ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

ORIGINAL RESEARCH

Cardiac Autonomic Neuropathy in Type 2 Diabetes Mellitus: A Link to Peripheral Vascular Disease

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Received date: 18 October, 2024 Accepted date: 29 November, 2024

Abstract

Background: Cardiovascular autonomic neuropathy (CAN) is a common and serious complication of type 2 diabetes mellitus (T2DM), characterized by damage to autonomic nerve fibers regulating cardiovascular functions. Peripheral vascular disease (PVD) frequently coexists with CAN, further complicating patient outcomes. This study aimed to evaluate the prevalence and severity of CAN and its association with PVD in patients with T2DM.

Material and methods: A cross-sectional study was conducted involving 215 T2DM patients at a tertiary care centre. CAN was assessed using Ewing's cardiovascular reflex tests and categorized as normal, mild, moderate, or severe. Peripheral vascular status was evaluated using the ankle-brachial index (ABI). Data were analyzed for associations between CAN severity, glycemic control (HbA1c), duration of diabetes, and PVD.

Results: Severe CAN was prevalent in 35.35% of patients, followed by normal CAN (31.63%), moderate CAN (20.47%), and mild CAN (4.65%). Patients with severe CAN had a significantly longer mean diabetes duration (10.63 years) and higher HbA1c levels (10.09) compared to those with normal CAN (3.23 years and 7.68, respectively; $p < 0.05$). A significant inverse relationship was observed between CAN severity and ABI, with severe CAN patients showing the lowest mean ABI (0.45), indicating advanced PVD. Correlation analysis revealed moderate negative associations between diabetes duration and heart rate variability, and strong negative correlations between HbA1c and ABI.

Conclusions: This study highlights the high prevalence of severe CAN in T2DM patients and its strong association with poor glycemic control and advanced PVD. Early screening for CAN and PVD, coupled with stringent glycemic management, is essential to mitigate complications and improve outcomes.

Keywords: Cardiovascular autonomic neuropathy, type 2 diabetes mellitus, peripheral vascular disease, glycemic control, ankle-brachial index

Introduction

Diabetes mellitus (DM) is a global health concern, with its complications contributing significantly to morbidity and mortality. Generalized atherosclerosis of the arterial bed is a

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

hallmark of DM, characterized by early onset and rapid progression. Peripheral arterial disease (PAD) is one of the critical macrovascular complications in diabetes, with the risk being two to three times higher in diabetic individuals compared to non-diabetics.[1] PAD, often presenting as intermittent claudication, not only affects quality of life but is also associated with an increased risk of cardiovascular (CVS) morbidity, mortality, and non-traumatic lower limb amputations.[2, 3]

Cardiac autonomic neuropathy (CAN), a prevalent but often underdiagnosed complication of diabetes, is a form of autonomic dysfunction that adversely affects heart rate control and vascular dynamics. CAN is a significant contributor to the heightened risk of cardiovascular mortality in diabetic patients, primarily due to its association with silent myocardial ischemia, cardiac arrhythmias, and sudden death.[4-6] Studies suggest that changes in autonomic system modulation precede structural atherosclerotic changes, such as increased carotid intima-media thickness, underscoring the role of CAN in the progression of cardiovascular complications in diabetes.[7, 8]

Peripheral vascular disease (PVD), another common manifestation of macrovascular complications in diabetes, results from narrowing or blockage of peripheral blood vessels, predominantly in the lower extremities. Factors such as hyperglycemia, hypertension, dyslipidemia, and poor glycemic control exacerbate PVD, leading to increased risks of infection, limb amputation, and other cardiovascular events.[9, 10] Both CAN and PVD significantly contribute to the increased morbidity and mortality seen in patients with type 2 diabetes mellitus (T2DM).

Despite their significant individual and combined impact, the interrelationship between CAN and PAD in patients with T2DM has not been thoroughly explored. The pathophysiology of CAN involves hyperglycemia-induced neuronal ischemia, oxidative stress, and autoimmune responses, while PVD is driven by endothelial dysfunction, inflammation, and vascular calcification. These overlapping mechanisms suggest a strong interplay between CAN and PVD, which may amplify the risk of adverse cardiovascular outcomes.

Understanding the association between CAN and PVD is crucial for early identification and management of at-risk individuals, potentially reducing the burden of severe complications such as lower limb amputations and cardiovascular deaths. This study aimed to evaluate the correlation between CAN and PAD in patients with T2DM, providing insights into their combined impact on cardiovascular health and emphasizing the importance of comprehensive management strategies.

Material and methods

This observational cross-sectional study was conducted in tertiary care hospital at Kolhapur. The study was carried out over two years after obtaining approval from the Institutional Ethical Committee. A total of 215 adults diagnosed with T2DM as per ICMR guidelines 2018 criteria were enrolled in the study. The exclusion criteria included was patients with T1DM, malignancy, pregnant or lactating mothers, known cases of peripheral vascular diseases, such as Berger's disease and Raynaud's disease,patients with uncontrolled hypertension, smokers and/or tobacco chewers, on medications with pro-arrhythmic or anti-arrhythmic effects on the heart, pre-existing heart disease or known cardiac arrhythmias.

