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Continuous glucose monitoring reveals a novel association between duration and severity of hypoglycemia, and small nerve fiber injury in patients with diabetes

Hoda Gad¹, Einas Elgassim¹, Ibrahim Mohammed^{1,2}, Ahmad Yaser Alhaddad³, Hussein Ahmed Hussein Zaky Aly⁴, John-John Cabibihan³, Abdulaziz Al-Ali⁴, Kishor Kumar Sadasivuni⁵, Aliyaa Haji¹, Neila Lamine¹, Adnan Khan⁶, Ioannis N Petropoulos¹, Georgios Ponirakis¹, Alise Kalteniece⁷, Maryam Ferdousi⁷, Shazli Azmi⁷, Uazman Alam^{8,9,10}, Wajeeha Abuhelaiqa¹¹, Amin Jayyousi¹¹, Dabia AlMohanadi¹¹, Khaled Baagar¹¹ and Rayaz A Malik^{1,7}

¹Department of Medicine, Weill Cornell Medicine-Qatar, Doha, Qatar

²Department of Internal Medicine, Albany Medical Center Hospital, Albany, New York, USA

³Department of Mechanical and Industrial Engineering, Qatar University, Doha, Qatar

⁴KINDI Center for computing research, Qatar University, Doha, Qatar

⁵Center for Advanced Materials, Qatar University, Doha, Qatar

⁶Faculty of Healthy Sciences, Khyber Medical University, Peshawar, Pakistan

⁷Institute of Cardiovascular Medicine, University of Manchester, Manchester, UK

⁸Diabetes and Neuropathy Research, Department of Eye and Vision Sciences and Pain Research Institute, Institute of Ageing and Chronic Disease,

University of Liverpool and Aintree University Hospital NHS Foundation Trust, Liverpool, UK

⁹Department of Diabetes and Endocrinology, Royal Liverpool and Broadgreen University NHS Hospital Trust, Liverpool, UK

¹⁰Division of Endocrinology, Diabetes and Gastroenterology, University of Manchester, Manchester, UK

¹¹Hamad Medical Corporation, National Diabetes Center, Doha, Qatar

Correspondence should be addressed to R A Malik: ram2045@qatar-med.cornell.edu

Abstract

Objective: Continuous glucose monitoring (CGM) has revealed that glycemic variability and low time in range are associated with albuminuria and retinopathy. We have investigated the relationship between glucose metrics derived from CGM and a highly sensitive measure of neuropathy using corneal confocal microscopy in participants with type 1 and type 2 diabetes.

Methods: A total of 40 participants with diabetes and 28 healthy controls underwent quantification of corneal nerve fiber density (CNFD), corneal nerve branch density (CNBD), corneal nerve fiber length (CNFL) and inferior whorl length (IWL) and those with diabetes underwent CGM for four consecutive days.

Results: CNBD was significantly lower in patients with high glycemic variability (GV) compared to low GV (median (range) (25.0 (19.0–37.5) vs 38.6 (29.2–46.9); $P = 0.007$); in patients who spent >4% compared to <4% time in level 1 hypoglycemia (54–69 mg/dL) (25.0 (22.9–37.5) vs 37.5 (29.2–46.9); $P = 0.045$) and in patients who spent >1% compared to <1% time in level 2 hypoglycemia (<54 mg/dL) (25.0 (19.8–41.7) vs 35.4 (28.1–44.8); $P = 0.04$). Duration in level 1 hypoglycemia correlated with CNBD ($r = -0.342$, $P = 0.031$). Duration in level 1 (181–250 mg/dL) and level 2 (>250 mg/dL) hyperglycemia did not correlate with CNFD ($P > 0.05$), CNBD ($P > 0.05$), CNFL ($P > 0.05$) or IWL ($P > 0.05$).

Conclusions: Greater GV and duration in hypoglycemia, rather than hyperglycemia, are associated with nerve fiber loss in diabetes.

Key Words

- ▶ CCM
- ▶ diabetes
- ▶ hypoglycemia
- ▶ peripheral neuropathy
- ▶ CGM
- ▶ TIR

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Introduction

Diabetic peripheral neuropathy (DPN) affects ~50% of people with diabetes mellitus (T1DM) and (T2DM) (1, 2). It has an insidious onset, which can lead to painful diabetic neuropathy, erectile dysfunction, foot ulceration and lower limb amputation (1). Recognized risk factors for DPN include poor glycemic control, obesity, hypertension and dyslipidemia (3, 4). However, HbA1c provides limited insight into the short-term variations in blood glucose, which may affect nerve fibers (5). Continuous glucose monitoring (CGM) provides not only time in range (TIR) which is directly related to HbA1c but also additional measures in relation to high and low blood glucose levels (6, 7).

