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Diabetic Peripheral Neuropathy and Glycemia Risk Index in Type 2 Diabetes: A Cross-Sectional Study

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Purpose: Diabetic peripheral neuropathy (DPN) is a prevalent chronic complication of diabetes which is linked to chronic hyperglycemia and glycemic variability. This study aimed to investigate the association between the glycemia risk index (GRI) and DPN in patients with type 2 diabetes mellitus (T2DM) using continuous glucose monitoring (CGM) data.

Patients and Methods: From 2019 to 2023, 862 adults diagnosed with T2DM were enrolled at a tertiary care diabetes center in Ningbo, China. The medical history and laboratory parameters were recorded. Neurophysiological examinations were performed to evaluate DPN. The CGM data were recorded for 14 days, and the GRI was calculated based on these data. Multivariate logistic regression analyses were conducted to assess the odds ratio (OR) for DPN with an increased GRI.

Results: The prevalence of DPN in the ascending GRI quartiles was 41.6%, 47.9%, 49.1%, and 59.5%, respectively (P for trend < 0.001). In the multivariable logistic analysis, the highest GRI quartile exhibited a 63% greater risk of DPN (OR 1.631, 95% CI: 1.071 to 2.484, $P = 0.023$) than the lowest quartile after adjusted for age, sex, body mass index, diabetes duration, blood pressure, creatinine, urinary albumin-to-creatinine ratio, lipid profile and glycated hemoglobin.

Conclusion: High GRI levels, as measured by CGM, were associated with a greater likelihood of DPN in T2DM patients.

Keywords: continuous glucose monitoring, glycemia risk index, diabetic peripheral neuropathy, microvascular complications

Introduction

As a prevalent chronic complication of diabetes, diabetic neuropathy can lead to foot ulcers and amputations, which are major causes of disability and death among diabetic patients, as well as significant economic burdens on healthcare systems.[1,2] Diabetic peripheral neuropathy (DPN), being the most prevalent type of diabetic neuropathy, has experienced a notable surge in its prevalence in accordance with the overall incidence of diabetes.[3] Thus, identifying modifiable risk factors is essential for early prevention and treatment strategies. Hyperglycemia is linked to the development of diabetic microvascular complications, including DPN, making adequate glycemic control crucial for prevention and progression.[4] While glycated hemoglobin (HbA1c) is widely used to assess long-term glycemic control, its limitations in capturing short-term glucose variability (GV) and hypoglycemic events necessitate the exploration of other glycemic metrics.[5] Repeated or large glucose swings may play a role in diabetes-related complications independent of HbA1c levels.[6]

In a continuous glucose monitoring (CGM) system, the glucose profile is monitored continuously over a period of days. It contains several indexes to assess an individual's current state of GV.[7] The glycemia risk index (GRI), a metric of CGM, reflects both the risk of hyperglycemia and the risk of hypoglycemia, aiding in the assessment of short-term glycemic control.[8] Increasing evidence indicates that GRI contributes to diabetic retinopathy, albuminuria, and increased arterial stiffness.[9–11] This study primarily aims to bridge the gap by investigating the potential link between GRI and the prevalence of DPN, a relationship that has not yet been thoroughly explored.

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Material and Methods

Study Population

This cross-sectional study included individuals with type 2 diabetes mellitus (T2DM) who underwent professional CGM and concurrently participated in the multi-hospital-based program at the National Metabolic Management Center (MMC)[12] from November 2019 to November 2023. The eligibility criteria included age 18–80 years, confirmed T2DM diagnosis (1999 WHO criteria),[13] and available CGM and electromyogram data. Initially, 988 participants were identified; those with inadequate CGM data (n = 14), missing electromyogram results (n = 72), incomplete laboratory data (n = 16), abnormal peripheral blood cell counts (acute infection/cirrhosis/hematological system diseases, n = 14), malignant tumors (n = 1), or beyond the age range (n = 9) were excluded. In total, 862 participants were included in the analysis. The study adhered to the Helsinki Declaration and was approved by the Ethics Committee of the First Affiliated Hospital of Ningbo University (2019-R057). Informed consent was obtained from all participants.

Demographic, Medical and Laboratory Data

Demographic information (age, sex, and diabetes duration), lifestyle habits (history of smoking and alcohol consumption), and medical history were obtained through standardized MMC questionnaires.[12] Well-trained nurses measured the height, weight, and blood pressure. Body mass index was calculated as the ratio of weight (kg) to height squared (m^2). Visceral fat area (VFA) was assessed using dual bioelectrical impedance analysis (BIA) with a UALSCAN HDS-2000 device (Omron, Japan).

