Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/r6923396

PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN DIABETIC PATIENTS

Dr. Usham Dharmaraja Meetei[1], Dr. Leisangthem Tarinita Devi[2*]

[1]Associate Professor, Department of Pharmacology, Regional Institute of Medical Sciences, Imphal, Manipur, India.
[2*]Associate Professor, Department of Pharmacology, Regional Institute of Medical Sciences, Imphal, Manipur, India.

Corresponding Author: Dr. Leisangthem Tarinita Devi
*Associate Professor, Department of Pharmacology, Regional Institute of Medical Sciences, Imphal, Manipur, India.

ABSTRACT

Background: Diabetic autonomic neuropathy is a stealthy complication of diabetes. CAN is usually detected at a subclinical stage by various tests of autonomic reflexes. Patients with diabetic autonomic neuropathy have three times higher mortality rates than diabetics without autonomic neuropathy. The purpose of this study was to determine the prevalence of cardiac autonomic neuropathy in type 2 diabetes mellitus patients, its early detection with simple bedside tests, and its association with the duration of diabetes.

Methods: 50 patients with diabetes without any complications presenting to the OPD over a period of one year were included in the study. Presence of cardiac autonomic neuropathy was assessed by doing the following tests: Heart rate variations during deep breathing, Heart rate changes from supine to standing, heart rate changes during Valsalva maneuver, presence of postural hypotension and diastolic BP in response to sustained hand grip.

Results: 12 (24%) of the patients had cardiac autonomic neuropathy, and 38 (76%) of the patients had either 1 or no tests positive while testing for cardiac autonomic neuropathy. Out of 17 patients with diabetes of duration >5 years, 9 (52.94%) had evidence of CAN, while of the remaining 33 patients with diabetes of duration <5 years, 3 (9%) had CAN. Postural dizziness was found in 16 (32%) and was the most common of all the autonomic symptoms. Other symptoms were gastroparesis 12 (24%), nocturnal diarrhea 4 (8%), sudomotor disturbances 11 (24%), neurogenic bladder 9 (18%), and weak erection. Out of 34 patients with BMI <25, only 3 (8%) had CAN, and out of 16 patients with BMI >25, 9 (56%) had CAN. Out of 12 patients with CAN, 6 (50%) had albuminuria, and out of 38 patients without CAN, 8 (21%) had albuminuria. Based on the tests conducted, 9 out of 27 (28.57%) of the patients with type 2 diabetes had CAN, whereas only 3 out of 13 (13.63%) of the type 1 diabetics had CAN.

Conclusion: The prevalence of cardiac autonomic neuropathy was increased with the increase in duration of diabetes. Patients who were overweight had higher incidence of cardiac autonomic neuropathy. There was no corelation between the sex of the patient and the prevalence of cardiac autonomic neuropathy.

Keywords: Cardiac Autonomic Neuropathy, Diabetes, Bedside Tests.

INTRODUCTION

Diabetes mellitus is a growing concern among the population all over the world, not only because of the metabolic consequences associated with it but also due to the chronic complications, especially nephropathy, retinopathy, and neuropathy. Further, diabetes is associated with increased mortality and morbidity, mostly due to coronary heart disease, cerebrovascular disease, and peripheral vascular disease. Besides these well-known complications, diabetic autonomic neuropathy also contributes to increasing mortality and morbidity. Diabetic autonomic neuropathy is a stealthy complication of diabetes, developing slowly over the years and quietly robbing diabetic patients of their ability to sense when they are likely to have a heart attack or become hypoglycemic. It impairs the ability to conduct activities of daily living, lowers quality of life, and increases the risk of death.[1]

Patients with diabetic autonomic neuropathy have three times higher mortality rates than diabetics without autonomic neuropathy over a 5-year period. Leading causes of mortality are heart disease and nephropathy. Diabetic autonomic neuropathy can also contribute to the progression of cardiovascular disease and diabetic neuropathy. Cardiac autonomic neuropathy causes abnormalities of heart rate control and vascular dynamics. It has been linked to postural hypotension, exercise intolerance, enhanced intraoperative cardiovascular liability, asymptomatic ischemia and myocardial infarction, and decreased survival after myocardial infarction. CAN is usually detected at a subclinical stage by various tests of autonomic reflexes.[2] The American Diabetes Association recommends the use of Ewing tests in the diagnosis of CAN.[3] These autonomic function tests are noninvasive and do not require sophisticated equipment, making them of great clinical and prognostic importance. The aim of this study is to determine the prevalence of cardiac autonomic neuropathy in type 2 diabetes mellitus patients, its early detection with simple bedside tests, and its association with the duration of diabetes. This study may help in identifying individuals with asymptomatic CAN, who would be at a greater risk of developing life-threatening complications, so that specific steps can be taken for their prevention.