Informed written consent was obtained from all participants in their preferred language before enrolment. The study procedure was explained to ensure cooperation. Each patient underwent a series of five cardiovascular autonomic reflex tests (CARTs) to detect cardiac autonomic neuropathy (CAN). Electrocardiogram (ECG) electrodes were placed to monitor heart rate variations during the tests. The tests used for evaluation included:

Valsalva maneuver (VM): Participants exhaled into a mouthpiece attached to a pressure meter, maintaining a pressure of 40 mmHg for 15 seconds with a closed glottis. The ratio of

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the longest R-R interval after the maneuver to the shortest R-R interval during the maneuver was calculated, and the average of three readings was taken.

Heart Rate Response to Standing: Participants stood up unassisted after lying supine for five minutes. The heart rate was measured at the 15th and 30th beats. The 30:15 ratio, defined as the longest R-R interval at the 30th beat divided by the shortest R-R interval at the 15th beat, was recorded.

Deep Breathing Test (DBT): Participants performed six cycles of slow deep breaths (five seconds for inspiration and five seconds for expiration) while ECG was continuously monitored. Delta heart rate, the difference between the maximum and minimum heart rates during inspiration and expiration, was averaged over six cycles.

Blood Pressure Response to Standing: Following ten minutes of supine rest, basal blood pressure was measured. Participants stood up unaided within three seconds, and blood pressure was measured at intervals of 0.5, 1, 2, 3, and 5 minutes. A drop in systolic blood pressure was recorded.

Blood Pressure Response to Sustained Handgrip: Baseline blood pressure was recorded before the maneuver. Using a handgrip dynamometer, participants performed a maximum voluntary contraction (MVC) and sustained it for four minutes. Blood pressure was measured at the 1st, 2nd, and 4th minutes of contraction. The increase in diastolic blood pressure above baseline was recorded.

Cardiac autonomic dysfunction was classified into five categories based on Ewing and Clarke criteria.

Statistical Analysis

Data were analyzed using SPSS software version 28.0. Continuous variables were expressed as mean and standard deviation, while categorical variables were presented as frequency and percentage. The normality of data distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. As the data were not normally distributed, the independent samples Kruskal-Wallis test was used to compare variables. A p-value of <0.05 was considered statistically significant.

Results

Out of the 215 study participants, 32% exhibited normal CAN, while 35% were classified as severe cases. The distribution of moderate, early, and mild cases was 20%, 8%, and 5%, respectively.

The mean duration of diabetes mellitus (DM) increased with the severity of CAN. Patients with normal CAN had a mean duration of DM of 3.23 ± 2.80 years, compared to 4.04 ± 3.53 years in early CAN, 6.20 ± 4.71 years in mild CAN, 7.73 ± 4.23 years in moderate CAN, and 10.63 ± 5.62 years in severe CAN. A statistically significant difference was observed in the mean duration of DM across different CAN severities (Table 1).

Table 1. Comparison of duration of diabetes according to the severity of CAN

Comparison of duration of DM					
CAN severity	**Test Statistic**	**Standard Error**	**Standard Test Statistic**	**Significance**	**P-value**
Normal vs early	-11.162	16.812	-0.664	0.507	1.000
Normal vs mild	-43.729	20.999	-2.082	0.037	0.373
Normal vs moderate	-64.120	11.996	-5.345	<0.001	0.000
Normal vs severe	-88.378	10.349	-8.539	0.000	0.000
Early vs mild	-32.568	24.709	-1.318	0.187	1.000
Early vs moderate	-52.959	17.706	-2.991	0.003	0.028

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Early vs severe	-77.216	16.634	-4.642	<0.001	0.000
Mild vs moderate	-20.391	21.720	-0.939	0.348	1.000
Mild vs severe	-44.649	20.857	-2.141	0.032	0.323
Moderate vs severe	-24.258	11.745	-2.065	0.039	0.389

The mean ABI was also significantly lower in patients with greater CAN severity. Normal CAN cases had an ABI of 1.11 ± 0.19, while early CAN was associated with a mean ABI of 1.05 ± 0.23. For mild, moderate, and severe CAN cases, the ABI values were 0.88 ± 0.06, 0.75 ± 0.21, and 0.45 ± 0.21, respectively. Significant reductions in ABI were noted in moderate and severe CAN cases compared to normal and early CAN (Table 2).