Venous blood and urine samples were collected in the morning following overnight fasting. HbA1c, fasting plasma glucose (FPG), fasting insulin, lipid profile, serum creatinine, uric acid, and routine blood tests were performed. The HOMA-IR index, reflecting insulin resistance, was calculated using the standard formula.[14] Urinary albumin-to-creatinine ratio (UACR) was determined from spot urine samples by assessing the ratio of urinary albumin to creatinine.

CGM Metrics

An intermittently scanned CGM system (The FreeStyle Libre system, Abbott Diabetes Care, Witney, UK) was used for 14 consecutive days. A well-trained nurse placed a continuous glucose sensor in the user's upper arm, and a separate touch-screen reader was used to read glucose levels.[15] GV metrics extracted from the CGM data encompassed standard deviation (SD), coefficient of variation (CV), mean amplitude of glycemic excursion (MAGE), mean of daily differences (MODD). The parameter in the formula calculating GRI is defined as the percentages of time spent in the glucose ranges of the following: (1) >13.9 mmol/L (VHigh); (2) 10.1 to 13.9 mmol/L (High); (3) 3 to 3.8 mmol/L (Low); (4) < 3 mmol/L (VLow). The formula is as follows:[16]

$$\mathrm{GRI} = (3.0 \times \ \mathrm{VLow}) + (2.4 \times \ \mathrm{Low}) + (0.8 \times \ \mathrm{High}) + (1.6 \times \ \mathrm{VHigh}).$$

Besides, the CGM also provides three key metrics: percentage of time within target glucose range (3.9 to 10.0 mmol/L, also called time in range, TIR), time below target glucose range (<3.9 mmol/L, TBR), and time above target glucose range (>10.0 mmol/L, TAR).[17] We excluded results containing monitoring data of less than three days.

Electrophysiological Examination

Electromyograms were obtained using an electromyography instrument (NDI-097; Haishen Medical Electronic Instruments, Shanghai, China). Surface electrodes were used to measure the conduction velocity, amplitude, and latency of the motor and sensory branches of the median, ulnar, tibial, and common peroneal nerves.

Diagnostic Criteria for Diseases and Related Grouping Definitions

A DPN diagnosis was made according to the Toronto Expert Consensus when patients had at least two abnormal results in EMG tests of the median, peroneal, and sural nerves, or when they had clinical signs and symptoms of neuropathy.[18]

Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg or antihypertensive medication use.[19] Dyslipidemia was defined fasting triglycerides (TG) ≥1.7mmol/L,

high-density lipoprotein cholesterol (HDL-c) ≤1.04 mmol/L (male) or ≤1.30 mmol/L (female), or low-density lipoprotein cholesterol (LDL-c) ≥ 2.60mmol/L determined by enzymatic assays.[20]

Participants were grouped by: (1) age (18–39, 40–59, ≥60 years); (2) duration of diabetes (≤60, 61–120, >120 months); (3) BMI (<24, 24–27.9, ≥28 kg/m^2);[21] (4) UACR (<30, 30–299, ≥300 mg/g); (5) HbA1c (<7, 7.0–8.9, ≥9%); and (6) smoking and drinking status (current or not) in the following analysis.

Statistical Analysis

The normality of all variables was examined by the *Kolmogorov–Smirnov* test. An independent-samples *t*-test was used to compare normally distributed continuous variables, which were presented as mean ± standard deviation (SD). The *Mann–Whitney U*-test was used to compare continuous variables with non-normal distributions, expressed as median and quartile spacing (M [25th percentile, 75th percentile]). The chi-square test was used to assess differences in clinical characteristics between patients with and without DPN based on categorical variables expressed as frequencies (percentages), as well as the prevalence of DPN among different CGM groups.

The primary analysis involved using multivariable logistic regression to assess the association between the GRI quartiles (Q1: GRI≤8.28, Q2: 8.28<GRI≤16.79, Q3: 16.79<GRI≤33.76 and Q4: GRI>33.76) and DPN. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each quartile of GRI. Four models were constructed with varying levels of adjustment to evaluate this relationship:

Model 1: Unadjusted model, providing crude ORs for the association between GRI quartiles and DPN.

