Association Between Impaired Cardiovascular Autonomic Function and Hypoglycemia in Patients With Type 1 Diabetes

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OBJECTIVE

We studied the association between glycemic variability (GV) reflecting hypoglycemic stress and cardiovascular autonomic function in subjects with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Forty-four type 1 diabetic patients (mean age 34 ± 13 years, 40% male, 86% Caucasian, mean diabetes duration 13 ± 6 years, mean hemoglobin A_{1c} [HbA_{1c}] 8.0 ± 1.2% [64 ± 5 mmol/mol]) without cardiovascular disease, dyslipidemia, or hypertension participated in this pilot study. Indices of GV reflective of hypoglycemic stress (low blood glucose index [LBGI] and area under the curve [AUC] for hypoglycemia) were computed using data obtained during 5-day continuous glucose monitoring. Cardiovascular autonomic neuropathy (CAN) was assessed using standardized cardiovascular reflex testing and measures of heart rate variability (HRV), which were analyzed as time and frequency domain measures.

RESULTS

Both LBGI and AUC hypoglycemia had a significant negative association with the low-frequency power of HRV ($r = -0.47$, $P = 0.002$; $r = -0.43$, $P = 0.005$, respectively) and with the high-frequency power of HRV ($r = -0.37$, $P = 0.018$; $r = -0.38$, $P = 0.015$, respectively). These inverse associations persisted after adjusting for HbA_{1c}, although they were attenuated in multivariable analysis after adjustment for age, diabetes duration, and several other covariates.

CONCLUSIONS

Increased GV promoting hypoglycemic stress was associated with reduced HRV independent of glycemic control as assessed by HbA_{1c}. These pilot data suggest that glucose variability may contribute to cardiovascular autonomic dysfunction among adults with type 1 diabetes.

Cardiovascular autonomic neuropathy (CAN) is a chronic complication of diabetes and an independent predictor of cardiovascular disease (CVD) morbidity and mortality (1–3). The mechanisms of CAN are complex and not fully understood. It can be assessed by simple cardiovascular reflex tests (CARTs) and heart rate variability (HRV) studies that were shown to be sensitive, noninvasive, and reproducible (3,4).

Landmark epidemiological studies have established the importance of intensive glycemic control in preventing CAN associated with diabetes (5,6). Traditionally, hemoglobin A_{1c} (HbA_{1c}) has been considered the gold standard for evaluating

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glycemic control and is used to set goals for reducing the risk of diabetes-related complications in clinical care and research (7). However, HbA_{1c} fails to capture information on the daily fluctuations in blood glucose levels, termed glycemic variability (GV). Recent observations have fostered the notion that GV, independent of HbA_{1c}, may confer an additional risk for the development of micro- and macrovascular diabetes complications (8,9).

While GV was shown to have an effect on cardiovascular complications in type 2 diabetes (10), the relationship between GV and chronic complications, specifically CAN, in patients with type 1 diabetes has not been systematically studied. In addition, limited data exist on the relationship between hypoglycemic components of the GV and measures of CAN among subjects with type 1 diabetes (11,12). Therefore, we have designed a prospective study to evaluate the impact and the possible sustained effects of GV on measures of cardiac autonomic function and other cardiovascular complications among subjects with type 1 diabetes (ClinicalTrials.gov, NCT01170832).

In the present communication, we report cross-sectional analyses at baseline between indices of hypoglycemic stress on measures of cardiac autonomic function.

RESEARCH DESIGN AND METHODS

Study Population and Design

This is a pilot study in 44 subjects with type 1 diabetes recruited from the University of Michigan Health System. These subjects are followed prospectively for up to 3 years while adhering to the current standard of care for type 1 diabetes (7). All study participants gave written informed consent, and the study was approved by the Institutional Review Board of the University of Michigan.

Main inclusion criteria were type 1 diabetes as defined by the American Diabetes Association diagnostic criteria (7), age of 18–65 years, diabetes duration of 5–10 years, and no signs of microvascular complications. Patients with a history of CVD (including any form of coronary artery disease, congestive heart failure, known arrhythmias, and valvular disease), hypertension, chronic kidney disease, elevated urinary albumin excretion, history of transplantation, or current use of glucocorticoids or other medication known to interfere with HRV were excluded from the study.

Demographic and anthropometric measures were collected through questionnaires and a physical examination; fasting blood and urine were obtained for the measurement of metabolic parameters, including HbA_{1c}, a lipid panel, and renal function tests.

