated the association between the cardiovascular autonomic neuropathy (CAN) diagnosis and glucose variability (GV) in type 1 diabetes (T1D), as autonomic dysfunction previously has been associated with increased GV.

RESEARCH DESIGN AND METHODS

CAN was assessed by three recommended cardiovascular reflex tests (CARTs). Glucose metrics were obtained from 10-day blinded continuous glucose monitoring (CGM). Between-group differences in GV indices were assessed by regression analyses in 24 participants with T1D with CAN and 24 matched control subjects without CAN.

RESULTS

The CAN diagnosis was associated with 4.9% (95% CI 1.0, 8.7) higher coefficient of variation (CV) (P = 0.014), 0.7 mmol/L (0.3, 1.1) higher SD (P = 0.002) of glucose, and 1.4 mmol/mol (0.0, 2.7) higher mean amplitude of glycemic excursions (P = 0.047). Lower measures of CARTs were associated with higher CV, SD, and time above range values.

CONCLUSIONS

The CAN diagnosis associates with a significantly higher GV in T1D, despite a high prevalence of routine CGM use.

Cardiovascular autonomic neuropathy (CAN) is a common and severe complication of diabetes linked to increased mortality and morbidity (1), with a prevalence of 20–60% (2). Dysglycemia is an established risk factor for CAN in diabetes (3). Glucose variability (GV) may be associated with autonomic dysfunction in people with type 1 diabetes (T1D) (4). Conversely, autonomic dysfunction may induce adverse changes in glucose metabolism (5). Thus, the causal direction of detrimental GV fluctuations and CAN is unknown. The clinical CAN diagnosis has not been associated with GV. Demonstrating such an association would enable the identification of people with detrimental glucose excursions, which by intervention could be mitigated.

We aimed to investigate the possible association between the CAN diagnosis and GV in T1D.

[1]*Clinical Research, Steno Diabetes Center Copenhagen, Copenhagen, Denmark*
[2]*Danish Diabetes Academy, Odense, Denmark*
[3]*Department of Clinical Medicine, Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark*

Corresponding author: Sara H. Naaman, sara_naaman@hotmail.com

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RESEARCH DESIGN AND METHODS

Study Design

Participants with T1D with established CAN or with no CAN were enrolled in a cross-sectional study from an ongoing neuropathy screening study at Steno Diabetes Center Copenhagen (Copenhagen, Denmark). Participants attended one physical study visit at which baseline characteristics were obtained. In this study, the CAN status was reaffirmed, and continuous glucose monitors (CGMs) were attached. Monitors and transmitters were returned at a second visit. The study was approved by the regional Committee (H-19029796) and the Danish Data Protection Agency (P-2019–291).

Study Population

Forty-eight participants were included by the following criteria: 20–80 years of age, T1D (World Health Organization criteria), and having CAN or no CAN. Participants with or without CAN were matched on age, sex, and CGM use.

Participants were excluded in the presence of ischemic cardiovascular disease, thyroid disease, atrial fibrillation, pacemaker, alcohol abuse, insulin pump use, pregnancy, cancer treatment, hypoglycemia at first visit (capillary blood glucose <3.9 mmol/L), or use of β-blockers or antidepressants.

CAN

The CAN diagnosis was assessed by the three cardiovascular reflex tests (CARTs) recommended for diagnosing CAN (Vagus device; Medicus Engineering, Aarhus, Denmark) (6): change in heart rate during lying-to-standing test (30/15), deep breathing test (E/I), and Valsalva maneuver (VM). Tests were performed after at least 2 h of fasting and caffeine refrainment and 24-h abstinence from strenuous activity.

The age-dependent cutoff levels of CARTs (7) were used to diagnose CAN in the presence of at least two pathological CARTs (1). Participants with no pathological CARTs constituted the control group.