MATERIALS & METHODS

50 patients with diabetes without any complications presenting to the OPD over a period of one year were included in the study. Diabetics with coronary artery disease, hypertension (160/90 mm Hg), heart failure, respiratory disease, anemia, fever, and neuropathy (due to other causes) patients on vasodilators, antihypertensives, neuroleptics, or antidepressants were excluded from the study.

Patients were assessed for other complications, like peripheral vascular diseases, ophthalmological assessment, and overt albuminuria. Overt autonomic neuropathy was assessed based on symptomatic postural hypotension, gastroparesis, sudomotor disorders, urinary symptoms, and erectile dysfunction. Presence of cardiac autonomic neuropathy was assessed by doing the following tests:

- Heart rate variations during deep breathing,
- Heart rate changes from supine to standing
- Heart rate changes during Valsalva maneuver
- Presence of postural hypotension.
- Diastolic BP in response to sustained hand grip.

RESULTS

The total number of patients in the study was 50. 12 (24%) of the patients had cardiac autonomic neuropathy, and 38 (76%) of the patients had either 1 or no tests positive while testing for cardiac autonomic neuropathy. Out of 50 patients, 36 (72%) were male and 14 (28%) were female. Out of 36 male patients, 7 (14%) had cardiac autonomic neuropathy, and 3 female patients (6%) had cardiac autonomic neuropathy. Out of 17 patients with diabetes of duration >5 years, 9 (52.94%) had evidence of CAN, while of the remaining 33 patients with diabetes of duration <5 years, 3 (9%) had CAN.

Presence or absence of autonomic symptoms was recorded in all 50 patients. Symptoms of postural dizziness were found in 16 (32%) and was commonest of all the autonomic symptoms. Other symptoms were gastroparesis 12 (24%), nocturnal diarrhea 4 (8%), sudomotor disturbances 11 (24%), neurogenic bladder 9 (18%), and weak erection. The percentage of symptoms was higher in type 1

than in type 2 diabetics. About 60% of the patients had one or more symptoms suggestive of overt autonomic neuropathy. The prevalence of overt dysautonomia was also high in patients with clinical signs and symptoms. In type 2 patients, BMI was very similar in patients with and those without dysautonomia.

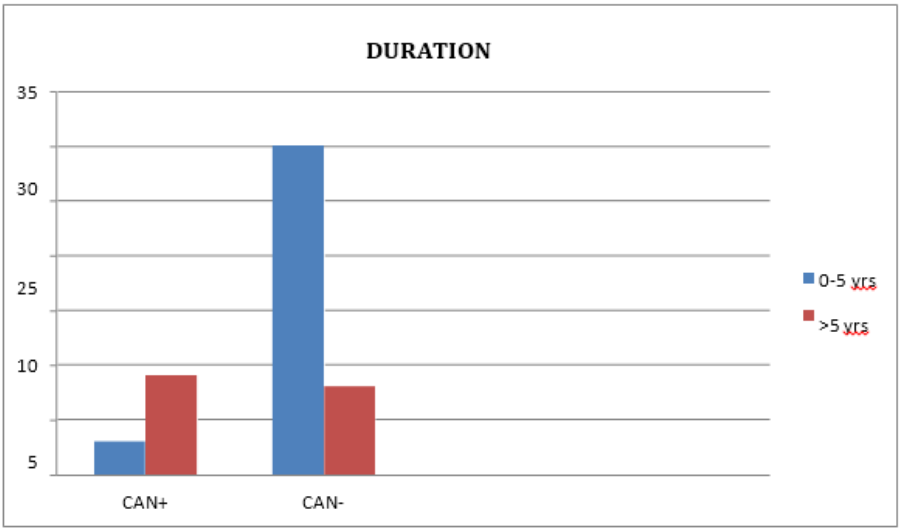

Figure 1

Out of the 50 patients, 34 (68%) had a BMI <25% and 16 (32%) had a BMI >25%. Out of 34 patients with BMI <25, only 3 (8%) had CAN, and out of 16 patients with BMI >25, 9 (56%) had CAN.
Out of 50 patients, only 14 (24%) had postural dizziness, whereas 36 (72%) did not have dizziness. Out of 14 patients with CAN, 9 (64%) had postural dizziness, whereas out of 36 patients without CAN, 5 (13.1%) had postural dizziness.

