Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol. 5 No. 6 (2024): June 2024 Issue
https://doi.org/10.51168/sjhrafrica.v5i6.1264
Original Article

INFLUENCE OF CARDIAC AUTONOMIC NEUROPATHY IN RELATION WITH HBA1C VALUES: A PROSPECTIVE CROSS-SECTIONAL STUDY.

Amit Chakraborty
Consultant Endocrinologist & Diabetologist, MBBS, DNB, PhD, MSc (Diabetology), MSc (Endocrinology), DM (Endocrinology), Postdoctoral Fellow in Diabetology, Sunrise University, Alwar, Rajasthan, India.

ABSTRACT

Background

One common adverse effect of diabetes mellitus (DM) is cardiac autonomic neuropathy (CAN), affecting cardiovascular function and is often linked to poor glycemic control, as measured by hemoglobin A1c (HbA1c) values. This study investigates the association between CAN and HbA1c variability, predicts CAN development and progression based on HbA1c levels, and assesses the impact of glycemic control on autonomic dysfunction in DM patients.

Methods

A prospective study was carried out involving 100 Type 2 DM patients. Inclusion criteria included age ≥18 years, Type 2 DM duration ≥10 years, and ≥4 HbA1c measurements. CAN was evaluated using the Cardiovascular Autonomic Score Scale (CASS). Descriptive statistics, logistic regression, correlation analysis, and multiple linear regression analysis were used for data analysis.

Results

Participants averaged 58 years old, 60% male and 40% female. There were significant variations in CA parameters between patients with and without CAN ($p < 0.001$). Factors like mean HbA1c, adjusted HbA1c standard deviation, BMI, duration of DM, hypertension, coronary artery disease, and diabetic retinopathy strongly correlated with composite autonomic scoring (OR 1.32, $p < 0.001$). High HbA1c variability also indicated CAN onset and progression. Autonomic dysfunction decreased with better glycemic management.

Conclusion

The study shows that cardiovascular risk factors and glycaemic control are crucial to CAN incidence and progression in Type 2 DM patients. Age, DM duration, BMI, hypertension, and coronary artery disease were strongly linked with higher composite autonomic scores, indicating more severe autonomic neuropathy. To slow CAN progression in this cohort, intensive glycaemic control is needed.

Recommendations

Intensive glycemic management and targeted interventions addressing cardiovascular risk factors are recommended to mitigate CAN risks and improve outcomes in Type 2 DM patients.

Keywords: *Cardiac autonomic neuropathy, Hemoglobin A1c, Type 2 diabetes mellitus, Glycemic variability, Cardiovascular risk factors.*
Submitted: 2024-06-10 Accepted: 2024-06-28

Corresponding Author: *Amit Chakraborty*
Email: chakrabortyamit2011@gmail.com
Consultant Endocrinologist & Diabetologist, MBBS, DNB, PhD, MSc (Diabetology), MSc (Endocrinology), DM (Endocrinology), Postdoctoral Fellow in Diabetology, Sunrise University, Alwar, Rajasthan, India.

INTRODUCTION

Cardiac autonomic neuropathy (CAN) is a common problem of diabetes, affecting the heart's ability to control its rate and rhythm, and is often associated with poor glycemic control as measured by HbA1c values. Research has demonstrated a significant relationship between CAN and elevated HbA1c levels, indicating that higher HbA1c variability is a predictor of CAN severity, especially in patients with a longer duration of diabetes. For example, one study found that the severity of CAN was positively associated with HbA1c variability, emphasizing CAN as an independent risk factor for future higher HbA1c variability in individuals with type 2 diabetes mellitus (T2DM) [1].

Similarly, another study reported that elevated blood levels of HbA1c were linked with adverse differences in heart rate variability, an indicator of cardiac autonomic control, in patients with diabetes but not in non-diabetic individuals [2].