Increased glycemic variability and low TIR were associated with albuminuria and retinopathy, whilst neuropathy was associated with the s.d. of blood glucose levels and mean amplitude of glycemic excursions (MAGE) (5). In a small proof-of-principle study, a higher mean glucose, M-value and greater glycemic excursions were demonstrated in patients with painful compared to painless diabetic neuropathy (8). A recent systematic review demonstrated that a 10% increase in TIR was associated with a reduction in the prevalence of DPN and cardiac autonomic neuropathy (CAN) (9).

Severe iatrogenic hypoglycemia can lead to neurological sequelae, including cerebral dysfunction, seizures and death, and recurrent hypoglycemia is associated with hypoglycemia-associated autonomic failure, reduced sympathetic neural responses and autonomic neuropathy (10, 11, 12). In a recent study, higher MAGE and CV and especially nocturnal hypoglycemia were associated with an increased risk of DPN (13). In a study of 80 adults with T1DM, the s.d., coefficient of variation (CV), mean amplitude of glycemic excursion, percent time in level 1 (glucose 54–69 mg/dL) and level 2 (glucose < 54 mg/dL) hypoglycemia, low blood glucose index and high blood glucose index were independently associated with CAN (14). Sudomotor dysfunction, a measure of peripheral autonomic dysfunction (15), has also been independently associated with TIR in T1DM (16) and T2DM (17).

Corneal confocal microscopy (CCM) is a rapid non-invasive ophthalmic imaging technique that can identify early small nerve fiber loss in patients with DPN (18) and has demonstrated comparable diagnostic utility to intra-epidermal nerve fiber density (4, 19, 20). A recent meta-analysis has confirmed the diagnostic utility of CCM in subclinical and clinical DPN (21). In the current study, we have investigated the relationship between different

glucose metrics obtained using CGM and corneal nerve pathology using CCM in patients with type 1 and type 2 diabetes.

Methods

Patients

We recruited 68 participants (20 T1DM, 20 T2DM and 28 healthy volunteers) between June 2021 and October 2021. Inclusion criteria were age \geq 18 years and treatment with insulin. Exclusion criteria included vitamin B₁₂ or folic acid deficiency, cancer, pregnancy, breastfeeding, or cardiac, liver or renal dysfunction. Participants were also excluded if they had corneal pathology, allergy to eye drops or previous ocular trauma or surgery in the past 6 months. The study was approved by the Ethics Committee of Weill Cornell Medicine-Qatar, Hamad Medical Corporation and Qatar University and was designed in accordance with the principles of the Helsinki Declaration. Written informed consent was obtained from all participants.

Basic and clinical demographics

Participants' height, weight, BMI and blood pressure were measured. Total cholesterol, triglyceride, HDL-C, LDL-C and HbA1c were assessed only in participants with diabetes.

Continuous glucose monitoring

The Freestyle Libre 1 system (Abbott) was used for s.c. interstitial CGM. The sensor recorded glucose levels every 5 min for four consecutive days. The sensor was placed on the upper back part of the arm. The recommended target TIR (70–180mg/dL) was >70% of the glucose readings (~16 h 48 min), time below range (TBR) <70 mg/dL was <4% of the readings (~58 min) (level 1 hypoglycemia), TBR <54 mg/dL was <1% of the readings (~14 min) (level 2 hypoglycemia), time above range (TAR) >180 mg/dL was <25% of the readings (~6 h) (level 1 hyperglycemia) and TAR >250 mg/dL was <5% of the readings (1 h 12 min) (level 2 hyperglycemia). Glycemic variability (GV) was defined as percent CV with a target \leq 36%. Hypoglycemia was defined according to continuous glucose reading of <70 mg/dL.

