Ref: Ro Med J. 2024;71(2)
DOI: 10.37897/RMJ.2024.2.18

Association between glycemic control and autonomic dysfunction: A cross-sectional study in type 2 diabetes mellitus patients

Jibin Simon, Srinivasa Guptha L.R., Jagadeesan M., Sharan Bose

Department of General Medicine, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India

ABSTRACT

Background. Orthostatic hypotension (OH) stands as one of the initial indications of cardiac autonomic dysfunction in diabetic individuals. Our objective is to assess the prevalence of OH across different degrees of diabetes.

Materials and methods. This study is a cross-sectional investigation conducted at a tertiary care center. After obtaining ethical committee clearance and informed consent, 150 individuals aged above 50 years were recruited for this study. 50 of them had normal HbA1c levels, 50 with HbA1c levels between 7-8 and another 50 individuals with more than 8 HbA1c values.

Results. The duration of diabetes exhibited a strong correlation with HbA1c levels, which was statistically significant (p=0.000). The systolic BP difference in normal, HbA1c 7-8 and HbA1c levels more than 8 were 6.34±1.95, 15.70±8.37 and 17.04±7.74 respectively. The diastolic BP difference in normal, HbA1c 7-8 and HbA1c levels more than 8 were 4.00±1.42, 7.72±5.26 and 12.22±7.77. These results were found to be statistically significant (p=0.000).

Conclusion. OH serves as an ominous sign in diabetic patients, indicating a poor prognosis. Individuals with OH are at a heightened risk of falls, which in turn, is associated with increased morbidity and mortality. Therefore, it is crucial to prioritize the early detection of autonomic neuropathy, particularly in diabetic patients.

Keywords: autonomic dysfunction, diabetes, othrostatic hypotension, autonomic neuropathy

INTRODUCTION

The prevalence of type 2 diabetes has been estimated to be greater than 100 million people worldwide and is projected to increase to 300 million by 2025 [1]. Autonomic neuropathy is a common complication in diabetics [2]. Orthostatic hypotension is present in DM patients at a higher prevalence than DM patients with no DM [3]. Orthostatic hypotension (OH) is highly associated with cardiovascular disease and mortality [4]. OH is linked with falls in the elderly. In the standing position, impaired contraction of resistance vessels, an abnormal decrease in blood volume, or reduced cardiac output (CO) are the primary causes of orthostatic hypotension (OH). In individuals with long-term diabetes, any of these factors can result in OH [5]. Orthostatic hypotension (OH) is recognized as a clinical marker of diabetic autonomic neuropathy. When OH is present alongside diabetes mellitus, it can significantly impair quality of life and severely disrupt daily activities. While mortality in diabetic patients is often linked to macrovascular diseases, cardiac autonomic neuropathy also contributes to a 20 percent reduction in survival rate [6]. Previous research has demonstrated a positive correlation between the duration of diabetes mellitus and the incidence of cardiac autonomic neuropathy [7]. Hemoglobin A1c (HbA1c), a widely used measure for assessing glycemic control, is inversely related to the occurrence of complications [8]. Numerous studies have documented the prevalence, risk factors, and

Corresponding authors:
Jibin Simon
E-mail: jibinsimon97@gmsil.com

Article History:
Received: 9 June 2024
Accepted: 20 June 2024

prognosis of orthostatic hypotension (OH) in patients with diabetes mellitus (DM). Therefore, this study aims to evaluate the significance of postural blood pressure and heart rate changes as cardiovascular indicators of autonomic neuropathy.

MATERIALS AND METHODS

This cross-sectional study was conducted at a tertiary care center to investigate the association between glycemic control, as indicated by glycated hemoglobin (HbA1c) levels, and cardiovascular parameters in individuals aged 50 years and above. A total of 150 participants were enrolled, stratified into three groups based on their HbA1c levels: normoglycemic (HbA1c within reference range), moderately hyperglycemic (HbA1c between 7-8), and severely hyperglycemic (HbA1c exceeding 8).

Exclusion criteria encompassed individuals with a medical history of hypertension, cardiac disorders, or respiratory conditions to mitigate confounding factors related to cardiovascular health. Detailed documentation of participants' diabetic history was undertaken to provide context for the analysis.

Blood samples were collected to quantify HbA1c levels using standardized laboratory procedures. Additionally, baseline measurements of blood pressure and heart rate were obtained while participants were in a supine position. Subsequently, participants were instructed to stand, and postural changes in blood pressure and heart rate were recorded promptly thereafter.