Model 2: Adjusted for basic demographic characteristics, including age and sex.

Model 3: Further adjusted for metabolic factors, including diabetes duration, SBP, BMI, UACR, serum creatinine, HDL-C, and LDL-C. These covariates were selected based on prior literature and results from univariate analyses.

Model 4: In addition to model 3, HbA1c was added to account for glycemic control, as this could influence the risk of DPN.

A series of models were conducted by sequentially excluding covariates to evaluate the impact on the relationship between GRI and DPN. The ORs for GRI quartiles remained consistent across these models, indicating that the findings are robust to changes in covariate adjustment.

Covariates were assessed for multicollinearity and no collinearity was found. To be specific, variance inflation factor (VIF) was used to assess potential collinearity among the independent variables. All VIF values were below 2, confirming that multicollinearity was not a concern in the models. P <0.05 (two-tailed) was considered statistically significant. IBM SPSS Statistics for Windows, version 27.0, was used for the data analysis.

Results

Baseline Characteristics According to DPN

A total of 862 T2DM patients, comprising 564 (65.4%) males and 298 (34.6%) females, were recruited for this cross-sectional study. The baseline characteristics of the study population were categorized according to DPN diagnosis (Table 1). The mean age of all participants was 52.95±12.02 years. A total of 427 (49.5%) were diagnosed with DPN.

Participants with DPN were generally older, had a longer duration of diabetes, higher BMI and VFA, and higher SBP, and were more likely to have a history of hypertension than those without DPN. These patients also had worse glucose control, manifested as higher mean FPG and HbA1c levels, and worse kidney function, manifested as higher serum creatinine and UACR levels. Corresponding to the glucose spectrum, both insulin and non-insulin antidiabetic agents were used more frequently in the DPN group. TC and LDL-C were slightly higher in the non DPN group than in the DPN group, but the proportion of patients with abnormal lipid metabolism was similar. Participants with DPN were more likely to be men, but there was no difference in current smoking and drinking habits compared with those without DPN.

On the other hand, most of the CGM metrics in the DPN group were significantly higher than those in the non-DPN group, including mean glucose (MG), SD, MAGE, MODD, TAR and GRI. Accordingly, TIR was significantly lower in the DPN group. No differences in CV or TBR were observed between groups (Table 2).

Table 1 Baseline Characteristics According to the Presence of DPN

	Without DPN (n = 435)	With DPN (n = 427)	*P* value
Age (years)	50.05±11.90	55.89±11.43	<0.001
Age group			<0.001
18–39	85 (19.5%)	40 (9.4%)	
40–59	256 (58.8%)	210 (49.2%)	
≥60	94 (21.6%)	177 (41.5%)	
Male (n, %)	265 (60.9%)	299 (70.0%)	0.005
Duration of T2DM (months)	25 (1, 112)	73 (10, 158)	<0.001
Duration group			<0.001
≤60	267 (61.4%)	185 (43.3%)	
61–120	62 (14.3%)	77 (18.0%)	
>120	106 (24.4%)	165 (38.6%)	
Current smoking (n, %)	139 (32.0%)	149 (34.9%)	0.360
Current drinking (n, %)	196 (45.1%)	205 (48.0%)	0.385
BMI (kg/m^2)	25.03±3.58	25.54±3.60	0.038
BMI group			0.230
<24	169 (38.9%)	142 (33.3%)	
24–27.9	184 (42.3%)	196 (45.9%)	
≥28	82 (18.9%)	89 (20.8%)	
VFA (cm^2)	91.21±35.85	101.41±44.31	<0.001
Hypertension (n, %)	228 (52.4%)	279 (65.3%)	<0.001
Systolic BP (mmHg)	133.04±17.58	136.99±18.74	0.001
Diastolic BP (mmHg)	80.68±11.19	79.96±11.22	0.346
Dyslipidemia (n, %)	378 (86.9%)	372 (87.1%)	0.922
Triglycerides (mmol/L)	1.53 (1.09, 2.27)	1.48 (1.03, 2.18)	0.398
Total cholesterol (mmol/L)	5.28±1.34	5.06±1.29	0.015
HDL-C (mmol/L)	1.26±0.29	1.23±0.29	0.165
LDL-C (mmol/L)	3.44±0.96	3.30±0.91	0.023
HbA1c (%)	8.0 (7.1, 9.7)	8.5 (7.3, 10.0)	0.008
HbA1c group			0.176
<7	96 (22.1%)	78 (18.3%)	
7.0–8.9	186 (42.8%)	175 (41.0%)	
≥9	153 (35.2%)	174 (40.7%)	
Fasting serum glucose (mmol/L)	8.51 (7.24, 11.12)	9.31 (7.56, 11.19)	0.019
Fasting insulin (mU/L)	62.87 (38.00, 101.25)	65.43 (36.18, 101.90)	0.745
HOMA-IR	3.68 (2.06, 6.05)	3.69 (2.27, 5.93)	0.696
Creatinine (μmol/L)	63.00±15.87	68.35±28.86	<0.001
Uric acid (μmol/L)	333.37±89.37	339.77±90.23	0.295
UACR (mg/g)	12.38 (7.23, 29.28)	15.63 (8.55, 54.64)	<0.001
UACR group			<0.001
<30	329 (75.6%)	274 (64.2%)	
30–299	95 (21.8%)	108 (25.3%)	
≥300	11 (2.5%)	45 (10.5%)	
Antihypertension agents	133 (30.6%)	187 (43.8%)	<0.001
Lipid-lowering agents	68 (15.6%)	90 (21.1%)	0.039
Antidiabetic agents			
Non-insulin	237 (54.5%)	298 (69.8%)	<0.001
Insulin	60 (13.8%)	88 (20.6%)	0.008