Corneal confocal microscopy

CCM was undertaken using the Heidelberg Retina Tomograph Cornea Module (Heidelberg Engineering,

Heidelberg, Germany). Both eyes were anesthetized with two drops of Bausch & Lomb Minims® (oxybuprocaine hydrochloride 0.4% w/v). A drop of hypotears gel (carbomer 0.2% eye gel) was placed on the tip of the objective lens, and a sterile disposable TomoCap was placed over the lens, allowing optical coupling of the objective lens to the cornea. Six images were selected from the sub-basal nerve plexus in the central cornea, and corneal nerve fiber density (CNFD) (fibers/mm²), corneal nerve branch density (CNBD) (branches/mm²) and corneal nerve fiber length (CNFL) (mm/mm²) were quantified manually using CCMetrics. Six images centered on the inferior whorl and immediately adjacent area were selected, and inferior whorl length (IWL) (mm/mm²) was quantified manually using the manual CNFL mode in CCMetrics. The investigator was blind to the study group when performing CCM and analyzing CCM images.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics software Version 27, and $P < 0.05$ was considered statistically significant. Normality of the data was assessed using the Shapiro–Wilk test and by visual inspection of the histogram and a normal Q–Q plot. Data are expressed as mean and s.d for the normally distributed variables and as median and range for the skewed variables. Inferential analyses were conducted for the corneal nerve parameters and clinical demographics using both parametric (*t*-test) and non-parametric (Mann–Whitney *U* test) tests, with *post-hoc* adjustment. To investigate the association between corneal nerve parameters and clinical and CGM variables, Pearson and Spearman correlations were performed as appropriate. Graph prism version 9 was used to build dot plots.

Results

A total of 40 participants with diabetes aged 37–48 years and 28 healthy controls aged 24–49 years were enrolled in the study. Participants with diabetes and controls had comparable systolic blood pressure (mmHg) ($P=0.45$), diastolic blood pressure (mmHg) ($P=0.45$) and BMI (kg/m²) ($P=0.20$) (Table 1). Interstitial glucose was in the range for 60% of participants with diabetes, 32% were above range and 8% were very high (Fig. 1). CNFD (fiber/mm²) (25.79 ± 5.96 vs 29.97 ± 6.02 ; $P=0.006$), CNBD (branch/mm²) (31 (26.0–40.60) vs 56.25 (46.87–68.75); $P < 0.001$), CNFL (mm/mm²) (16.78 ± 4.10 vs 22.55 ± 3.57 ;

$P < 0.001$) and IWL (mm/mm²) (15.35 ± 6.2 vs 20.82 ± 5.07 ; $P < 0.001$) were significantly lower in participants with diabetes compared to controls (Table 1). Participants with diabetes spent $50 \pm 22.4\%$ (719.4 ± 322.7 min) of the TIR, $27 \pm 15\%$, 388.62 ± 223.57 min above range (level 1 hyperglycemia) and 73.77 ± 76.70 min (level 1 hypoglycemia) below range with an average of 2.9 hypoglycemic events over a period of 4 days (Table 1).

CCM in relation to CGM

CNFD ($P=0.50$), CNBD ($P=0.68$), CNFL ($P=0.71$) and IWL ($P=0.10$) did not differ between patients who had diabetes duration for <10 years, >10 years or more than 20 years (Table 2). There was no difference in CNFD ($P=0.67$), CNBD ($P=0.89$), CNFL ($P=0.85$) and IWL ($P=0.47$) between participants with an HbA1c <8% or >8%. CNBD was significantly lower in patients with high GV compared to low GV (25.0 (19.0–37.5) vs 38.6 (29.2–46.9); $P=0.007$). There was no difference in CNFD ($P=0.62$), CNFL ($P=0.09$) and IWL ($P=0.73$) between patients with high GV compared to low GV. There was no significant difference in CNFD ($P=0.64$), CNBD ($P=0.75$), CNFL ($P=0.91$) and IWL ($P=0.59$) between participants with diabetes who spent >70% TIR (70–180 mg/dl) and <70% TIR. CNBD was significantly lower (25.0 (22.9–37.5) vs 37.5 (29.2–46.9); $P=0.045$) with no difference in CNFD ($P=0.38$), CNFL ($P=0.51$) and IWL ($P=0.35$) in patients who spent >4% compared to <4% in level 1 (54–69 mg/dL) hypoglycemia. CNBD (25.0 (19.8–41.7) vs 35.4 (28.1–44.8); $P=0.04$) was significantly lower, whilst CNFD ($P=0.79$), CNFL ($P=0.36$) and IWL ($P=0.62$) did not differ between patients who spent >1% compared to <1% time in level 2 (<54 mg/dL) hypoglycemia. CNFD ($P=0.71$), CNBD ($P=0.09$), CNFL ($P=0.43$) and IWL ($P=0.37$) did not differ between patients who had >1 hypoglycemic event compared to those who had no hypoglycemic events. CNFD ($P=0.61$), CNBD ($P=0.44$), CNFL ($P=0.83$) and IWL ($P=0.62$) did not differ between patients who spent >25% compared to <25% time in level 1 (181–250 mg/dL) hyperglycemia. CNFD ($P=0.59$), CNBD ($P=0.97$), CNFL ($P=0.89$) and IWL ($P=0.14$) did not differ between patients who spent >5% compared to <5% in level 2 hyperglycemia (>250 mg/dL) (Table 1). CNFD ($P=0.11$) did not differ significantly between patients in TIR, TAR or TBR compared to healthy controls. CNBD ($P < 0.0001$) and CNFL ($P < 0.0001$) were significantly lower in participants with diabetes in TIR, TAR and TBR compared to healthy controls (Fig. 2A–G).