GV

Masked 10-day CGM were recorded (Dexcom G6; Dexcom). If a minimum of 7 days were recorded, data were included (8). Participants continued routine CGM use if part of prestudy treatment. The glycemic metrics determined were: mean sensor glucose, coefficient of variation (CV), SD, mean amplitude of glycemic excursions (MAGE), continuous overlapping net glycemic action, time in range (TIR) 3.9–10 mmol/L, time above range (TAR) >10 mmol/L, and time below range (TBR) <3.9 mmol/L.

Distal Symmetric Polyneuropathy

Distal symmetric polyneuropathy was assessed by the following and by use of age- and height-dependent thresholds where possible: light touch perception by 10-g monofilament, pain sensation by 40-g pinprick, vibration perception threshold, sural nerve function by conduction velocity, and amplitude potential as applied in previous studies (9).

Neuropathy, Gastroparesis, and Hypoglycemia Symptom Assessment

The Michigan Neuropathy Screening Instrument was used to assess neuropathy symptoms, with a score ≥ 4 constituting neuropathy (10). Gastroparesis was assessed by the Gastroparesis Cardinal Symptom Index; a score >1.9 constituted gastroparesis. Gastroparesis cases were not confirmed by patient record screening. Hypoglycemia unawareness was evaluated by a validated questionnaire according to Pedersen-Bjergaard. Unawareness was categorized as: aware, impaired awareness, and unaware (11).

Statistical Analyses

For descriptive statistics of continuous data, the Student *t* test was used for parametric data and Wilcoxon-Mann-Whitney test was used for nonparametric data. For categorical variables, a χ^2 test (if exact value ≥ 5) or Fisher exact test (if exact value <5) was used.

Linear regression analyses were applied to assess associations between the CAN diagnosis or CARTs as determinants and GV measures as outcomes by unadjusted models, as no relevant confounders were identified. Exploratory adjustments were done for HbA_{1c} and diabetes duration. Estimates are presented as percentages (95% CIs).

CARTs were log1.5-transformed. GV outcomes were log-transformed by the natural logarithm. Estimates were back-transformed. Estimates are difference in percentage in outcomes by a 50% lower CART. Analyses were performed in SAS Enterprise Guide 7.1 (SAS Institute).

Power Calculation

The primary outcome was difference in CV between participants with and without CAN. We hypothesized a difference in CV between participants with and without CAN of 7, with an SD of 0.065 mmol/L (12). With 90% power and a two-sided significance level of 0.05, the sample size needed was 20 in each group. With dropout of ∼10%, the sample size was set at 24 per group.

RESULTS

Fifty-eight participants were screened: eight participants were excluded because of early CAN (one pathological CART) and two participants dropped out during CGM due to insufficient data ($n = 1$) or bleeding from the insertion site ($n = 1$). This left 48 participants with T1D for analyses. Twenty-four participants had CAN, and 24 participants had no CAN (mean age [years]: 54.6 ± 14.4 vs. 54.0 ± 12.8, $P = 0.875$; HbA_{1c} [mmol/mol]: 66.4 ± 12.5 vs. 57.8 ± 7.7, $P = 0.006$; HbA_{1c} [%]: 8.2 ± 1.1 vs. 7.4 ± 0.7, $P = 0.006$; diabetes duration [years]: 34 ± 14 vs. 23 ± 12, $P = 0.004$). Eighteen participants in each group used prestudy CGM; among these, eight (CAN group) and two (control subjects) had alarm features (Table 1). Four patients with CAN had gastroparesis. No cases were confirmed in their patient records.

Participants in the CAN group presented a higher degree on all measures of peripheral neuropathy when compared with control subjects (Table 1).

Glycemic Parameters in CAN Versus No CAN

Participants with CAN had a higher CV, SD, and MAGE compared with participants with no CAN with higher estimates as follows: CV, 4.9% (95% CI 1.1, 8.7; $P = 0.014$); SD, 0.7 mmol/L (95% CI 0.3, 1.1; $P = 0.002$); and MAGE, 1.4% (95% CI 0.0, 2.7; $P = 0.047$). No other differences in GV indices or hypoglycemia awareness were found (Table 1). In models adjusted for diabetes duration and gastroparesis, CV and SD retained significant associations, while CV retained significant associations in HbA_{1c}-adjusted models (data not shown).