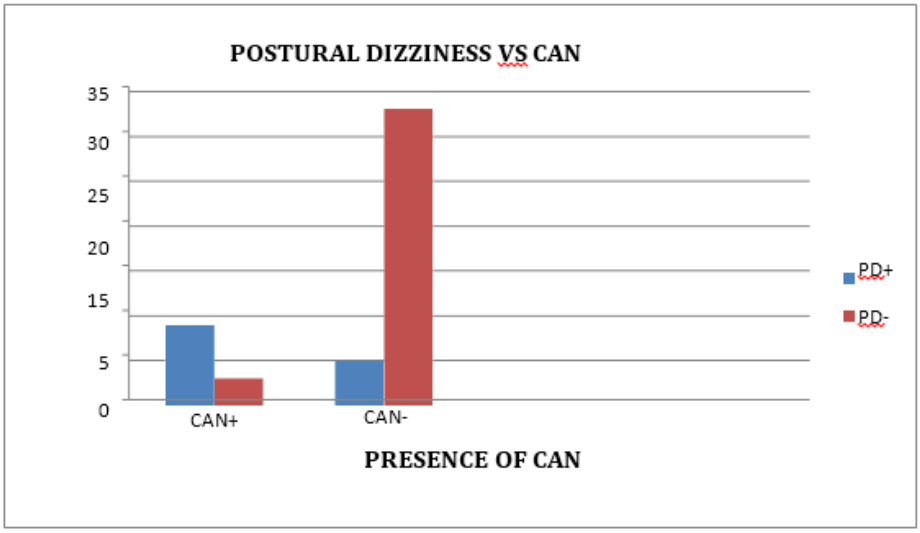

Figure 2

Out of 50 patients, only 14 (28%) had albuminuria, whereas 36 (72%) did not have albuminuria. Out of 12 patients with CAN, 6 (50%) had albuminuria, and out of 38 patients without CAN, 8 (21%) had albuminuria.

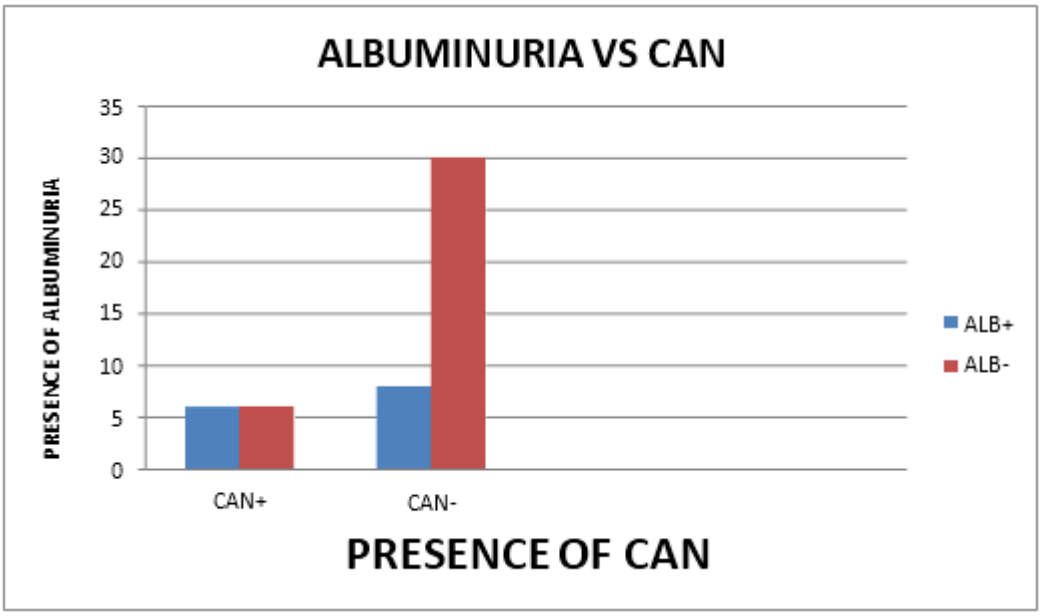

Figure 3

Out of 50 patients, 22 (44%) had evidence of retinopathy, whereas 28 (56%) did not have retinopathy. Out of 22 patients with retinopathy, 9 (40%) had CAN, and out of 28 patients without retinopathy, 5 (17%) had CAN.