Table 1 Demographics of participants with diabetes and controls.

Demographics	Controls	Diabetes	P-value
Subjects	n = 28	T1DM (n = 20) T2DM (n = 20)	-
M:F ratio	22:6	28:12	-
Age (years)	36 (24-49)	41(37-48)	0.11
Diabetes duration (years)	-	-	-
<10 years		9 (22.5)	
10-20 years		23 (56.5)	
21-40 years		8 (20)	
SBP (mmHg)	122 (120-136)	123 (119-127)	0.45
DBP (mmHg)	79.04 ± 10.58	77.03 ± 10.39	0.45
BMI (kg/m ²)	27.05 ± 5.48	28.84 ± 5.69	0.20
TC (mmol/L)	-	4.38 (3.90-4.95)	-
TG (mmol/L)	-	1.86 ± 2.33	-
HDL-C (mmol/L)	-	1.30 ± 0.36	-
LDL-C (mmol/L)	-	2.30 (0.90-3.60)	-
Average CGM glucose (mg/dL)	-	178.77 ± 47.38	-
HbA1c (%)	-	8.85 ± 1.70	-
CNFD (fiber/mm ²)	29.97 ± 6.02	25.79 ± 5.96	0.006 ^a
CNBD (branch/mm ²)	56.25 (46.87-68.75)	31 (26.0-40.60)	<0.001 ^a
CNFL (mm/mm ²)	22.55 ± 3.57	16.78 ± 4.10	<0.001 ^a
IWL (mm/mm ²)	20.82 ± 5.07	15.35 ± 6.21	<0.001 ^a
TIR % (min) (glucose 70-180mg/dL)	-	50 ± 22.4 (719.4 ± 322.7)	-
TAR % (min) level 1 hyperglycemia (glucose 181-250mg/dL)	-	27 ± 15 (388.62 ± 223.57)	-
TBR % (min) level 1 hypoglycemia (glucose 54-69mg/dL)	-	2 (0-29) (73.77 ± 76.70)	-
Number of hypoglycemic events	-	2.90 ± 3.43	-

CGM, continuous glucose monitoring; CNBD, corneal nerve branch density; CNFD, corneal nerve fiber density; CNFL, corneal nerve fiber length; DBP, diastolic blood pressure; F, female; HbA1c, glycated hemoglobin; IWL, inferior whorl length; M, male; SBP, systolic blood pressure; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TAR, time above range; TBR, time below range; TC, total cholesterol; TG, triglycerides; TIR, time in range.

Data are expressed as mean ± SD or median (range).

^aSignificant at $P < 0.05$.

Correlation between corneal nerve parameters and CGM indicators of glycemia

Duration of diabetes (years), plasma glucose, average interstitial glucose and HbA1c did not correlate with CNFD ($P > 0.05$), CNBD ($P > 0.05$), CNFL ($P > 0.05$) and IWL ($P > 0.05$) (Table 3). GV correlated significantly with CNBD ($r = -0.398$, $P = 0.011$) (Fig. 3A) but did not correlate with CNFD ($P > 0.05$), CNFL ($P > 0.05$) or IWL ($P > 0.05$). Duration

in level 1 and level 2 hyperglycemia did not correlate with CNFD ($P > 0.05$), CNBD ($P > 0.05$), CNFL ($P > 0.05$) and IWL ($P > 0.05$). However, duration in level 1 hypoglycemia correlated significantly with CNBD ($r = -0.342$, $P = 0.031$) (Fig. 3B) but not with CNFD ($P > 0.05$), CNFL ($P > 0.05$) and IWL ($P > 0.05$). The number of hypoglycemic events did not correlate with CNFD ($P > 0.05$), CNBD ($P > 0.05$), CNFL ($P > 0.05$) or IWL ($P > 0.05$).

