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PROSPECTIVE ANALYSIS OF THE EFFECT OF CHRONIC STRESS ON GLYCEMIC VARIABILITY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

Background: Chronic psychological stress is increasingly recognized as a significant factor influencing glycemic control in individuals with Type 2 Diabetes Mellitus (T2DM). Stress may contribute to glycemic variability (GV) through its effects on hormonal regulation and behavioral patterns. This study aimed to prospectively evaluate the relationship between chronic stress and GV in patients with T2DM.

Materials and Methods: A total of 120 patients diagnosed with T2DM were enrolled in a 6-month prospective observational study. Participants were evaluated for chronic stress using the Perceived Stress Scale (PSS-10) at baseline and at 3-month intervals. Glycemic variability was assessed through continuous glucose monitoring (CGM) parameters, including standard deviation (SD), coefficient of variation (CV), and mean amplitude of glycemic excursions (MAGE). Data were analyzed using Pearson correlation and multivariate regression to identify associations between stress levels and GV indices.

Results: Patients with high chronic stress (PSS $\geq$ 20) showed significantly increased GV parameters compared to those with lower stress levels. The mean SD of glucose readings in the high-stress group was 54.8 ± 11.3 mg/dL versus 42.7 ± 9.5 mg/dL in the low-stress group ($p < 0.001$). Similarly, MAGE was elevated in the high-stress group (102.3 ± 18.7 mg/dL) compared to the low-stress group (85.6 ± 15.2 mg/dL; $p = 0.002$). A positive correlation ($r = 0.62$, $p < 0.001$) was observed between PSS scores and GV metrics. Multivariate regression confirmed chronic stress as an independent predictor of increased GV.

Conclusion: Chronic stress significantly contributes to increased glycemic variability in patients with T2DM, independent of HbA1c levels and medication adherence. Routine assessment and management of psychological stress may play a crucial role in optimizing glycemic outcomes in diabetic care.

Keywords: Type 2 Diabetes Mellitus, Chronic Stress, Glycemic Variability, Perceived Stress Scale, Continuous Glucose Monitoring

Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired glucose regulation, contributing to long-term complications affecting various organ systems (1). Effective glycemic control is essential in minimizing the risk of microvascular and

macrovascular complications in individuals with T2DM (2). While glycated hemoglobin (HbA1c) remains a standard marker for long-term glycemic control, it does not reflect daily glycemic fluctuations, which are increasingly recognized as independent predictors of diabetes-related complications (3,4).

Glycemic variability (GV) refers to the oscillations in blood glucose levels throughout the day and across days, including both hypoglycemic and hyperglycemic episodes (5). Emerging evidence suggests that increased GV is associated with oxidative stress, endothelial dysfunction, and inflammation, thereby potentially accelerating the progression of diabetic complications even when average glucose levels remain within acceptable ranges (6,7). Psychological stress, particularly when chronic, has been shown to adversely affect glycemic control in T2DM patients. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased secretion of cortisol and catecholamines, which interfere with insulin sensitivity and glucose metabolism (8,9). Furthermore, stress may negatively influence self-care behaviors such as medication adherence, dietary choices, and physical activity, thereby compounding its impact on glycemic control (10). Despite the known effects of stress on blood glucose levels, limited studies have specifically examined the relationship between chronic stress and glycemic variability in T2DM. Most existing literature has focused on stress and mean glucose control or HbA1c levels, without addressing the dynamic fluctuations that occur throughout the day. Continuous glucose monitoring (CGM) provides an opportunity to measure GV in a detailed manner, allowing for better assessment of the physiological impact of stress (11,12). This prospective study aims to evaluate the effect of chronic stress on glycemic variability among patients with T2DM, utilizing CGM parameters and standardized stress assessment tools. Understanding this relationship may offer insights into more comprehensive management strategies for individuals living with diabetes.

Materials and Methods

Study Design and Setting

This was a prospective observational study conducted over a period of 6 months in the outpatient endocrinology department of a tertiary care hospital. Written informed consent was obtained from all participants.