Presence of abnormalities in a minimum of two tests was essential for diagnosis of CAN. 9 out of 27 (28.57%) of the patients with type 2 diabetes had CAN, whereas only 3 out of 13 (13.63%) of the type 1 diabetics had CAN. Results of the cardiac autonomic function tests performed are as follows.

Test		**Type 1**	**Type 2**
HRV to Standing	12	3	9
DB on Heart Rate	16	5	11
Valsalva	10	1	9
Postural Hypotension	6	0	6
DBP to Hand Grip	5	0	5

Table 1: Cardiac autonomic function tests results

DISCUSSION

A number of easy tests based on cardiovascular reflexes can be used to evaluate the autonomic nervous system's integrity. These tests rely on how the blood pressure and heart rate react to various stimuli.[4]

In diabetic individuals, CAN is a seriously incapacitating yet underdiagnosed illness. According to the Diabetes Control and Complications Trial's main preventive cohort, the prevalence might vary from 2.5% to 90% of individuals with type 1 diabetes. Orthostatic hypotension and myocardial infarction are examples of clinical presentations.[5] Silent ischemia in diabetic patients may result from CAN. Altered pain thresholds, sub-threshold ischemia not sufficient to induce pain, and dysfunction of the afferent cardiac autonomic nerve fibers have all been suggested as possible mechanisms.[6] Clinical manifestations of CAN depend on disease progression. The first sign of subclinical CAN is decreased HR variability. In clinical CAN, resting tachycardia and decreased exercise tolerance may be observed in the early stages as sympathetic tone increases. Orthostatic hypotension and sympathetic denervation of the heart are manifestations of severe CAN. At CAN, other symptoms such as syncope, dizziness, visual abnormalities, frequent falls, and nocturnal hypertension brought on by a paradoxical rise in sympathetic tone may also be noted.[7,8]

The present study included 50 diabetics to assess the prevalence of cardiac autonomic neuropathy. Abnormality in more than one test was considered necessary for diagnosis of CAN. The prevalence

of cardiac autonomic neuropathy was 24% according to this study, which is less than the French multicenter study[9] in which abnormality of only one test was taken for diagnosis of cardiac autonomic neuropathy, whereas in this study impairment of two or more tests was taken for diagnosis of cardiac autonomic neuropathy.

Bhaskar Thakuria et al,[10] evaluated 93 patients with type 2 diabetes for signs of cardiovascular autonomic neuropathy using simple bedside autonomic reflex testing, regardless of the duration of diabetes. Autonomic neuropathy symptoms were present in just 33 individuals. Their study found that 67.7% of people had cardiac autonomic neuropathy overall, with 25.8% having severe autonomic dysfunction and 41.9% having borderline autonomic dysfunction.

In a study involving 60 patients, Murthy ANLN et al,[11] found that 21 (35%) of the diabetic patients had cardiac autonomic neuropathy, 13 (21.6%) exhibited early signs of CAN, and 26 (43.3%) did not have CAN. In contrast, CAN was absent in 86.6% of controls and present in 2 (3.3%) of controls. There was statistical significance in this observation. The average age of the early and definitive CANs was 52 ± 6.17 and 57.38 ± 7.2 years, respectively. Among the diabetics, there was a statistically significant correlation (p value - 0.0001) between CAN and growing age.

Out of 36 male patients in the present study, 7 (14%) had cardiac autonomic neuropathy, and 3 female patients (6%) had cardiac autonomic neuropathy. Symptoms of postural dizziness were found in 16 (32%) and were the most common of all the autonomic symptoms in our study. Other symptoms were gastroparesis 12 (24%), nocturnal diarrhea 4 (8%), sudomotor disturbances 11 (24%), neurogenic bladder 9 (18%), and weak erection. The percentage of symptoms was higher in type 1 than in type 2 diabetics. One or more symptoms that were suggestive of overt autonomic neuropathy were present in about 60% of the patients. Patients who had clinical signs and symptoms also had a significant rate of overt dysautonomia. 14% of the patients experienced postural dizziness, which did not correspond with a higher postural drop in blood pressure. This shows that severe sympathetic dysfunction is a less common consequence than parasympathetic dysfunction. Also, parasympathetic dysfunction occurs early in the disease as compared to sympathetic dysfunction, adding credence to the fact that autonomic neuropathy is a length-dependent neuropathy.