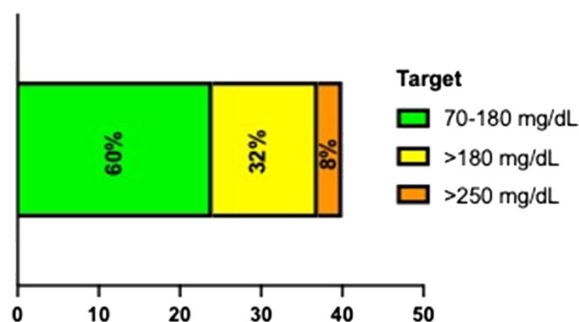


Figure 1 Distribution of participants with diabetes based on their interstitial glucose targets.

Discussion

We have demonstrated that increased GV and hypoglycemia detected using CGM are associated with lower CNBD in patients with type 1 and type 2 diabetes. Studies have reported an association between corneal nerve measures and the duration of diabetes (22, 23) and HbA1c (24, 25) in people with type 1 and type 2 diabetes. Several large clinical trials have shown that improved glycemic control can prevent the development and progression of diabetic neuropathy in type 1 diabetes (26) but not type 2 diabetes (27, 28, 29, 30). However, smaller interventional studies utilizing CCM in type 1 and type

Table 2 Changes in corneal nerve morphology in relation to duration of diabetes and different glucose metrics on CGM.

Glycemic control indicators	CNFD	CNBD	CNFL	IWL
Duration of diabetes				
<10 years	27.21 ± 5.99	35.40 (25.0–50.0)	17.28 ± 2.17	15.54 ± 6.96
10–20 years	24.83 ± 5.64	29.2 (25.0–39.6)	16.32 ± 4.19	13.89 ± 5.57
21–40 years	26.96 ± 7.10	39.6 (18.7–55.2)	17.55 ± 5.62	19.31 ± 6.08
P-value	0.50	0.68	0.71	0.10
HbA1c%				
<8%	26.49 ± 6.30	33.3 (25.0–43.7)	17.0 ± 2.44	16.60 ± 5.57
>8%	25.55 ± 6.30	30.2 (25.0–40.6)	16.71 ± 4.56	14.93 ± 6.44
P-value	0.67	0.89	0.85	0.47
GV (%CV)				
Low <36%	26.17 ± 6.26	38.6 (29.2–46.9)	17.68 ± 4.64	5.63 ± 6.82
High >36%	25.21 ± 5.65	25.0 (19.0–37.5)	15.43 ± 2.75	14.92 ± 5.34
P-value	0.62	0.007 ^a	0.09	0.73
TIR (glucose 70–180 mg/dL)				
In range >70%	26.70 ± 4.66	31.25 (26.0–44.8)	16.94 ± 3.0	14.29 ± 6.26
In range <70%	25.56 ± 6.29	31.20 (25.0–40.6)	16.74 ± 4.37	15.61 ± 6.27
P-value	0.64	0.75	0.91	0.59
TBR (glucose 54–69 mg/dL) level 1 hypoglycemia				
Below range >4%	27.0 ± 5.08	25.0 (22.9–37.5)	16.15 ± 2.31	14.02 ± 6.45
Below range <4%	25.20 ± 6.35	37.5 (29.2–46.9)	17.08 ± 4.75	15.99 ± 6.11
P-value	0.38	0.045 ^a	0.51	0.35
TBR (glucose <54 mg/dL) level 2 hypoglycemia				
Severely below range >1%	26.37 ± 6.6	25.0 (19.8–41.7)	15.66 ± 2.93	14.42 ± 6.63
Severely below range <1%	25.65 ± 5.86	35.4 (28.1–44.8)	17.11 ± 4.38	15.62 ± 6.17
P-value	0.79	0.040 ^a	0.36	0.62
Hypoglycemic events				
>1 event	26.1 ± 5.38	28.1 (25.0–39.6)	16.33 ± 3.51	14.59 ± 5.77
No events	25.37 ± 6.83	37.5 (29.2–51.0)	17.39 ± 4.84	16.38 ± 6.78
P-value	0.71	0.08	0.43	0.37
TAR (181–250 mg/dL) level 1 hyperglycemia				
Above range >25%	25.34 ± 6.92	36.5 (25.0–50.0)	16.90 ± 5.23	15.80 ± 6.18
Above range <25%	26.33 ± 4.67	30.2 (25.0–37.5)	16.63 ± 2.19	14.79 ± 6.38
P-value	0.61	0.44	0.83	0.62
TAR (>250 mg/dL) level 2 hyperglycemia				
Severely above range >5%	25.51 ± 6.33	31.20 (25.0–41.70)	16.74 ± 4.46	16.13 ± 6.48
Severely above range <5%	26.74 ± 4.72	31.20 (27.10–43.70)	16.94 ± 2.75	12.53 ± 4.44
P-value	0.59	0.97	0.89	0.14