Study Population

A total of 120 adult patients diagnosed with Type 2 Diabetes Mellitus (T2DM), aged between 35 and 65 years, were recruited. Inclusion criteria were a minimum duration of diabetes of 2 years and stable antidiabetic medication for at least the previous 3 months. Patients with type 1 diabetes, major psychiatric disorders, chronic systemic illnesses (e.g., cancer, end-stage renal disease), or recent hospitalization were excluded.

Assessment of Chronic Stress

Chronic psychological stress was evaluated using the 10-item Perceived Stress Scale (PSS-10), a validated questionnaire designed to measure the perception of stress over the preceding month. Scores ranged from 0 to 40, with higher scores indicating greater perceived stress. Participants were categorized into low stress (PSS score <14), moderate stress (14–19), and high stress (≥20).

Glycemic Variability Monitoring

All participants underwent continuous glucose monitoring (CGM) using a standardized CGM device for a period of 14 days. The device recorded interstitial glucose levels every 5 minutes. Glycemic variability parameters calculated included:

- **Standard Deviation (SD)** of glucose levels
- **Coefficient of Variation (CV)**
- **Mean Amplitude of Glycemic Excursions (MAGE)**

These values were averaged for each participant over the 2-week monitoring period.

Data Collection and Follow-Up

In addition to stress and CGM data, baseline demographic and clinical data were collected, including age, sex, duration of diabetes, BMI, HbA1c levels, and current medications. Participants were followed up at 3 and 6 months for repeat stress assessment and glucose monitoring.

Statistical Analysis

Data were entered into SPSS version 25.0 for statistical analysis. Descriptive statistics were used to summarize baseline characteristics. Pearson correlation was employed to explore the relationship between PSS scores and glycemic variability parameters. Multivariate linear regression was used to adjust for potential confounding variables including age, sex, BMI, HbA1c, and medication use. A p-value of <0.05 was considered statistically significant.

Results

A total of 120 patients with Type 2 Diabetes Mellitus were included in the study. The mean age of the participants was 52.4 ± 8.6 years, with 65 males and 55 females. The mean duration of diabetes was 8.2 ± 3.4 years. Baseline clinical characteristics of the study population are presented in **Table 1**.

Table 1: Baseline Characteristics of Study Participants (n = 120)

Variable	Mean ± SD or n (%)
Age (years)	52.4 ± 8.6
Gender (Male/Female)	65 (54.2%) / 55 (45.8%)
Duration of Diabetes (years)	8.2 ± 3.4
BMI (kg/m²)	27.5 ± 2.9
HbA1c (%)	7.8 ± 0.9
Use of Insulin Therapy	38 (31.7%)

Participants were grouped based on their Perceived Stress Scale (PSS-10) scores into low (n=40), moderate (n=42), and high stress levels (n=38). Glycemic variability parameters were compared among these groups using standard deviation (SD), coefficient of variation (CV), and mean amplitude of glycemic excursions (MAGE). Significant differences were observed across all GV metrics between the high-stress and low-stress groups (**Table 2**).

Table 2: Comparison of Glycemic Variability Parameters by Stress Levels

Stress Level	SD (mg/dL)	CV (%)	MAGE (mg/dL)
Low Stress (n=40)	42.7 ± 9.5	26.4 ± 5.2	85.6 ± 15.2
Moderate (n=42)	48.5 ± 10.1	30.2 ± 4.8	92.1 ± 17.3
High Stress (n=38)	54.8 ± 11.3	34.5 ± 6.1	102.3 ± 18.7
p-value	<0.001	<0.001	0.002

There was a statistically significant positive correlation between PSS scores and GV parameters (SD: $r = 0.59$, $p < 0.001$; MAGE: $r = 0.62$, $p < 0.001$; CV: $r = 0.55$, $p < 0.001$) (**Table 3**).

Table 3: Correlation Between PSS Scores and Glycemic Variability Parameters

Glycemic Parameter	Correlation Coefficient (r)	p-value
SD	0.59	<0.001
CV	0.55	<0.001
MAGE	0.62	<0.001

Multivariate regression analysis demonstrated that high perceived stress was an independent predictor of increased glycemic variability, even after adjusting for confounding variables such as age, BMI, HbA1c, and insulin use (**Table 4**).