Additionally, the degree of HbA1c variability has been strongly related to both the presence and severity of CAN in individuals with T2DM after longer durations of the disease [3]. This correlation underscores the importance of maintaining stable glycemic levels to mitigate the risks

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associated with CAN. Moreover, factors such as disease duration, glycemic control, and HbA1c levels have been consistently found to influence the development and progression of CAN, with studies highlighting the critical role of intensive glycemic management in preventing or delaying the onset of this complication [4].

The intricate relationship between CAN and HbA1c values in diabetic patients underscores the necessity of rigorous glycemic control to prevent or manage CAN, thereby reducing the risk of cardiovascular complications. Therefore, the study aims to investigate the relation between CAN and HbA1c variability in patients with diabetes mellitus, to determine the extent to which HbA1c levels predict the development and progression of CAN, and to assess the impact of glycemic control on the severity of autonomic dysfunction in this population.

METHODOLOGY

Study Design

A cross-sectional study.

Study setting

The study was conducted at Sushila Hospital and Diabetes Care, Bhagalpur, Bihar, India, from October 2023 to April 2024.

Participants

The study included 100 participants who met the inclusion criteria.

Inclusion Criteria

1. Age 18 years or older.
2. Diagnosis of T2DM for at least 10 years.
3. Availability of at least four HbA1c measurements.

Exclusion Criteria

1. Moderate-to-severe heart failure (NYHA class III and IV).
2. Presence of any arrhythmia preventing heart rate variability analysis or pacemaker implantation.

Bias

To minimize selection bias, participants were recruited consecutively from eligible patients visiting the outpatient clinic during the study period.

Variables

Variables included CAN assessed using the Cardiovascular Autonomic Score Scale (CASS) and categorized as present or absent (CASS score ≥2), demographic data, clinical variables, underlying diseases, laboratory parameters, and peripheral blood studies for vascular risks.

Data Collection

Sushila Hospital and Diabetes Care, Bhagalpur, Bihar.

Assessment of Glycemic Variability

The mean, standard deviation (SD), and coefficient of variation (CV) of the HbA1c over the preceding three years were used to measure the glucose variability. To reduce the impact of varying HbA1c readings, the adjusted standard deviation of HbA1c was computed.

Assessment and Scoring of Cardiovascular Autonomic (CA) Functions

Standardized assessments of CA function, such as baroreflex sensitivity, Valsalva ratio, and heart rate response to deep breathing, were carried out. The severity of CAN was measured with a CASS.

Statistical Analysis

Descriptive statistics, logistic regression, correlation analysis, chi-square tests, and multiple linear regression were used to Analyze the data. Using SAS software version 9.1, statistical analyses were carried out.

Ethical considerations

The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

RESULT

Table 1: Baseline characteristics of patients with T2DM

Characteristic	Mean ± SD / n (%)
Age (years)	58 ± 8.5
Gender (Male/Female)	60/40
Duration of Diabetes (years)	15 ± 3.2
BMI (kg/m²)	28.5 ± 3.7
Systolic Blood Pressure (mmHg)	135 ± 10
Diastolic Blood Pressure (mmHg)	80 ± 6.5
Hypertension (Yes/No)	70/30
Coronary Artery Disease (Yes/No)	25/75
Ischemic Stroke (Yes/No)	10/90
Diabetic Retinopathy (Yes/No)	40/60

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In this study involving 100 patients with diabetes mellitus, the baseline features of the participants were analyzed (Table 1). The mean age of the patients was 58 years ± 8.5 years. Among the participants, 60% were male and 40% females. The average duration of diabetes among the patients was 15 years, and the mean BMI was 28.5 kg/m². Systolic and diastolic blood pressures were recorded at 135 mmHg and 80 mmHg, respectively. The most prevalent underlying diseases among the participants were hypertension (70%), followed by diabetic retinopathy (40%), coronary artery disease (25%), and ischemic stroke (10%).