CARTs and GV

A 50% lower 30/15 ratio was associated with a higher CV and SD: 21% (95% CI

Table 1—Participant characteristics according to CAN diagnosis and estimates of analyses

	T1D no CAN (n = 24)	T1D CAN (n = 24)	P for group difference
Sex (male), n (%)	15 (63)	15 (63)	1
Age (years)	54.0 ± 12.8	54.6 ± 14.4	0.875
BMI (kg/m^2)	26.7 ± 4.2	26.3 ± 5.3	0.815
Systolic blood pressure (mmHg)	124 ± 19	133 ± 16	0.057
Diastolic blood pressure (mmHg)	74 ± 11	76 ± 9	0.441
Diabetes duration (years)	23 ± 12	34 ± 14	0.004
Regular exercise >30 min/day	18 (75)	10 (42)	0.019
Carbohydrate count	11 (46)	6 (25)	0.131
CGM user	18 (75)	18 (75)	1
CGM user, with alarms	2 (8)	8 (33)	0.033
Cardiovascular disease	1 (4)	8 (33)	0.023
Retinopathy			0.003
No retinopathy	14 (58)	5 (22)	
Background	9 (38)	8 (35)	
Proliferative	1 (4)	10 (43)	
Albuminuria			0.028
Normoalbuminuria	23 (96)	15 (65)	
Microalbuminuria	1 (4)	7 (30)	
Macroalbuminuria	0 (0)	1 (4)	
Biochemical measures			
HbA_{1c} (mmol/mol)	58 ± 8	66 ± 12	0.006
HbA_{1c} (%)	7.4 ± 0.7	8.2 ± 1.1	0.006
eGFR (mL/min/1.73 m^2)	94 ± 14	85 ± 20	0.092
Urinary albumin creatinine ratio (mg/g)	5 (3, 11)	23 (9, 68)	0
LDL cholesterol (mmol/L)	2.07 ± 0.59	2.25 ± 0.98	0.437
Medication			
ACE inhibitors and/or ARBs	7 (29)	15 (63)	0.021
Diuretics	2 (8)	7 (29)	0.137
Other hypotension drugs	2 (8)	7 (29)	0.137
Statins	15 (63)	16 (67)	0.763
Daily fast-acting insulin (units/day)	20 (14, 29)	16 (11, 29)	0.451
Daily long-acting insulin (units/day)	20 (14, 28)	24 (17, 32)	0.235
CAN measures			
30/15 ratio	1.21 (1.13, 1.36)	1.01 (1.00, 1.05)	0
E/I ratio	1.25 (1.18, 1.31)	1.03 (1.01, 1.05)	0
VM ratio	1.62 (1.46, 1.93)	1.17 (1.08, 1.32)	0
Peripheral neuropathy measures			
Bio-Thesiometer, bilaterally impaired	15 (63)	20 (83)	0.104
Monofilament, bilaterally impaired	0	3 (13)	0.234
Pinprick, bilaterally impaired	0	3 (13)	0.234
DPN, bilaterally impaired (n = 31)	3 (16)	9 (75)	0.001
Questionnaires			
MNSI score	2 (1.5, 2)	3.5 (2, 6)	0.001
MNSI score ≥4	1 (4)	11 (46)	0.001
DN4, painful neuropathy	0	5 (21)	0.05
GCSI, gastroparesis	0	4 (17)	0.109
Hypoglycemia awareness			0.466
Hypoglycemia, aware	13 (54)	9 (38)	
Hypoglycemia, impaired	8 (33)	12 (50)	
Hypoglycemia, unaware	3 (13)	3 (13)	
			Estimates (95% CI; P value)
GV indices and regression analysis estimates			
CGM indices			
CV (%)	32 ± 6	37 ± 7	4.9 (1.0, 8,7; 0.014)
SD (mmol/L)	3.1 ± 0.8	3.8 ± 0.6	0.7 (0.3, 1.1; 0.002)