CGM, continuous glucose monitoring; CNBD, corneal nerve branch density; CNFD, corneal nerve fiber density; CNFL, corneal nerve fiber length; GV, glucose variability; HbA1c, glycated hemoglobin; IWL, inferior whorl length; TAR, time above range; TBR, time below range; TIR, time in range.

^aSignificant at *P* < 0.05.

2 diabetes have demonstrated that lowering HbA1c is associated with an increase in corneal nerve parameters (31, 32, 33, 34). We have recently shown in patients with type 2 diabetes taking glucose-lowering therapies associated with weight gain and hypoglycemia that despite an improvement in HbA1c there was a reduction in CNBD (35).

Therefore, the relationship between glycemic control and complications is complex, and whilst HbA_{1c} is an important measure of overall glucose control, it fails to capture the magnitude and frequency of glucose variation and the contribution of hypoglycemia. Indeed, intensive glycemic control is associated with an increased incidence of hypoglycemia and adverse cardiovascular outcomes

(36). Hence, there has been an increasing emphasis on defining the role of optimal glucose range and GV in the development of diabetic complications (37). Diabetic neuropathy has been associated with an increase in the s.d. of blood glucose and MAGE (5), and a recent study also demonstrated that TIR was associated with DPN symptoms (38). A systematic review showed that a 10% increase in TIR was associated with a reduction in the prevalence of DPN and CAN (9). Whilst higher MAGE and CV were associated with an increased risk of DPN, there was also a significant association with the occurrence of nocturnal hypoglycemia (13). Furthermore, in adults with T1DM, a range of indices of hypoglycemia have been independently associated with CAN (14).