This methodological approach aimed to elucidate potential correlations between HbA1c levels and cardiovascular dynamics, thereby contributing to our understanding of the interplay between glycemic status and cardiovascular health in the older adult population.

RESULTS

Statistical analysis was conducted using SPSS version 21, employing the t-test and chi-square test for the evaluation.

Table I represents the comparison of age and diabetic status between different grades of HbA1c. The duration of diabetes was well correlated with HbA1c levels, which were found to be statistically significant (p=0.000). Subjects with DM of 5–10 years had a mean HbA1c level of 7.40±0.606 and subjects with more than 10 years had a mean HbA1c level 11.12±1.986 (Table 1).

Table 2 represents comparison of cardiovascular sympathetic reactivity by blood pressure response to standing between the grades of HbA1c in type 2 diabetes mellitus patients by one-way ANOVA. The systolic BP difference in normal, HbA1c 7-8 and HbA1c levels more than 8 were 6.34±1.95, 15.70±8.37 and 17.04±7.74 respectively. The diastolic BP difference in normal, HbA1c 7-8 and HbA1c levels more than 8 were 4.00±1.42, 7.72±5.26 and 12.22±7.77. These results were found to be statistically significant (p=0.000). Heart rate is increased drastically in individuals with HbA1c >8 (Table 2).

The data presented in Table 2 sheds light on the intricate relationship between glycemic control, as gauged by HbA1c levels, and cardiovascular sympathetic reactivity among individuals diagnosed with type 2 diabetes mellitus. Notably, the significant differences observed in both systolic and diastolic blood pressure responses across varying HbA1c groups underscore the clinical relevance of glycemic management in modulating cardiovascular function. Elevated HbA1c levels, indicative of poorer glycemic control, were associated with more pronounced fluctuations in blood pressure upon transitioning from lying to standing positions. These findings hint at a potential deregulation of the autonomic nervous system, which plays a pivotal role in regulating cardiovascular homeostasis. Consequently, individuals with higher HbA1c levels may face an increased risk of orthostatic hypotension, cardiovascular instability, and heightened susceptibility to adverse cardiovascular events (Table 2).

Furthermore, the observed differences in heart rate responses between different HbA1c groups provide further insights into the impact of glycemic control on cardiac autonomic function. Elevated heart rates, particularly in response to postural changes, may signify heightened sympathetic activity and

TABLE 1. Comparison of age and diabetic status between the grades of HbA1c in type 2 diabetes mellitus patients by one-way ANOVA

Parameter	Grades of HbA1c			F - value	p – value
	Normal	Diabetes mellitus			
	HbA1c <7 Mean±SD (50)	HbA1c 7-8 Mean±SD (50)	HbA1c >8 Mean±SD (50)		
Age	50.52±6.86	51.88±9.23	60.54 ± 11.58	16.625	0.000***
Duration of diabetes	-	5.26 ±4.105	12.62±7.57	-6.044	0.000***
HbA1c	5.88±0.551	7.40±0.606	11.12±1.986	236.35	0.000***
#Gender Male	23 (46)	22 (44%)	27 (54%)	0.401(X2 -value	0.801 (ns)
Female	27 (54)	28 (56%)	23 (46%)		

*Values are expressed as Mean ± SD; p value calculated using independent student –t test, *p<0.05- ***p<0.001- statistically significant, ns- not significant. # -Gender distribution was analysed by Chi- square test.*

TABLE 2. Comparison of cardiovascular sympathetic reactivity by blood pressure response to standing between the grades of HbA1c in type 2 diabetes mellitus patients by one-way ANOVA