Continued on p. 2464

Table 1—Continued

			Estimates (95% CI; *P* value)
Mean (mmol/L)	9.7 ± 1.9	10.5 ± 2.0	0.8 (−0.4, 1.9; 0.190)
CONGA (mmol/L)	8.7 ± 1.8	9.6 ± 1.9	0.9 (−0.2, 2.0; 0102)
MAGE (mmol/L)	5.8 ± 2.4	7.2 ± 2.2	1.4 (0.0, 2.7; 0.047)
TIR (%)	56 ± 18	48 ± 16	7.2 (−3.9, 18.3; 0.198)
TBR (%)	3 ± 2	4 ± 5	−8.2 (−18.2, −1.9; 0.110)
TAR (%)	42 ± 20	49 ± 19	−0.8 (−1.8, 3.4; 0.529)

Descriptive statistics with continuous outcomes are calculated using a Student *t* test for parametric data and the Wilcoxon-Mann-Whitney test for nonparametric data. For categorical variables, a χ^2 test is performed if the exact value is >5. If the exact value is <5, then a Fisher exact test for categorical variables is used instead. Data are in means ± SD, medians (interquartile range [IQR]; quartile 1, quartile 3), or *n* (%). Linear regression analyses were applied to assess associations between the CAN diagnosis as determinant and GV measures as outcomes. Estimates are differences in percentages (95% CI) in outcome variables in participants with CAN compared with participants with no CAN. ARB, angiotensin II receptor blocker; CONGA, continuous overlapping net glycemic action; DN4, Douleur Neuropathique en 4 Questions; DPN, distal polyneuropathy; eGFR, estimated glomerular filtration rate; MNSI, Michigan Neuropathy Screening Instrument.

3, 43; *P* = 0.026) and 34% (95% CI 11, 63; *P* = 0.004), respectively. A 50% E/I ratio was associated with a higher CV and SD: 26% (95% CI 1, 57; *P* = 0.039) and 50% (95% CI 18, 92; *P* = 0.002), respectively. A 50% lower VM ratio was associated with a higher SD, lower TIR, and higher TAR: 21% (6, 39; *P* = 0.006), −25% (−42 to −3; *P* = 0.033), and 35% (2, 79; *P* = 0.034), respectively (Supplementary Table 1).

CONCLUSIONS

The main finding of the study was that CAN diagnosis in T1D was associated with higher CV, SD, and MAGE. This clear association between CAN and greater GV has not been demonstrated previously. In addition, we demonstrated that lower values of all CARTs were associated with greater GV. This indicates that both parasympathetic and sympathetic dysfunction are associated with increased GV, as the E/I ratio is mainly a parasympathetic measure, while the 30/15 ratio and VM ratio are mixed parasympathetic and sympathetic measures (13). Also, lower values of the VM ratio were associated with more time spent in hyperglycemia, indicating that autonomic dysfunction is attributable to the risk of time spent in detrimental hyperglycemia.

We saw no group differences in TIR, TAR, or mean sensor glucose despite a higher HbA_{1c}, indicating that the study may have induced better self-management behavior. Despite this bias, CAN was still associated with higher GV.

CAN reduces counterregulatory catecholamine responses, increasing the risk of severe hypoglycemia (14). However, no association between hypoglycemia (TBR) and the CAN diagnosis was seen. This could be explained by routine use of CGM with alarms (15). Eight of 18 CGM users with CAN had alarms. In contrast, 2 of 18 CGM users with no CAN had alarms. This imbalance could have biased the results.

Conclusion

The CAN diagnosis in T1D associated with higher GV. In addition, both parasympathetic and sympathetic dysfunction were associated with greater GV and with more time in hyperglycemia. Thus, CAN screening in T1D may enable identification of people with detrimental GV. Interventional studies are needed to investigate causality between CAN and GV.

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