In the Ganesamoorthy Karupasamy et al.,[12] study, nocturnal diarrhoea and constipation affected 5% (1/19) of individuals under 50. Nocturnal diarrhea and constipation were observed in 27.6% (8/29) in the 50–60 age group. Of the patients, 40% (24/60) had peripheral neuropathy. The number of patients with observed pupillary alterations was 46.6% (28/60). Pupillary alterations were present in 95.8% (23/24) of patients with peripheral neuropathy. 36.7% of patients had postural hypotension (22/60).

Out of 17 patients with diabetes of duration >5 years, 9 (52.94%) had evidence of CAN, while of the remaining 33 patients with diabetes of duration <5 years, 3 (9%) had CAN. As in various previous studies, with increasing duration of diabetes, the prevalence of diabetic neuropathy increased, which points to the importance of interpreting the tests according to the age, but autonomic neuropathy can occur early in diabetes.

4% (1/24) of individuals with diabetes for less than five years exhibited irregular sweating, according to Ganesamoorthy Karupasamy et al., 44.8% (13/29) of patients who had diabetes for five to ten years experienced irregular sweating. Sweating abnormalities were observed in 57.1% (4/7) of patients with diabetes for more than 10 years, which was indicative of the beginning of autonomic neuropathy.

According to Bhaskar Thakuria et al.,[10] the greatest majority of patients had altered heart rate responses to standing and Valsalva. In line with earlier similar studies by Mohan et al.,[13] which revealed that 53.8% of patients with more than 10 years of diabetes had an aberrant CAN score, the prevalence of autonomic neuropathy showed an increasing trend with increasing duration of diabetes. According to Satchi A. Surendran et al.,[14] 58% of patients with type 2 diabetes mellitus had CAN.

The average duration of diabetes in cases was 7.28 + 3.61 years, according to a study by Murthy ANLN et al.,[11] it was found that diabetics' chance of developing CAN increased with the length of their diabetes. This result was consistent with other earlier investigations that were carried out to determine the frequency of CAN. According to research by Mohan et al.,[13] the longer a person has had diabetes, the higher the prevalence of CAN. According to this study, diabetics had higher mean RHRs, higher SBPs, and higher DBPs than non-diabetics, all of which were statistically significant.

A constant heart rate and resting tachycardia are typical late findings in diabetes patients with vagal dysfunction.[15]

The mean drop in blood pressure when standing was -20.86 millimeters of mercury in the study by Ganesamoorthy Karupasamy,[12] while the control group experienced a drop of 9.8 millimeters of mercury. 36.7% (22/60) of the patients experienced a drop in blood pressure of more than 30 millimeters of mercury. Additionally, 26.7% (26/60) of the study group's patients exhibited borderline mercury falls between 11 and 29 millimeters. The research group's mean increase in diastolic blood pressure was 8.14, whereas the control group's was 16.4. Of the patients, 46.7% (28/60) experienced a blood pressure increase of less than 10 mm of mercury. Additionally, 23.3% (14/60) saw a slight increase in blood pressure of 10–16 millimeters of mercury. The mean drop in SBP in participants with definite CAN was 12.78 + 6.02 mm Hg, which was statistically significant (p value <0.0001) when compared to 5.53 + 1.58 mm Hg in subjects without CAN in the Murthy ANLN et al.,[13] study's lying to standing test, which assesses the sympathetic component. In the Hand Grip Test, the average rise in DBP in cases was 15.8 + 3.91 mm Hg, which was less than the 18.1 + 2.00 mm Hg in controls. Comparing diabetic patients to healthy volunteers revealed that this result was statistically significant. Diabetics' blood pressure response to prolonged handgrip was considerably lower. The difference in DBP to sustained handgrip between well-controlled and poorly controlled diabetics, as well as between controls and well-controlled and poorly controlled diabetics, was extremely significant. In their study of the impact of prolonged hand grip on blood pressure variation in 90 participants, Popovic et al., found that type II diabetics had aberrant blood pressure fluctuation in comparison to other groups.[16]