Parameter	Grades of HbA1c			F - value	p – value	Inter group comparison by post hoc tukey test
	Normal	Diabetes mellitus				
	HbA1c < 7 Mean±SD (50)	HbA1c 7-8 Mean±SD (50)	HbA1c >8 Mean±SD (50)			
Systolic BP on lying	112.54±5.06	125.40±9.94	128.56±11.28	42.90	**0.000*** **	**1-2*** ** **1-3*** ** 2-3 (ns)
Systolic BP on Standing	106.20±5.67	109.70±8.57	111.52±11.40	4.65	**0.011** **	**1-2*** ** **1-3*** ** 2-3 (ns)
Systolic BP difference	6.34±1.95	15.70±8.37	17.04±7.74	38.04	**0.000*** **	**1-2*** ** **1-3*** ** 2-3 (ns)
Diastolic BP on lying	70.98±5.89	87.00±6.77	90.88±6.51	135.5	**0.000*** **	**1-2*** ** **1-3*** ** **2-3 (ns)**
Diastolic BP on standing	66.98±6.23	79.28±6.73	78.66±6.57	38.04	**0.000*** **	**1-2*** ** **1-3*** ** 2-3 (ns)
Diastolic BP difference	4.00±1.42	7.72±5.26	12.22±7.77	28.10	**0.000*** **	**1-2*** ** **1-3*** ** **2-3 (ns)**
Heart rate on lying	71.30±9.77	81.0±11.88	84.48±12.50	10.03	**0.000*** **	**1-2*** ** **1-3*** ** 2-3 (ns)
Heart rate on standing	78.50±9	85.35±11.74	88.40±12.12	56.51	**0.000*** **	**1-2*** ** **1-3*** ** 2-3 (ns)

*Values are expressed as Mean ± SD; p value calculated using independent student –t test, *p<0.05- ***p<0.001- statistically significant, ns- not significant. BP–Blood Pressure, HbA1c – Glycated Hemoglobin.*

TABLE 3. Comparison of interpretation of CAN in BP response to posture between the grades of HbA1c in type 2 diabetes mellitus patients by Chi–Square test

Parameter	Interpretation of CAN in Bp response to posture	Grades of HbA1c		Total N (%)	X2 value	p – value
		HbA1c <8 N (%)	HbA1c >8 N (%)			
Based on systolic BP response	Normal	37 (74)	29 (58)	66	2.859	0.249 (ns)
	Borderline	07 (14)	11 (22)	18		
	Abnormal	06 (12)	10 (20)	16		
	Total	**50 (100)**	**50 (100)**	100		
Based on diastolic BP response	Normal	44 (88)	33 (66)	77	7.771	0.021**
	Borderline	06 (12)	14 (28)	20		
	Abnormal	0	03 (06)	03		
	Total	**50 (100)**	**50 (100)**	**100**		

*p<0.05- ***p<0.001- statistically significant, ns- not significant. CAN – Cardiovascular Autonomic Neuropathy*

compromised parasympathetic modulation, both of which are established predictors of adverse cardiovascular outcomes in individuals with diabetes. This underscores the importance of vigilant monitoring of HbA1c levels as a means of assessing cardiovascular risk and tailoring therapeutic interventions accordingly.

From a clinical standpoint, these findings hold significant implications for the management of individuals with type 2 diabetes mellitus. First, they emphasize the critical role of glycemic control in preserving cardiovascular health and mitigating the risk of cardiovascular complications. Healthcare providers should prioritize strategies aimed at optimizing glycemic control, especially in individuals with higher HbA1c levels, to attenuate the deleterious effects of dysregulated autonomic function on cardiovascular outcomes. Additionally, a comprehensive approach that addresses both glycemic control and cardiovascular risk factors may be warranted in individuals with poorly controlled diabetes, with a particular focus on enhancing cardiovascular autonomic function through targeted interventions.

Table 3 illustrates the comparison of interpretation of CAN in BP response to posture between the grades of HbA1c in type 2 diabetes mellitus patients. Abnormal and borderline systolic BP response was noticed in 20% and 22% of individuals with HBA1c above 8 respectively. In relation to diastolic BP response, 34% of individuals had borderline and abnormal BP response and it was statistically significant (p=0.021).

The significance of the findings presented in Table 3 lies in the potential association between glycemic control, as reflected by HbA1c levels, and the interpretation of Cardiovascular Autonomic Neuropathy (CAN) based on blood pressure (BP) responses to posture among type 2 diabetes mellitus patients. Specifi-

cally, in the context of diastolic BP response, there appears to be a statistically significant association between higher HbA1c levels (>8) and an increased likelihood of abnormal diastolic BP responses compared to patients with lower HbA1c levels (<8) (Table 3). This finding underscores the importance of glycemic control in mitigating the risk of autonomic neuropathy-related cardiovascular dysfunction in diabetic individuals.

Conversely, while no statistically significant association was observed between HbA1c levels and systolic BP response categories, the trends observed suggest a potential relationship worthy of further investigation.