Notes: Data are presented as the mean ± SD or median (interquartile range), or number (percentage). An independent-samples *t*-test was used to compare normally distributed continuous variables; the *Mann–Whitney U*-test was used to compare continuous variables with non-normal distributions; the chi-square test was used to compare categorical variables. $P < 0.05$ was considered statistically significant.

Abbreviations: DPN, diabetic peripheral neuropathy; BMI, body mass index; VFA, visceral fat area; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; HOMA-IR, insulin resistance index; UACR, urinary albumin-to-creatinine ratio.

Table 2 Continuous Glucose Monitoring Metrics According to the Presence of DPN

	Without DPN	With DPN	*P* value
Mean glucose (mmol/L)	7.07±1.57	7.46±1.83	<0.001
Coefficient of variation (%)	27.73 (23.65, 32.66)	28.66 (24.56, 34.18)	0.058
SD	1.86 (1.53, 2.42)	2.03 (1.65, 2.69)	<0.001
MAGE	4.73 (3.82, 5.79)	4.84 (4.00, 6.11)	0.029
MODD	1.39 (1.12, 1.75)	1.51 (1.22, 1.99)	<0.001
TIR (%)	87.82 (77.71, 94.00)	84.71 (71.19, 91.86)	<0.001
TBR (%)	0.83 (0, 4.70)	0.92 (0, 4.78)	0.847
TAR (%)	7.39 (2.32, 17.40)	10.38 (3.76, 23.10)	<0.001
GRI	15.49 (7.08, 29.74)	19.91 (9.30, 37.86)	<0.001

Notes: Data are mean ± SD or median (quantile spacing). An independent-samples *t*-test was used to compare normally distributed continuous variables; the *Mann–Whitney U*-test was used to compare continuous variables with non-normal distributions. *P* <0.05 was considered statistically significant.
Abbreviations: DPN, diabetic peripheral neuropathy; SD, standard deviation; MAGE, mean amplitude of glycemic excursion; MODD, mean of daily differences; TIR, time in range; TBR, time below range; TAR, time above range; GRI, glycemia risk index.

Prevalence of DPN Among Different CGM Groups

Further analyses revealed that the prevalence of DPN was higher with increasing GRI quartiles (Figure 1). The prevalence of DPN was 41.6%, 47.9%, 49.1%, and 59.5% in the ascending GRI quartiles, respectively (*P* for trend < 0.001). Meanwhile, the prevalence of DPN demonstrated an opposite trend with increasing TIR quartiles (*P* for trend < 0.001). When the participants were stratified based on the quartiles of HbA1c, significant ascending trend was also observed (*P* for trend = 0.019).

Associations Between GRI and the Prevalence of DPN

In the multivariable logistic analysis, the highest GRI quartile (Q4) exhibited a 63% greater risk of DPN (OR 1.631, 95% CI: 1.071 to 2.484, p = 0.023) than the lowest quartile (Q1) after adjusted for age, sex, body mass index, diabetes duration, blood pressure, creatinine, urinary albumin-to-creatinine ratio, lipid profile and glycated hemoglobin (Table 3).