Assessment of CAN Measures

Standardized CAN evaluations were performed on all subjects after an overnight fast. Subjects were asked to avoid caffeine and tobacco products for 8 h prior to testing and to hold any medication (except for basal insulin) until HRV testing was completed. Subjects who experienced a hypoglycemic episode after midnight (blood glucose $\leq$50 mg/dL [2.77 mmol/L]) prior to the testing were rescheduled. The electrocardiogram recordings were obtained in the supine position using a physiologic monitor (Nightingale PPM2, Zoe Medical Inc.), and data were collected during a resting study (5 min) and during several standardized CARTs obtained under paced breathing (R-R response to deep breathing, Valsalva maneuver, and postural changes) as previously described (6). HRV studies were analyzed according to current guidelines (13) using the continuous wavelet transform methods with the ANX 3.1 (ANSAR Inc.). This method incorporates respiratory activity in the formula and is reported to be superior for the analysis of nonstationary signals compared with Fourier transform. The following measures of CAN were predefined as outcomes of interests and analyzed: expiration-to-inspiration ratio (E:I), Valsalva ratio, 30:15 ratios, low-frequency (LF) power (0.04 to 0.15 Hz), high-frequency (HF) power (0.15 to 0.4 Hz), and LF/HF at rest and during CARTs.

Assessment of GV

At the same visit, the sterile, disposable continuous glucose monitoring (CGM) sensor iPro CGM System (Medtronic, Northridge, CA) was inserted subcutaneously and calibrated according to the standard operating guidelines. Subjects were instructed to record at least four glucometer readings per day for a correct calibration. CGM data were obtained at 5-min intervals over a period of 5 days, and at the end of the 5-day sessions, the sensor and meter data were downloaded on the dedicated clinical center computer and used to calculate measures of GV as described (14).

Briefly, indices of GV reflective of hypoglycemic stress included the low blood glucose index (LBGI) and area under the curve (AUC) for hypoglycemia. LBGI was computed as described by Kovatchev et al. (15) using a transformed glucose scale symmetric of $\sim$0 (equivalent to blood glucose of 11.5 mg/dL) to correct the skewness of the glycemic range by expanding the hypoglycemic range and reducing the hyperglycemic range. The AUC for hypoglycemia plots depict the degree of glucose deviation below set glycemic limits. The AUC for hypoglycemia (blood glucose $<$70 mg/dL) was computed using a trapezoidal numerical integration function (15). Approximately 5% of the CGM data were gaps. Some of these were a single missing time point; others were a series of time points constituting a period of a couple of hours. Missing values were interpolated from the adjacent observed values.

Statistical Analysis

Statistical analysis was performed using SAS software (SAS Institute Inc., Cary, NC). Descriptive statistics were reported as mean and SD for the continuous variable and *n* (%) for categorical variables. Nonnormally distributed data are presented as median and interquartile range. Associations between GV (LBGI and AUC hypoglycemia) and CAN (LF power and HF power) were estimated using Pearson correlation. Log transformations were applied to LF and HF power as they were not normally distributed. Linear regression models were built to assess the relationship between HRV and GV. The unadjusted model was built first (model 1), sequentially followed by adjustment for HbA_{1c} (model 2), age (model 3), diabetes duration (model 4), and BMI (model 5). A nominal value of $P \leq 0.05$ was considered statistically significant.

RESULTS

The clinical characteristics of the 44 subjects with type 1 diabetes are summarized in Table 1. The mean age of the subjects was 34 $\pm$ 13 years, mean duration of diabetes was 13 $\pm$ 6 years, and