Table 2. Comparison of ABI according to CAN severity

Comparison of ABI					
CAN severity	**Test Statistic**	**Standard Error**	**Standard Test Statistic**	**Significance**	**P-value**
Normal vs early	10.713	16.789	0.638	0.523	1.000
Normal vs mild	43.790	20.970	2.088	0.037	0.368
Normal vs moderate	68.628	11.979	5.729	<0.001	0.000
Normal vs severe	118.705	10.335	11.486	0.000	0.000
Early vs mild	33.076	24.675	1.340	0.180	1.000
Early vs moderate	57.915	17.681	3.276	0.001	0.011
Early vs severe	107.992	16.612	6.501	<0.001	0.000
Mild vs moderate	24.839	21.690	1.145	0.252	1.000
Mild vs severe	74.916	20.828	3.597	<0.001	0.003
Moderate vs severe	50.077	11.729	4.270	<0.001	0.000

Duration of DM demonstrated no significant correlation with heart rate (HR) response during deep breathing ($r = 0.10$, $p = 0.078$) or resting HR response ($r = 0.01$, $p = 0.471$). However, moderate negative correlations were observed with HR response during standing ($r = -0.17$, $p = 0.006$) and the Valsalva maneuver ($r = -0.18$, $p = 0.003$). Similarly, duration of DM showed negative correlations with BP during sustained handgrip ($r = -0.22$, $p = 0.001$) and ABI ($r = -0.62$, $p < 0.001$), indicating worsening autonomic function with prolonged diabetes duration. HbA1c levels were strongly negatively correlated with ABI ($r = -0.72$, $p < 0.001$), signifying greater reductions in ABI with higher HbA1c values (Table 3).

Table 3. Correlation between duration of DM, HbA1c, and various clinical parameters

Correlation variables		**Correlation coefficient (r)**	**T statistic**	**P value**
Duration of Diabetes	HR(RES)	0.01	0.07	0.471
Duration of Diabetes	HR(DB)	0.10	1.43	0.078
Duration of Diabetes	HR(STD)	-0.17	-2.55	0.006
Duration of Diabetes	HR(VAL)	-0.18	-2.74	0.003
Duration of Diabetes	BP(PH)	0.13	1.94	0.027
Duration of Diabetes	BP(HG)	-0.22	-3.26	0.001
Duration of Diabetes	ABI	-0.62	-11.50	<0.001
HbA1c	ABI	-0.72	-15.13	<0.001

Discussion

The present study aimed to evaluate the prevalence and severity of CAN among patients with T2DM and its association with PVD.Our findings underscore the intricate interplay between

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 12, 2024

autonomic neuropathy and peripheral vascular complications, emphasizing the need for early detection and comprehensive management strategies.

The distribution of CAN severity among the participants revealed a significant burden of severe cases (35%), followed by normal autonomic function (32%), early CAN (8%) moderate CAN (20%), and mild CAN (5%). This prevalence highlights the advanced stage of autonomic dysfunction in a considerable proportion of T2DM patients. Early detection and timely intervention are crucial to mitigate the progression of CAN and its associated complications.Our findings differ from those of Haq T et al., who reported higher rates of severe CAN (59.68%), with early and definitive CAN at 14.52% and 26.67%, respectively.[11] Similarly, Karthikeyan A et al. observed that 57.1% of patients had early CAN, while 28.6% and 14.3% had definitive and no CAN, respectively.[12] These variations may attributed from differences in study populations, diagnostic criteria, or geographic and environmental factors.

A strong correlation was observed between diabetes duration and CAN severity. Patients with severe CAN had an average diabetes duration of 10.63 years, significantly longer than those with normal CAN (3.23 years). This finding aligns with existing literature suggesting that chronic hyperglycemia leads to cumulative damage to the autonomic nervous system, contributing to the progression of CAN.[12-15]

A significant relationship was observed between CAN severity and ankle-brachial index (ABI) values. Patients with severe CAN exhibited the lowest mean ABI (0.45), indicative of advanced PVD, while those with normal CAN had the highest ABI (1.11). This interrelationship suggests that autonomic dysfunction exacerbates peripheral vascular complications. Similar findings were reported by Moțățăianu A et al., supporting the hypothesis that advanced autonomic dysfunction correlates with worsening peripheral vascular health.[15]

Our analysis demonstrated moderate negative correlations between diabetes duration and heart rate variability parameters, such as HR (STD) and HR (VAL), indicating reduced autonomic function over time. Furthermore, the negative correlation between HbA1c and ABI underscores the detrimental impact of poor glycemic control on peripheral vascular health. These findings highlight the interconnected nature of autonomic neuropathy, glycemic control, and vascular complications in diabetes management.

Our study highlights the significant burden of severe CAN in T2DM patients and its strong association with glycemic control and PVD. The findings underscore the importance of early screening for CAN and PVD in diabetic patients, coupled with effective glycemic management to reduce the risk of severe complications.

Conclusion

This study provides significant insights into the prevalence and severity of CAN in T2DM patients and its association with PVD. Early detection, stringent glycemic control, and comprehensive management of diabetes complications are essential to mitigate the progression of autonomic and vascular dysfunction. Future research should focus on longitudinal studies and multi-centre designs to validate these findings and expand their applicability.

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