Discussion

In this study, we observed a significant positive correlation between the risk of DPN and the GRI in individuals with T2DM. Patients with the highest GRI quartile exhibited a 63% greater risk of DPN than those with the lowest quartile after adjusting for possible confounders.

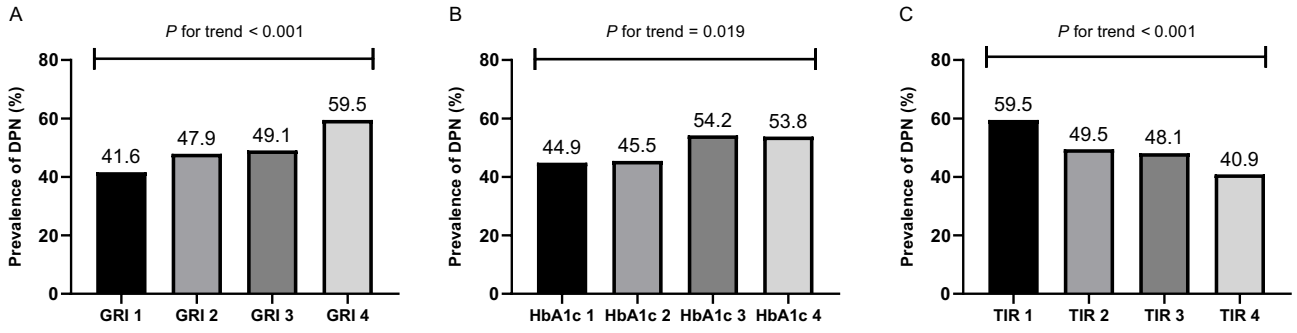

Figure 1 Prevalence of DPN among quartiles (Q1-Q4) of (**A**) GRI, (**B**) HbA1c, and (**C**) TIR. (**A**) Q1: GRI≤8.28, Q2: 8.28<GRI≤16.79, Q3: 16.79<GRI≤33.76 and Q4: GRI>33.76. (**B**) Q1: HbA1c≤7.2, Q2: 7.2<HbA1c≤8.3, Q3: 8.3<HbA1c≤9.8 and Q4: HbA1c>9.8. (**C**) Q1: TIR≤74.4%, Q2: 74.4%<TIR≤86.5%, Q3: 86.5%<TIR≤92.9% and Q4: TIR>92.9%. *P* <0.05 was considered statistically significant.
Abbreviations: DPN, diabetic peripheral neuropathy; GRI, glycemia risk index; HbA1c, glycated hemoglobin; TIR, time in range.

Table 3 Associations Between Glycemia Risk Index and DPN

	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
GRI quartiles								
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	1.293 (0.883, 1.891)	0.186	1.271 (0.858, 1.884)	0.232	1.258 (0.841, 1.880)	0.264	1.194 (0.796, 1.792)	0.391
Q3	1.353 (0.925, 1.981)	0.119	1.242 (0.838, 1.842)	0.281	1.170 (0.775, 1.765)	0.454	1.070 (0.703, 1.629)	0.752
Q4	2.066 (1.406, 3.036)	<0.001	1.867 (1.253, 2.781)	0.002	1.754 (1.159, 2.654)	0.008	1.631 (1.071, 2.484)	0.023
P for trend	<0.001		0.004		0.016		0.043	

Notes: Multivariable logistic regression was used to assess the association between the GRI quartiles (Q1: GRI≤8.28, Q2: 8.28<GRI≤16.79, Q3: 16.79<GRI≤33.76 and Q4: GRI>33.76) and DPN. Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, BMI, diabetes duration, blood pressure, creatinine, urinary albumin-to-creatinine ratio, and lipid profile; Model 4: Model 3 + glycated hemoglobin. *P* <0.05 was considered statistically significant.

Abbreviations: GRI, glycemia risk index; OR, odds ratio; CI, confidence interval.

As a novel metric of CGM, GRI provides a comprehensive assessment of glycemic risk by incorporating both hypoglycemia and hyperglycemia, with a particular focus on severe episodes. Despite being a well-established and easy-to-understand metric for assessing glycemia quality, TIR is not sensitive enough to identify out-of-range profiles, especially hypoglycemic profiles,[16] whereas GRI gives a greater weighting to hypoglycemia than hyperglycemia. Severe hypoglycemia may be related to an increased risk of mortality in diabetes patients,[22] so identifying those with hypoglycemia, especially severe hypoglycemia or recurrent hypoglycemia, adjusting the treatment plan, and broadening the goal of blood glucose control is essential.