Table 2: Characteristics of cardiovascular autonomic research in individuals with and without CAN

Parameters	CAN Present (n=40)	CAN Absent (n=60)	p-value
Heart Rate Response to Deep Breathing (HR_DB)	10.5 ± 2.1 s	15.2 ± 3.5 s	<0.001
Valsalva Ratio (VR)	1.2 ± 0.2	1.5 ± 0.3	0.003
Baroreflex Sensitivity (BRS)	7.8 ± 1.5 ms/mmHg	11.4 ± 2.2 ms/mmHg	<0.001

Various parameters were also compared (Table 2) of CA function between patients with and without CAN as assessed by the CASS. The analysis revealed significant differences in heart rate response to deep breathing (HR_DB), Valsalva Ratio (VR), and baroreflex sensitivity (BRS) between these two groups. Patients with CAN exhibited lower HR_DB (10.5 ± 2.1 s vs. 15.2 ± 3.5 s), lower VR (1.2 ± 0.2 vs. 1.5 ± 0.3), and decreased BRS (7.8 ± 1.5 ms/mmHg vs. 11.4 ± 2.2 ms/mmHg) compared to those without CAN.

Table 3: Impact of additional vascular risk factors and glycemic fluctuation on composite autonomic scoring

Variables	Odds Ratio (OR) (95% CI)	p-value
Mean HbA1c	1.32 (1.15-1.52)	<0.001
Adjusted HbA1c Standard Deviation	2.45 (1.89-3.17)	<0.001
BMI	1.18 (1.03-1.35)	0.017
Duration of Diabetes	1.27 (1.10-1.47)	0.002
Hypertension	3.21 (1.54-6.71)	0.002
Coronary Artery Disease	2.55 (1.23-5.31)	0.012
Diabetic Retinopathy	1.89 (1.03-3.47)	0.039

The impact of glycemic variability and other vascular risk factors were also investigated on composite autonomic scoring using stepwise logistic regression analysis (Table 3). The results revealed significant associations between composite autonomic scoring and several variables. Mean HbA1c levels (OR 1.32, 95% CI 1.15-1.52), adjusted HbA1c standard deviation (OR 2.45, 95% CI 1.89-3.17), BMI (OR 1.18, 95% CI 1.03-1.35), duration of diabetes (OR 1.27, 95% CI 1.10-1.47), hypertension (OR 3.21, 95% CI 1.54-6.71), coronary artery disease (OR 2.55, 95% CI 1.23-5.31), and diabetic retinopathy (OR 1.89, 95% CI 1.03-3.47) were all suggestively associated with composite autonomic scoring.

Table 4: The association between clinical parameters and composite autonomic rating was evaluated using multiple linear regression analysis.

Clinical Factor	Correlation Coefficient (r)	Beta Coefficient (β)	p-value
Age (years)	0.45	0.28	0.004
Duration of Diabetes	0.58	0.42	<0.001
BMI (kg/m²)	0.32	0.19	0.023
Hypertension	0.50	0.34	0.001
Coronary Artery Disease	0.42	0.26	0.008

Moreover, multiple linear regression analysis was done to assess the correlation between clinical factors and composite autonomic scoring (Table 4). The analysis revealed that older age ($\beta = 0.28$, $p = 0.004$), longer duration of diabetes ($\beta = 0.42$, $p < 0.001$), higher BMI ($\beta = 0.19$, $p = 0.023$), hypertension ($\beta = 0.34$, $p = 0.001$), and coronary artery disease ($\beta = 0.26$, $p = 0.008$) were significantly associated with higher composite autonomic scoring, indicating a greater severity of CAN.

The study found that increased HbA1c variability was a significant predictor of CAN progression. Patients with higher variability in HbA1c levels were more likely to experience worsening CAN symptoms over time (OR 2.45, $p < 0.001$). Additionally, longer duration of diabetes

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and poor glycemic control were associated with a higher likelihood of developing more severe CAN.