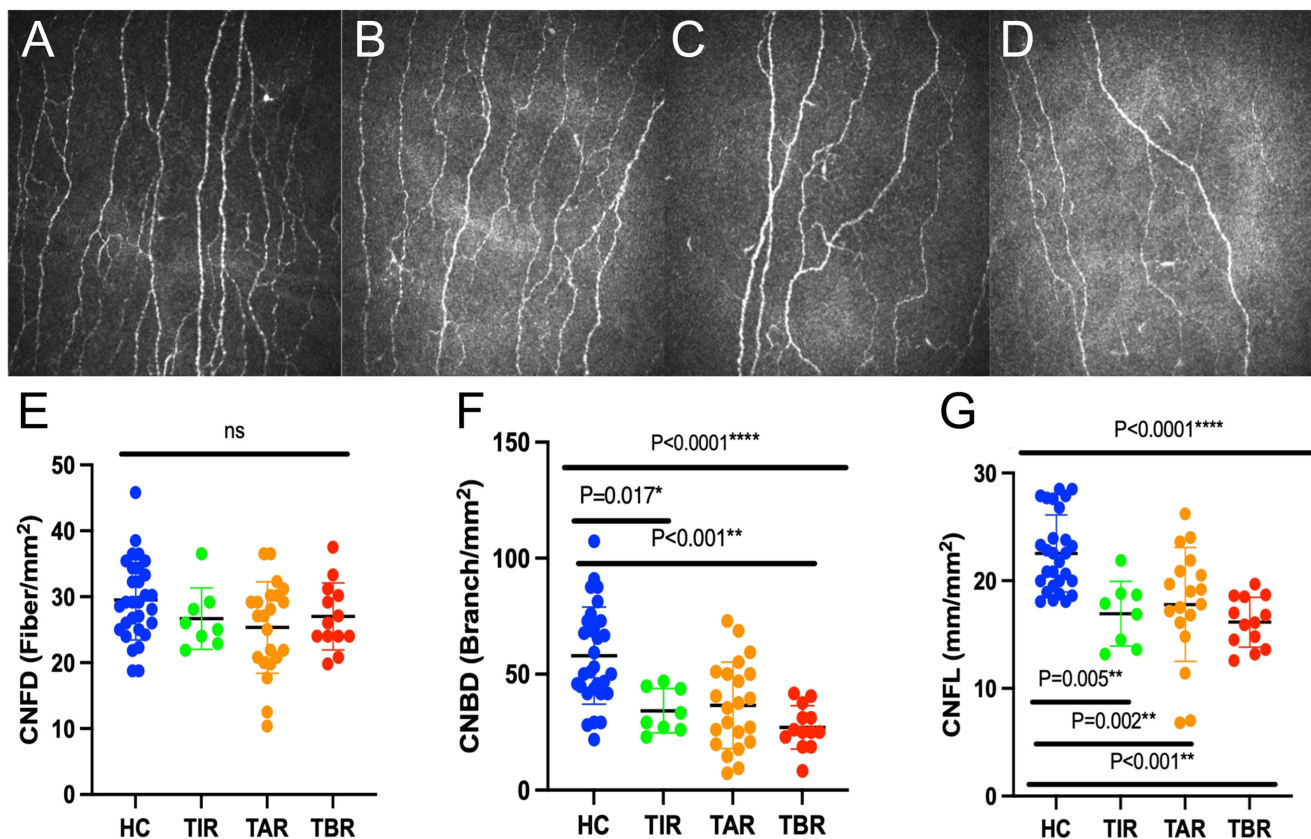


Figure 2

Corneal nerve fiber morphology and CCM parameters in participants with diabetes compared to healthy controls based on glycemic targets. CNFD: corneal nerve fiber density; CNBD, corneal nerve branch density; CNFL, corneal nerve fiber length; HC, healthy control; TAR, time above range; TBR, time below range; TIR, time in range; (A) HC; (B) Participant with diabetes in TIR; (C) Participant with diabetes in TAR; (D) Participant with diabetes in TBR; (E) CNFD in HC vs participant with diabetes in TIR, TAR and TBR; (F) CNBD in HC vs participant with diabetes in TIR, TAR and TBR; (G) CNFL in HC vs participant with diabetes in TIR, TAR and TBR.

Sudomotor dysfunction has been independently associated with nocturnal TIR in T1DM (16) and T2DM (17). In a recent study, GV assessed by calculating the continuous overall net glycemic action and the percentage of time in normal and high range glucose was associated with nerve excitability and IWL but not CNFD or CNFL in a cohort of patients with T1DM (39). We now show that

increased GV and TBR were associated with small nerve fiber damage evidenced by lower CNBD in patients with type 1 and type 2 diabetes. We believe the underlying mechanisms of nerve damage are very different from the severe insulin-induced experimental hypoglycemic neuropathy characterized by reduced motor and sensory nerve conduction velocities and a distal dying back axonal

Table 3 Correlation between CCM parameters and glycemic variables derived using CGM.

Glycemic indicators	CNFD (fiber/mm ²)	CNBD (branch/mm ²)	CNFL (mm/mm ²)	IWL (mm/mm ²)
Duration of diabetes (years)	0.112 (0.49)	0.101 (0.53)	0.008 (0.96)	0.004 (0.98)
Plasma glucose (mmol/L)	0.195 (0.25)	-0.051 (0.77)	0.075 (0.66)	0.080 (0.64)
Average interstitial glucose (mg/dL)	-0.097 (0.55)	0.042 (0.79)	0.071 (0.66)	0.093 (0.57)
HbA1c (%)	-0.079 (0.63)	0.068 (0.67)	-0.046 (0.78)	-0.004 (0.98)
GV (%)	0.043 (0.79)	-0.398 (0.011) ^a	-0.281 (0.08)	-0.050 (0.76)
Duration in level 1 hyperglycemia (min)	0.152 (0.35)	0.246 (0.12)	0.266 (0.09)	0.156 (0.337)
Duration in level 2 hyperglycemia (min)	-0.114 (0.48)	0.024 (0.88)	0.053 (0.74)	0.152 (0.35)
Duration in level 1 hypoglycemia (min)	0.121 (0.46)	-0.342 (0.031) ^a	-0.232 (0.15)	-0.088 (0.59)
Number of hypoglycemic events	0.072 (0.66)	-0.258 (0.11)	-0.187 (0.25)	-0.074 (0.65)