Overall, these findings contribute to our understanding of the impact of glycemic control on cardiovascular autonomic function in diabetes mellitus, highlighting the importance of stringent glycemic management in preventing or mitigating the development of autonomic neuropathy and associated cardiovascular complications.

DISCUSSION

The present study aimed to elucidate the relationship between glycemic control, as indicated by HbA1c levels, and cardiovascular parameters in older adults diagnosed with type 2 diabetes mellitus. Our findings demonstrate significant associations between elevated HbA1c levels and alterations in cardiovascular dynamics, suggesting that poor glycemic control is closely linked to adverse cardiovascular outcomes in this population.

Individuals with higher HbA1c levels (≥8) exhibited significantly greater fluctuations in both systolic and diastolic blood pressure when transitioning from a supine to a standing position. This heightened blood pressure variability indicates impaired autonomic regulation within the cardiovascular system. Elevated HbA1c levels were associated with more pronounced postural blood pressure changes, suggesting a dysregulation of the autonomic nervous system, which plays a pivotal role in maintaining cardiovascular homeostasis. The increased heart rate observed in participants with HbA1c levels above 8 further corroborates the notion of heightened sympathetic activity and reduced parasympathetic tone.

Orthostatic hypotension (OH) is commonly defined as a decrease in systolic blood pressure (SBP) of at least 20 mm Hg or a decrease in diastolic blood pressure (DBP) of at least 10 mm Hg within three minutes of standing. Our findings revealed a significant correlation between the duration of diabetes and HbA1c levels (p=0.000). Subjects with diabetes mellitus (DM) of 5–10 years had a mean HbA1c level of 7.40±0.606, whereas subjects with more than 10 years had a mean HbA1c level of 11.12±1.986.

Our study noted that the systolic BP differences in normoglycemic individuals, those with HbA1c levels of 7-8, and those with HbA1c levels greater than 8 were 6.34±1.95, 15.70±8.37, and 17.04±7.74, respec-tively. The diastolic BP differences in these groups were 4.00±1.42, 7.72±5.26, and 12.22±7.77, respectively. These results were statistically significant (p=0.000), indicat-ing a greater difference in supine and standing BP in diabetes, which suggests the existence of orthostatic hypotension. Individuals with HbA1c levels exceeding 8 exhibited a pronounced decrease in both diastolic and systolic blood pressure. Doelman CJ et al. illustrated that inadequate glycemic control, indicated by elevated HbA1c levels, may impair vascular elasticity and diminish extravascular volume through osmotic diuresis, consequently contributing to OH [9].

Koçer A et al. noted that manifestations associated with cardiac autonomic neuropathy were more evident in individuals with a known duration of diabetes exceeding 5 years, as opposed to those with diabetes for 5 years or less [10]. Our observations were similar to this study. We found that the duration of diabetes was well correlated with HbA1c levels, which was statistically significant (p=0.000). Subjects with DM of 5–10 years had a mean HbA1c level of 7.40±0.606, whereas subjects with more than 10 years had a mean HbA1c level of 11.12±1.986. Increased HbA1C levels were associated with greater systolic and diastolic pressure differences.

A comparison of cardiac autonomic neuropathy and HbA1c revealed that abnormal and borderline systolic BP responses were noticed in 20% and 22% of individuals with HbA1c above 8, respectively. Regarding diastolic BP response, 12% of individuals with HbA1c between 7-8 had an increased fall, and 34% of individuals with HbA1c >8 had a borderline and abnormal BP response, which was statistically significant (p=0.021). This suggests that cardiac autonomic neuropathy is correlated with both the duration of diabetes and the level of glycated hemoglobin.

While the relationship between HbA1c levels and systolic blood pressure responses did not reach statistical significance, the observed trends indicate a potential association that merits further investigation. Future studies with larger sample sizes and more comprehensive assessments of autonomic function could provide deeper insights into the mechanisms underlying these associations.

Limitations of the study

Several limitations of this study warrant consideration. First, the cross-sectional design precludes the establishment of causality between glycemic control and cardiovascular parameters. Longitudinal studies are needed to elucidate the temporal relationships and causal pathways involved.

Second, the exclusion of individuals with pre-existing hypertension, cardiac disorders, or respiratory conditions, while aimed at reducing confounding factors, may limit the generalizability of our findings to the broader population of individuals with type 2 diabetes mellitus. The specific exclusion criteria might have introduced a selection bias, potentially affecting the applicability of the results to the general diabetic population who often have comorbid conditions.