Table 1—Clinical characteristics of subjects with type 1 diabetes

Variable	Type 1 diabetes (n = 44)
Age, years	34 ± 13
Sex, male/female	17 (39%)/27 (61%)
Race/ethnicity	
Caucasian	38 (86%)
African American	3 (7%)
Hispanic	3 (7%)
Diabetes duration, years	13 ± 6
Current smoker	2 (5%)
HbA_{1c}	
%	8.0 ± 1.2
mmol/mol	64 ± 5
Fasting blood glucose, mg/dL	156 ± 77
BMI, kg/m^2	26 ± 4
Systolic blood pressure, mmHg	117 ± 11
Diastolic blood pressure, mmHg	72 ± 8
Heart rate, bpm	88 ± 15
LDL cholesterol, mg/dL	89 ± 23
HDL cholesterol, mg/dL	65 ± 20
Triglycerides, mg/dL	69 ± 32
eGFR, mL/min	89 ± 21
AER, mg/gm	12 ± 14
Insulin dose, units/kg/day	0.7 ± 0.2
E:I	1.22 ± 0.12
Valsalva ratio	1.34 ± 0.24
30:15 ratio	1.22 ± 0.15
LF power, ms^2	1.92 (1.09, 3.36)
HF power, ms^2	1.59 (0.94, 3.07)
LF:HF ratio	1.39 (1.12, 2.98)
Deep breathing LF power, ms^2	0.68 (0.28, 1.19)
Deep breathing HF power, ms^2	16.36 (5.55, 31.39)
Deep breathing LF:HF ratio	0.43 (0.06, 1.33)
AUC hypoglycemia, mg/dL*min	1,371.5 (560.3, 3,798.2)
LBGI	2.28 (0.76, 4.15)

All data are reported as either mean ± SD, median (interquartile range), or n (%). eGFR, estimated glomerular filtration rate (by the MDRD formula); AER, urinary microalbumin excretion rate.

mean HbA_{1c} was 8.0 ± 1.2% (64 ± 5 mmol/mol). Approximately 40% of the subjects were male, and 86% were Caucasian. Consistent with the inclusion criteria, blood pressure, lipid profile, and renal function were normal in all subjects. Total daily insulin dose was within the expected ranges given the degree of glycemic control and BMI in these subjects (Table 1). As seen in Table 1, standardized CARTs ratios in these subjects were within the normal ranges according to published normative data (16,17).

Figure 1 shows the correlation between the GV (LBGI and AUC hypoglycemia) and HRV parameters during rest. LBGI was negatively correlated with both lnLF power (r = −0.47; P = 0.002) and lnHF power (r = −0.37; P = 0.018). Thus the higher the LBGI (implying longer and more severe hypoglycemia) values, the lower the lnLF power and lnHF power. Similarly, AUC hypoglycemia had a significant inverse association with lnLF (r = −0.43; P = 0.005) and lnHF power (r = −0.38; P = 0.015).

No significant associations were observed between any of the standard CARTs ratios (E:I, Valsalva, 30:15 ratios) and either LBGI or AUC hypoglycemia (data not shown).

The results of the linear regression models are shown in Tables 2 and 3. Unadjusted analyses showed the same trends of negative associations between indices of HRV, LBGI, and AUC hypoglycemia (model 1). The associations between lnLF and lnHF power and the LBGI and AUC hypoglycemia persisted after adjusting for the HbA_{1c} as the accepted measure of glucose control (model 2; $P < 0.05$). In multivariable analyses that adjusted for several other covariates, including age, diabetes duration, and BMI, performed in a stepwise approach, the strength of these associations was attenuated (Tables 2 and 3, models 3–5).

CONCLUSIONS

This pilot study evaluated novel measures of GV and hypoglycemic stress, and examined their association with measures of CAN. We found that LBGI and AUC hypoglycemia were associated with reduced LF and HF power of HRV, suggesting an impaired autonomic function, which was independent of glucose control as assessed by the HbA_{1c}. No correlations were found in this pilot study between indices of hypoglycemic stress and the standard CARTs ratios, which could be due to the relatively small size of this pilot and possibly to the fact that these indices are mainly providing information on the cardiovagal function (3,16,17).

The reduction in both LF and HF power of HRV in these subjects in the absence of clear abnormalities in the CARTs is somewhat paradoxical, as one would have expected these subjects to exhibit robust signs of sympathetic activation associated with hypoglycemic stress. From the current data, it is hard to conclude whether the observed changes are a direct consequence of absolute reductions in the sympathetic or parasympathetic function or whether the reductions in the LF spectral component of HRV might result mainly from pure sympathetic activation without any concomitant vagal withdrawal as previously described (12).