Studies have shown that high variability in blood sugar levels (glycemic variability) is linked to both the risk of hypoglycemia and increased mortality in intensive care settings.[23,24] Notably, studies have suggested that fluctuations in HbA1c, rather than the average HbA1c level itself, are more strongly associated with diabetic complications.[25] Furthermore, increased glycemic variability has been linked to impaired blood vessel function.[26] Consistent with these findings, elevated GRI has been shown to correlate with various long-term diabetic complications, including arterial stiffness,[11] albuminuria (protein in the urine),[10] and diabetic retinopathy.[9] Our study adds to the growing body of evidence by demonstrating a novel association between GRI and DPN, further highlighting the potential of GRI as a valuable predictor of microvascular complications in diabetes.

While our study highlighted the link between GRI and DPN risk, other CGM metrics, such as TIR, did not show a significant association after accounting for HbA1c (Supplementary Table S1). This difference can be attributed to the definitions of the metrics. GRI specifically considers both severe hypoglycemia and hyperglycemia, which are known risk factors for DPN development.[27,28] In contrast, TIR simply measures the percentage of time a patient's blood sugar remains within the target range without distinguishing between the time spent above or below the desired range.

Several studies have examined the connection between DPN and CGM metrics. Li et al discovered a positive association between the TIR and peripheral nerve function.[29] However, their study focused solely on hospitalized patients, potentially limiting its applicability to typical outpatient scenarios. Additionally, the three-day CGM data may not have been sufficient for analyzing other metrics, such as the GRI. In another study by Yang et al, a negative correlation between TIR and an increasing risk of pain in hospitalized DPN patients was noted.[30] Nonetheless, this study excluded patients without DPN, and the prevalence of painful DPN was higher than in other studies.[31] In our study, TIR levels were generally high, leading to fewer discernible differences between the two groups and consequently impacting its correlation with DPN. The TIR is a widely recognized metric for glycemic control and is frequently utilized in various clinical and scientific contexts. We believe that examining the TIR and GRI across a broader population base could offer deeper insights into the underlying correlation between CGM metrics and diabetic complications.

Diabetes complications have been linked to oxidative stress in both types of diabetes.[32] Hyperglycemia, hypoglycemia and glycemic variability have all been linked to reactive oxygen species (ROS).[33] A variety of mechanisms linked with hyperglycemia contribute to the overproduction of ROS, including the production of advanced glycation end-products, protein kinase C activation, accumulation of sorbitol, and hyperactivity of the hexosamine pathway.[34] The

production of ROS is greater in GV than chronic hyperglycemia, leading to vascular damage.[35] On the other hand, a growing body of evidence suggests that diabetic vascular disorders are exacerbated by hypoglycemia, which contributes to oxidative stress, inflammation, hypercoagulability, and endothelial dysfunction.[36] Based on the mechanisms above, GRI combining both hypoglycemic and hyperglycemic status might present greater advantages in predicting complications.

Several limitations exist in this research work. First, this was a cross-sectional study with a small sample size, and causality between DPN and GRI could not be determined. Second, the GRI combines TAR and TBR and places the greatest weight on time in VLow. However, the low TBR proportions in this study may have underestimated the GRI and affected the reliability of the results. Owing to the use of a touchscreen reader, participants were able to react to hypoglycemia in time and prevent severe hypoglycemia, which constituted VLow. Moreover, the study population consisted of patients with T2DM, and the hypoglycemic risk of overall antidiabetic therapy was much lower than that of insulin-based treatment. Therefore, the application of the GRI in patients with type 1 diabetes or in trials with blind designs may provide more valuable results. Third, data on additional potential risk factors, including lifestyle and socioeconomic factors, were unavailable in the present study. Thus, we were not able to include all confounders that might be related to DPN in the multivariate-adjusted model. To verify the association between DPN and GRI, further prospective studies should be conducted with a larger number of participants who frequently experience hypoglycemia.

Conclusion

In conclusion, our study revealed an association between diabetic peripheral neuropathy (DPN) and GRI, indicating the potential value of the GRI as an indicator of DPN. Further prospective studies are necessary to validate the role of the glycemia risk index in the progression of microvascular complications.

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Disclosure

The authors report no conflicts of interest in this work.

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