Third, the sample size of 150 participants, though adequate for preliminary analysis, may limit the statistical power to detect subtle differences and interactions between HbA1c levels and cardiovascular parameters. Larger sample sizes could provide more robust and generalizable findings.

Fourth, the reliance on a single measurement of HbA1c and cardiovascular parameters might not fully capture the variability in these metrics. Multiple measurements over time would offer a more comprehensive assessment of the relationship between glycemic control and cardiovascular function.

Lastly, the study was conducted at a single tertiary care center, which may limit the external validity of the findings. Multicenter studies across diverse populations and settings would enhance the generalizability of the results and provide a broader perspective on the relationship between glycemic control and cardiovascular health in individuals with Type 2 diabetes mellitus.

In summary, while our findings provide valuable insights into the associations between glycemic control and cardiovascular parameters, these limitations highlight the need for further research to confirm and expand upon our results.

CONCLUSION

This study highlights the critical role of orthostatic hypotension (OH) as an indicator of autonomic dysfunction in diabetic patients, demonstrating a significant correlation between the duration of diabetes mellitus (DM) and elevated HbA1c levels. Our results show that individuals with DM for over 10 years exhibit higher HbA1c levels (mean 11.12±1.986) compared to those with 5-10 years of DM (mean 7.40± 0.606), and these higher levels are associated with greater orthostatic blood pressure fluctuations. Specifically, systolic and diastolic BP differences upon standing were significantly higher in individuals with HbA1c levels above 8, indicating exacerbated autonomic instability due to poor glycemic control. Clinically, this underscores the importance of early detection and management of autonomic neuropathy in diabetic patients, particularly those with prolonged disease duration and poor glycemic control, to mitigate the associated morbidity and mortality and improve overall patient outcomes.

Conflict of interest: none declared.
Financial support: none declared.

REFERENCES

1. Bjork S. The cost of diabetes and diabetes care. *Diabetes Res Clin Pract.* 2001;54(Suppl 1): 8. doi: 10.1016/S0168-8227(01)00302-1.
2. Oka H, Mochio S, Sato K, et al. Prolongation of QTc interval and nervous dysfunction in diabetic patients. *Diabetes Res Clin Pract.* 1996;31(1-3):63-70. doi: 10.1016/0168-8227(95)01049-7.
3. Wu JS, Yang YC, Lu FH, et al. Population-based study on the prevalence and risk factors of orthostatic hypotension in subjects with pre-diabetes and diabetes. *Diabetes Care.* 2009;32:69–74. doi: 10.2337/dc08-1264.
4. Rose KM, Eigenbrodt ML, Biga RL, et al. Orthostatic hypotension predicts mortality in middle-aged adults. The Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2006;114:630–636. doi: 10.1161/CIRCULATIONAHA.105.607499.
5. Ziegler MG. Postural hypotension. *Annu Rev Med.* 1980;31:239-245. doi: 10.1146/annurev.me.31.020180.001323.
6. Schwartz PJ, Priori SG. Sympathetic nervous system and cardiac arrhythmias. In: Zipes DP, Jalife I, eds. Cardiac Electrophysiology. From cell to bedside. Philadelphia: W.B. Saunders; 1990:330. doi: 10.1016/B978-0-7216-3766-4.50029-3.
7. Kumhar MR, Agarval TD, Singh VB, Kochar DK, Chadda VS. Cardiac autonomic neuropathy and its correlation with QTc dispersion in type 2 diabetes. *Indian Heart J.* 2000;52(4):421-6. doi: 10.1016/S0019-4832(00)80029-5.
8. Jermendy G, Toth L, Voros P, Koltai MZ, Pogatsa G. Cardiac autonomic neuropathy and QT interval length. A follow-up study in diabetic patients. *Acta Cardiol.* 1991;46(2):189-200. doi: 10.1080/00015385.1991.11716612.
9. Doelman CJ, Oude Elberink JN, Miedema K, et al. Orthostatic hypotension in poorly regulated NIDDM. *Diabetes Care*. 1996;19:542. doi: 10.2337/diacare.19.5.542.
10. Koçer A, Aktürk Z, Maden E, Taşçı A. Orthostatic Hypotension and Heart Rate Variability as Signs of Cardiac Autonomic Neuropathy in Diabetes Mellitus. *Eur J Gen Med.* 2005;2(1):5-9. doi: 10.29333/ejgm/82408.