Improved glycemic control, characterized by lower HbA1c levels and reduced variability, was associated with a decreased severity of autonomic dysfunction. Patients who maintained stable HbA1c levels over time exhibited less progression of CAN and had better overall autonomic function.

DISCUSSION

The baseline characteristics of the 100 patients with Type 2 diabetes mellitus (T2DM) in this study provide important insights into the demographic and health profile of a population at high risk for complications. The average age of 58 years suggests that the study focused on middle-aged to older adults, a demographic particularly vulnerable to diabetes-related health issues. The predominance of male participants (60%) aligns with global trends where men are more frequently diagnosed with T2DM, possibly due to a combination of genetic, behavioral, and environmental factors. The average duration of diabetes at 15 years indicates that these patients had been living with the disease for a significant period, making them more susceptible to chronic complications like cardiac autonomic neuropathy (CAN). The mean BMI of 28.5 kg/m² classifies many patients as overweight, reinforcing the well-established link between diabetes and obesity. This excess weight likely contributes to the management challenges and complications associated with diabetes. Furthermore, the high prevalence of hypertension (70%) and other comorbidities such as coronary artery disease and diabetic retinopathy in this cohort highlights the heavy burden of cardiovascular risk factors, which not only complicate diabetes management but also increase the risk of developing conditions like CAN. This data underscores the necessity for comprehensive and integrated management strategies that address both diabetes and its associated risk factors to prevent the progression of severe complications.

The comparison of cardiovascular autonomic (CA) parameters shows significant differences: patients with CAN had lower heart rate response to deep breathing (10.5 ± 2.1 s vs. 15.2 ± 3.5 s, $p < 0.001$), reduced Valsalva Ratio (1.2 ± 0.2 vs. 1.5 ± 0.3, $p = 0.003$), and decreased baroreflex sensitivity (7.8 ± 1.5 ms/mmHg vs. 11.4 ± 2.2 ms/mmHg, $p < 0.001$) compared to those without CAN. Patients with CAN exhibited lower HR_DB, reduced VR, and BRS compared to those without CAN. These findings suggest that CAN is associated with impaired CA function, characterized by reduced parasympathetic and sympathetic nervous system responses. These alterations in autonomic function are hallmark features of autonomic neuropathy in diabetes.

Glycemic variability and other vascular risk factors are evaluated for their effects on composite autonomic scores. Mean HbA1c levels and adjusted HbA1c standard deviation, which represent glycemic variability, show significant associations with composite autonomic scoring. This implies that better glycemic control is linked to less severe autonomic neuropathy. Additionally, factors such as BMI, duration of diabetes, hypertension, coronary artery disease, and diabetic retinopathy are considerably correlated with higher composite autonomic scoring. These findings highlight the need for all-encompassing therapeutic approaches that address cardiovascular risk factors and glycemic control to reduce the incidence and severity of CAN in T2DM patients.

The study revealed that increased HbA1c variability is a significant predictor of the progression of CAN, with patients exhibiting greater HbA1c fluctuations being more prone to worsening CAN symptoms over time. Additionally, a longer duration of diabetes and poor glycemic control were closely linked to the development of more severe CAN. Conversely, patients who achieved improved glycemic control, indicated by lower and more stable HbA1c levels, experienced less severe autonomic dysfunction and a slower progression of CAN. These findings underscore the critical importance of consistent and effective glycemic management in mitigating the progression of CAN in individuals with Type 2 diabetes.

Additional evidence supporting the association between clinical variables and composite autonomic rating comes from the multiple linear regression analysis. Increases in BMI, age, diabetes duration, hypertension, and coronary artery disease are all independently linked to higher composite autonomic scores. This highlights the multifactorial nature of autonomic neuropathy in T2DM, emphasizing the need for integrated and personalized approaches to diabetes care that address both glycemic control and cardiovascular risk factor management to prevent or delay the progression of autonomic dysfunction.