CCM, corneal confocal microscopy; CGM, continuous glucose monitoring; CNBD, corneal nerve branch density; CNFD, corneal nerve fiber density; CNFL, corneal nerve fiber length; GV, glucose variability; HbA1c, glycated hemoglobin.

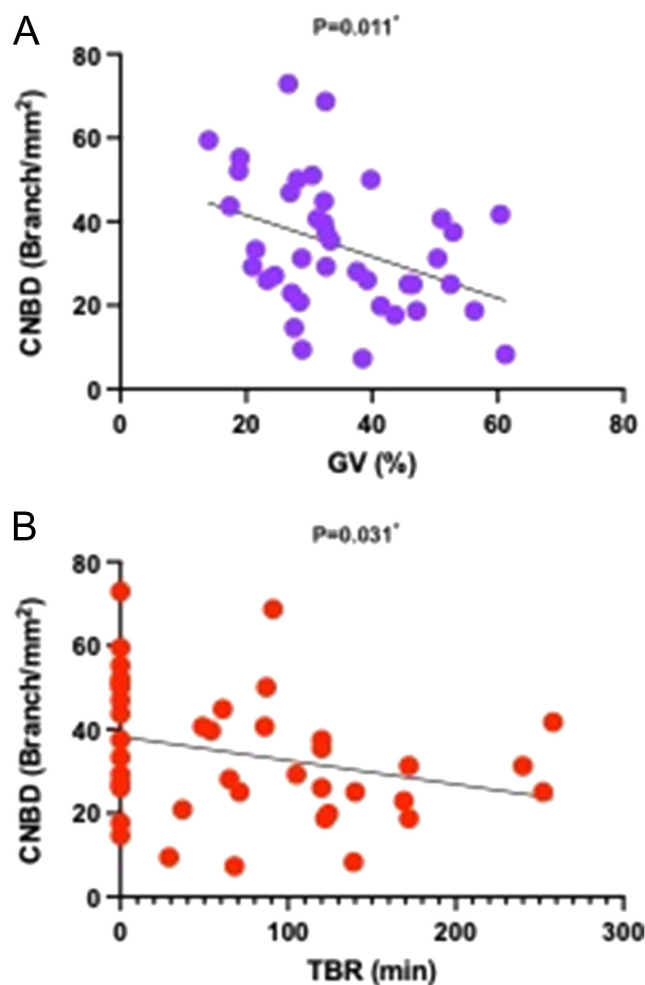


Figure 3
Correlation between CNBD vs GV (%) and TBR (min) in participants with diabetes. CNBD, corneal nerve branch density; GV, glucose variability; TBR, time below range.

degeneration affecting motor more than sensory axons (40) and axonal degeneration (41) in the proximal sciatic rather than distal plantar nerves (42), with myelinated nerve fiber damage (43) in motor rather than sensory roots (44). Indeed, in a study of diabetic BB rats with insulin implants to induce moderate hypoglycemia, there was evidence of shorter and thinner intraepidermal nerve fibers (45). Thus, in the current study, we show sensory small nerve fiber pathology characterized by a lower CNBD in patients with level 1 and level 2 hypoglycemia. In a case report of a 26-year-old female with T1DM, frequent silent hypoglycemia (average <60 mg/dL) was associated with numbness and tingling in both hands and feet, which resolved with the resolution of hypoglycemia (46). Several mechanisms may underlie hypoglycemia-induced nerve injury, including reduced nerve blood flow and hypoxia (47, 48, 49) and a slowing of axonal transport (50).

We acknowledge the limitations of the current study which include the lack of prior power calculation, relatively small cohort size and short duration of CGM. Nevertheless, CCM shows small nerve fiber damage in participants with diabetes with higher GV and in those who spent a longer duration in hypoglycemia. CGM and CCM are highly sensitive technologies to explore the relationship between glycemic variability and nerve damage and provide novel insights into the development of diabetic neuropathy.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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