Our findings are in concordance with a recent report demonstrating attenuation of the baroreflex sensitivity and of the sympathetic response to various cardiovascular stressors after antecedent hypoglycemia among healthy subjects who were exposed to acute hypoglycemic stress (18). Similar associations between depressed HRV derived from 48-h electrocardiogram Holter monitoring and spontaneous hypoglycemic episodes analyzed from continuous interstitial glucose measurements were also reported in a small study of

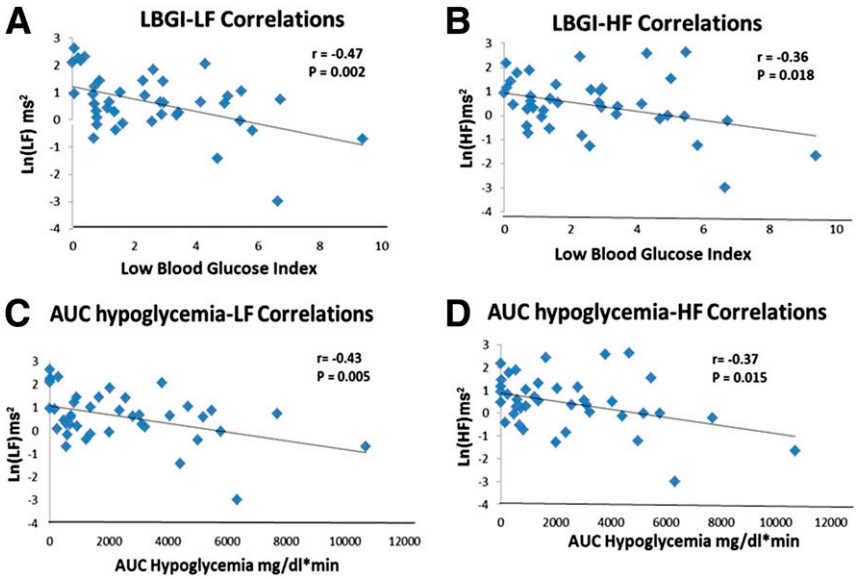

Figure 1—Correlations between LBGI and AUC hypoglycemia and HRV (lnLF and lnHF power) parameters using Pearson correlation coefficient. *A*: LBGI-lnLF correlation coefficient $r = -0.47$. *B*: LBGI-lnHF correlation coefficient $r = -0.36$. *C*: AUC(hypoglycemia)-lnLF correlation coefficient $r = -0.43$. *D*: AUC (hypoglycemia)-lnHF correlation coefficient $r = -0.37$.

subjects with type 2 diabetes (19). To place our data into context, one should consider that the relationship between CAN and hypoglycemia in patients with diabetes is complex and may have different, yet important, clinical implications. For instance, higher GV and hypoglycemic stress may have an acute effect on modulating autonomic control with inducing a sympathetic/vagal imbalance and a blunting of the cardiac vagal control (18). The impairment in the normal counter-regulatory autonomic responses induced by hypoglycemia on the cardiovascular system could be important in healthy individuals but may be particularly detrimental in individuals with diabetes who have hitherto compromised cardiovascular function and/or subclinical CAN. In these individuals, hypoglycemia may also induce QT interval prolongation, increase plasma catecholamine levels, and lower serum potassium (19,20). In concert, these changes may lower the threshold for serious arrhythmia (19,20) and could result in an increased risk of cardiovascular events and sudden cardiac death. Conversely, the presence of CAN may increase the risk of hypoglycemia through hypoglycemia unawareness and subsequent impaired ability to restore euglycemia (21) through impaired sympathoadrenal response to hypoglycemia or delayed gastric emptying.

A possible pathogenic role of GV/hypoglycemic stress on CAN development and progressions should be also considered. Prior studies in healthy and diabetic subjects have found that higher exposure to hypoglycemia reduces the counter-regulatory hormone (e.g., epinephrine, glucagon, and adrenocorticotropic hormone) and blunts autonomic nervous system responses to subsequent hypoglycemia (21). Other studies reported that controlled hypoglycemia induced during hypoglycemic clamps resulted in a progressive reduction in measures of HRV in both healthy volunteers and type 1 diabetic subjects (11). In addition, a recent study that used CGM to evaluate the effects of spontaneous hypoglycemia in adults with type 1 diabetes reported that higher incidence of spontaneous nocturnal hypoglycemia was associated with reduction in the LF power (12). Our data also suggest that wide glycemic fluctuations, particularly hypoglycemic stress, may increase the risk of CAN in patients with type 1 diabetes. Although this cannot be concluded from the current analyses due to the cross-sectional nature of this study, we demonstrated that these associations are independent of glucose control, which is a novel finding.