About 43.5% of the participants with CAN in the Murthy ANLN et al,[11] study had abnormal deep breathing test results, and CAN was missing in 96.2% of the subjects with normal DBT results. There was statistical significance in this. When compared to controls, DBT was considerably lower (p<0.0001) in both diabetic groups. This demonstrates that diabetics have gradual parasympathetic dysfunction, with poorly managed diabetics experiencing this more than others. In this study, the valsalva ratio was aberrant in 60.9% of the CAN individuals and nonexistent in 88.7% of the normal VR subjects. The LST (30:15) ratio was abnormal in about 34.8% of CAN subjects, while it was absent in 94.4% of normal LST (30:15) R test subjects. Using a 24-hour ECG recording, Spallone V et al.,[17] measured the HRV (Heart Rate Variability) from lying to standing in 35 normotensive diabetic participants as part of a cardiovascular autonomic function test. They discovered a significant difference in HRV between the two states (P<0.02).

Five of the 93 patients in the Bhaskar Thakuria et al.,[10] study had abnormal results (score 2) for heart rate variability to deep breathing, fourteen for heart rate response to Valsalva, five for heart rate response to standing, five for blood pressure response to hand grip, and five for abnormal blood pressure response to standing. Of the 93, 11.4% of those with diabetes for 10 years had abnormal CAN scores. Chi-square tests revealed a strong correlation between CAN scores and the length of DM.

Tests for cardiac autonomic neuropathy function and blood sugar levels did not correlate in this study. When BMI was considered, patients, especially Type 2 diabetics, with BMI >25 had a higher prevalence of cardiac autonomic neuropathy than in patients with BMI <25. Obese subjects may have restricted lung excursions leading to attenuation of chest reflexes. Patients with newly diagnosed type 2 diabetes may be most affected by this component, as seen by their peripheral autonomic dysfunction.

Out of 12 patients with CAN in the present study, 6 (50%) had albuminuria, and out of 38 patients without CAN, 8 (21%) had albuminuria. In the study by Beijers et al.,[18] after adjustments for age, sex, glucose tolerance status, and other risk factors, C-AD was associated with microalbuminuria (β = 0.16 [95% CI 0.01–0.33]), and both microalbuminuria (RR 2.09 [1.07–4.08]) and C-AD (1.74 [1.04–2.89]) were associated with cardiovascular mortality.

55% of the patients in the Ganesamoorthy Karupasamy et al.,[12] research had at least one autonomic dysfunction symptom. They also found that autonomic neuropathy and stomach function are

improved by proper glycemic management. Smaller, more frequent meals that are high in fiber, easy to digest, low in fat, and have been shown to reduce gastroparesis symptoms.[19]

In their study, J.M. Papapachan, J. Sebastian, et al.,[20] also demonstrated that the incidence of diabetic autonomic neuropathy rose with duration and poor glycemic management. According to early research findings, the best strategy to postpone the development of CAN and stop its progression appears to be maintaining close to normal glycemic control. For people with autonomic dysfunction, it is crucial to emphasize strict glycemic management and re-educate the patient about the necessity of frequent monitoring and hypoglycemia.

An association between cardiac autonomic neuropathy and specific microangiopathic complications has been reported many times. Likewise, a significant correlation between cardiac autonomic neuropathy function tests and retinopathy and albuminuria was found in the study. This suggests that autonomic neuropathy may contribute to the development of retinal neovascularization as retinal vessels have receptors of the sympathoadrenal system. Loss of responsiveness of the retinal vessels to metabolic or hemodynamic stimuli could lead to uncontrolled retinal hypo- or hyperperfusion. However, the association between cardiac autonomic neuropathy and proliferative retinopathy may not imply a causative relationship. This suggests that cardiac autonomic neuropathy is only a risk indicator, a marker of processes that underlie retinopathy. Specifically, the aldose reductase pathway may be in charge of the intracellular buildup of sorbitol in retinal pericytes and is implicated in the development of diabetic neuropathy. Microalbuminuria is also linked to the prevalence of cardiac autonomic neuropathy. It is thought that the kidney may become more susceptible to the effects of systemic blood pressure if the brain's control over renal hemodynamics is lost.

The major limitation of the present study was that it was done in a small group and the results may not reflect the findings in the whole population.