Table 4: Multivariate Regression Analysis for Predictors of Glycemic Variability (SD)

Variable	β Coefficient	95% CI	p-value
PSS Score	0.88	0.61 to 1.15	<0.001
HbA1c (%)	1.21	0.48 to 1.95	0.002
BMI (kg/m²)	0.37	-0.12 to 0.86	0.138
Insulin Use (Yes)	3.52	1.14 to 5.91	0.004

The findings indicate that patients with higher levels of chronic stress demonstrated significantly greater glycemic fluctuations as measured by CGM-based indices (Table 2, Table 3, Table 4).

Discussion

The present study demonstrated a significant association between chronic psychological stress and increased glycemic variability (GV) in patients with Type 2 Diabetes Mellitus (T2DM). Patients reporting higher stress levels, as measured by the Perceived Stress Scale (PSS-10), exhibited elevated values of standard deviation (SD), coefficient of variation (CV), and mean amplitude of glycemic excursions (MAGE), suggesting that stress is an important determinant of daily glucose fluctuations, independent of HbA1c levels.

Glycemic variability is increasingly recognized as an independent risk factor for the development of diabetes-related complications, including cardiovascular events and microvascular damage (1,2). Unlike HbA1c, which provides a measure of average glucose levels over a period of 2–3 months, GV reflects acute fluctuations in glucose, which may have a stronger link to oxidative stress and inflammatory responses (3,4). Our findings align with earlier studies reporting that high GV contributes to endothelial dysfunction and vascular injury in diabetic individuals (5,6).

Chronic stress activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, leading to increased cortisol and catecholamine secretion. These hormones promote hepatic gluconeogenesis and impair insulin sensitivity, resulting in hyperglycemia and increased glucose oscillations (7,8). Furthermore, chronic stress often leads to maladaptive behaviors such as poor dietary choices, sedentary lifestyle, and inconsistent medication adherence, which may further compound glycemic instability (9,10).

Previous research has suggested that psychological stress can impair overall glycemic control, often leading to elevated HbA1c levels (11,12). However, few studies have focused specifically on the role of stress in influencing GV, especially in patients with stable antidiabetic regimens. Our study contributes to this limited body of literature by demonstrating a clear correlation between PSS scores and CGM-based GV parameters, which persisted even after adjusting for potential confounders such as age, BMI, and insulin use.

Notably, the correlation coefficients between PSS scores and GV indices such as MAGE and SD were moderate to strong ($r = 0.62$ and $r = 0.59$, respectively), reinforcing the physiological impact of stress on glycemic dynamics. This supports earlier findings by Rod et al., who reported that chronic stress exposure predicted poor glycemic outcomes over time in diabetic patients (13). Similarly, a study by Surwit et al. showed that stress reduction interventions improved glycemic control, although GV was not specifically measured (14,15).

The use of continuous glucose monitoring (CGM) in this study allowed for detailed and accurate assessment of glycemic fluctuations, a strength that enhances the clinical relevance of our results. Moreover, the prospective design and follow-up assessments provided insights into the consistency of stress-related effects over time. Nevertheless, this study has limitations. It relied on self-reported stress assessment, which may be subject to recall bias. Although the PSS-10 is widely validated, objective stress biomarkers such as salivary cortisol were not used. In addition, the study was conducted in a single center with a modest sample size, which may limit the generalizability of findings. Future research should consider larger multicentric studies, integration of biochemical stress markers, and evaluation of interventions aimed at stress reduction, such as mindfulness-based cognitive therapy or physical activity, on GV outcomes. Investigating the interaction between stress and other psychosocial factors like depression and social support may also yield further insights.

Conclusion

In conclusion, our findings indicate that chronic psychological stress is significantly associated with increased glycemic variability in individuals with T2DM. Addressing stress as a modifiable risk factor may help improve glycemic stability and potentially reduce the burden of diabetes-related complications.

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