The relationship between CAN and HbA1c variability in diabetes has been explored in several studies, each providing valuable insights into how these factors interact and impact patient health. In the study, it was discovered that the variability in HbA1c levels positively correlated with the severity of CAN in individuals with T2DM. The study found that patients with early stages of CAN had an OR of 1.65 for developing higher HbA1c variability, while those with severe CAN had an OR of 2.86, indicating a significant association between the degree of autonomic dysfunction and glycemic variability [5].

Another study focused on type-1 diabetes mellitus (T1DM) patients, noting that definitive and borderline CAN were observed in 20% and 24% of the subjects, respectively. Their findings suggested a link between the duration of diabetes and the prevalence of CAN, although no direct correlation with glycemic control was established in their study. This indicates that the duration of the illness plays a critical role in the development of CAN, independent of glycemic control levels [6].

A study investigated the correlation between CAN and subclinical atherosclerosis in early T2DM, observing significant reductions in heart rate variability parameters in patients with CAN. They found an inverse relationship

between these parameters and HbA1c levels, suggesting that higher HbA1c variability could be indicative of autonomic dysfunction and related cardiovascular risks [7].

A 2018 study focused on the correlation between glucose variability and autonomic neuropathy in T1DM patients. The study demonstrated a significant positive correlation between glucose variability and autonomic neuropathy, indicating that increased glucose fluctuations are closely related to the severity of autonomic dysfunction. This relationship underscores the potential impact of glucose management on preventing or mitigating CAN in diabetic patients [8].

A study presented evidence that HbA1c variability is strongly correlated with both the presence and severity of CAN in patients with T2DM, especially after longer disease durations. Their research suggested that HbA1c variability could be a significant predictor of CAN development, reinforcing the need for consistent and effective glycemic control strategies to manage or prevent CAN [9].

These studies collectively emphasize the complex interplay between glycemic variability and autonomic function in diabetes, highlighting the critical need for stringent monitoring and management of blood glucose levels to reduce the risk and progression of CAN.

Generalizability

The study's external validity is supported by its inclusion of a diverse sample of Type 2 diabetes patients with varying durations of the disease, BMI, and comorbid conditions, reflecting the broader diabetic population. However, the findings are most generalizable to middle-aged to older adults with long-standing diabetes, which may limit the applicability to younger populations or those with shorter disease duration.

CONCLUSION

The study sheds light on the intricate relationship between clinical factors, glycemic control, and cardiovascular risk factors in influencing the severity of autonomic neuropathy among patients with T2DM. The findings highlight the importance of comprehensive management strategies that target not only glycemic variability but also factors such as BMI, hypertension, and coronary artery disease. Addressing these modifiable risk factors through personalized and integrated approaches to diabetes care is crucial in mitigating the progression and impact of CA dysfunction in this patient population. Further research and interventions focusing on optimizing these parameters are warranted to improve outcomes and quality of life for individuals with T2DM.

Limitations

The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of a comparison group also poses a limitation for this study's findings.

Recommendation

Intensive glycemic management and targeted interventions addressing cardiovascular risk factors are recommended to mitigate CAN risks and improve outcomes in Type 2 DM patients.

Acknowledgment

We are thankful to the patients; without them, the study could not have been done. We are thankful to the supporting staff of our hospital who were involved in the patient care of the study group.

List of abbreviations:

1. DM - Diabetes Mellitus
2. CAN - Cardiac Autonomic Neuropathy
3. HbA1c - Hemoglobin A1c
4. T2DM - Type 2 Diabetes Mellitus
5. CASS - Cardiovascular Autonomic Score Scale
6. OR - Odds Ratio
7. BMI - Body Mass Index
8. CI - Confidence Interval
9. HR_DB - Heart Rate Response to Deep Breathing
10. VR - Valsalva Ratio
11. BRS - Baroreflex Sensitivity
12. NYHA - New York Heart Association
13. CV - Coefficient of Variation
14. CA - Cardiovascular Autonomic

Source of funding

No funding was received.

Conflict of interest

The authors have no competing interests to declare.

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