The central dogma of diabetes management has been and continues to be that glucose control as documented strictly by HbA_{1c} values is the main factor that promotes the risk of developing diabetes complications (22,23). This is based on strong evidence proven to decrease the incidence and progression of diabetic microvascular complications in both type 1 and type 2 diabetes (22,23) and CVD in type 1 diabetes (24). However, an increased incidence of hypoglycemia, which is usually a serious consequence of strict glycemic control, has challenged this dogma and raised the question of potential detrimental impact on various outcomes in patients with diabetes, including mortality, cognitive impairment, and/or hypoglycemia-associated autonomic failure (21,25–28). More recently, experimental and epidemiological evidence suggests that increased frequency and magnitude of GV may also be important in the development and/or progression of

Table 2—Models of the associations between LBGI and indices of HRV

Linear regression models for LBGI	LF power β (SE)	*P* value	Model R^2	HF power β (SE)	*P* value	Model R^2
Model 1: unadjusted	−0.22 (0.067)	0.0019	0.220	−0.18 (0.076)	0.018	0.135
Model 2: model 1 + HbA_{1c}	−0.25 (0.075)	0.0019	0.247	−0.21 (0.081)	0.012	0.199
Model 3: model 2 + age	−0.204 (0.076)	0.0093	0.340	−0.13 (0.072)	0.070	0.445
Model 4: model 3 + diabetes duration	−0.208 (0.076)	0.0096	0.343	−0.12 (0.073)	0.088	0.449
Model 5: model 4 + BMI	−0.205 (0.076)	0.022	0.351	−0.12 (0.071)	0.10	0.499

Unadjusted and adjusted linear regression models. The dependent variables were ln(LF) and ln(HF). The independent variable was LBGI. β, parameter estimate; model R^2, coefficient of determination.

Table 3—Models of the associations between the AUC (hypoglycemia <70 mg/dL) and indices of HRV

Linear regression models for AUC (hypoglycemia <70 mg/dL)	LF power β (SE)	*P* value	Model R^2	HF power β (SE)	*P* value	Model R^2
Model 1: unadjusted	−0.00019 (0.00006)	0.0049	0.185	−0.000179 (0.000070)	0.0146	0.143
Model 2: model 1 + HbA_{1c}	−0.00022 (0.00007)	0.0038	0.219	−0.00020 (0.000076)	0.010	0.207
Model 3: model 2 + age	−0.00017 (0.00007)	0.023	0.306	−0.000120 (0.00006)	0.087	0.439
Model 4: model 3 + diabetes duration	−0.000173 (0.00007)	0.024	0.308	−0.000115 (0.000070)	0.107	0.443
Model 5: model 4 + BMI	−0.00016 (0.00007)	0.029	0.316	−0.000106 (0.000068)	0.129	0.493

Unadjusted and adjusted linear regression models. The dependent variables were ln(LF) and ln(HF). The independent variable was AUC (hypoglycemia). β, parameter estimate; model R^2, coefficient of determination.

complications, possibly via generation of reactive oxygen species or activation of inflammatory pathways (8,29–31). A retrospective analysis of the Diabetes Control and Complications Trial (DCCT) blood glucose data that defined GV based on the SD of the blood glucose and the mean amplitude of glycemic excursions refuted a role of GV in the development of peripheral and autonomic neuropathy (32). However, the GV measures (SD and mean amplitude of glycemic excursions) used in this study were derived from the rather insensitive seven-point blood glucose profiles collected every 3 months as opposed to the more comprehensive glycemic profile data collected with CGM.

Strengths of our study are the comprehensive characterization of cardiac autonomic function in these subjects, the analyses of novel measures of GV and hypoglycemic stress derived from CGM over longer duration, and findings of their associations independent of glucose control as documented by the HbA_{1c}. Limitations are the relatively small size and the cross-sectional nature of these initial analyses that prevents inferring a causal relationship between these measures.

In summary, in this cohort of relatively young and uncomplicated patients with type 1 diabetes, GV and higher hypoglycemic stress were associated with impaired HRV reflective of sympathetic/parasympathetic dysfunction with potential important clinical consequences. The prospective follow-up of this cohort is ongoing, during which indices of GV are collected at 3-month intervals and indices of CAN are obtained annually. The temporal analysis between measures of CAN, and measures of GV and hypoglycemic stress, may help us better evaluate the link between cardiac autonomic dysfunction and GV and whether a causative effect may be the case. Large prospective cohort studies are required to fully elucidate the intricate relationship between hypoglycemia and cardiac autonomic dysfunction.

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