CONCLUSION

Cardiac autonomic neuropathy is one of the commonest but most overlooked complications of diabetes mellitus. With an increase in the duration of diabetes, the prevalence of cardiac autonomic neuropathy increases. In the present study, there was an increase in the incidence of retinopathy and albuminuria among patients with cardiac autonomic neuropathy. Patients who were overweight had a higher prevalence of cardiac autonomic neuropathy. There was no correlation between the sex of the patient and the prevalence of cardiac autonomic neuropathy. Simple bedside tests provide an objective guide for the early identification of patients at higher risk of developing life-threatening complications of CAN so that steps can be taken to halt disease progression, modify lifestyle, and initiate exercise programs to improve the quality of life.

REFERENCES

[1] Report and Recommendations of the San Antonio Conference on Diabetic Neuropathy. Diabetes 1988;37(7):1000-4.
[2] Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. Br Med J 1982;285:916-18.
[3] Boulton AJM, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care 2005;28(4):956-62.
[4] Larsen PR, Kronenberg HM, Melmed S, Polonsky KS. Williams's textbook of endocrinology. 10th edn. Saunders 2002.
[5] Agashe S, Petak S. Cardiac autonomic neuropathy in diabetes mellitus. Methodist Debakey Cardiovasc J 2018;14(4):251-6.
[6] Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation 2007;115(3):387-97.
[7] Dimitropoulos G, Tahrani AA, Stevens MJ. Cardiac autonomic neuropathy in patients with diabetes mellitus. World J Diabetes 2014;5(1):17-39.

[8] Balcıoğlu AS, Müderrisoğlu H. Diabetes and cardiac autonomic neuropathy: clinical manifestations, cardiovascular consequences, diagnosis and treatment. Diabetes Care 2010;33(2):434-41.
[9] Ziegler D. Diabetic cardiovascular autonomic neuropathy: prognosis, diagnosis and treatment. Diabetes Metab Rev 1994;10:339-83.
[10] Thakuria B, Deka BP. Prevalence of cardiovascular autonomic neuropathy among type 2 diabetes mellitus patients. International Journal of Medical Science in Clinical Research and Review 2023;6(2):384-91.
[11] Murthy ANLN, Lakshmaiah V, Aswathanarayana A. Study of cardiac autonomic neuropathy in type 2 diabetes mellitus. J Clin Biomed Sci 2018;8(2):49-56.
[12] Karupasamy G, Karthick K. Autonomic dysfunction in cardiovascular system of type 2 diabetic mellitus – a bedside evaluation. IAIM 2018;5(3):30-3.
[13] Mohan V, Sastry NG, Premalatha G. Autonomic Neuropathy in NIDDM and fibrocalculus pancreatic diabetes in south India, Diabet Med 1996;13(12):1038-43.
[14] Surendran SA. A Study on Prevalence of Cardiac Autonomic Neuropathy in Type 2 Diabetes Mellitus and use of QTc interval in its prediction. Medicine 2017.
[15] Hage FG, Iskandrian AE. Cardiovascular imaging in diabetes mellitus. J Nucl Cardiol 2011;18:959–65.
[16] Popović-Pejičić S, Todorović-Đilas L, Pantelinac P. The role of autonomic cardiovascular neuropathy in pathogenesis of ischemic heart disease in patients with diabetes mellitus. Med Pregl 2006;59(3-4):118-23.
[17] Spallone V, Bellavere F, Scionti L, Maule S, Quadri R, Bax G, et al. Recommendations for the use of cardiovascular tests in diagnosing diabetic autonomic neuropathy. Nutr Metab Cardiovasc Dis 2011;21(1):69-78.
[18] Beijers HJ, Ferreira I, Bravenboer B, Dekker JM, Nijpels G, Heine RJ, et al. Microalbuminuria and cardiovascular autonomic dysfunction are independently associated with cardiovascular mortality: evidence for distinct pathways: the Hoorn Study. Diabetes Care 2009;32(9):1698-703.
[19] Ziegler D. Cardiovascular autonomic neuropathy: clinical manifestations and measurement. Diabetes Rev 1999;7:342-57.
[20] Pappachan JM, Sebastian J, Bino BC, Jayaprakash K, Vijayakumar K, Sujathan P, et al. Cardiac autonomic neuropathy in diabetes mellitus: prevalence, risk factors and utility of corrected QT interval in the ECG for its diagnosis. Postgraduate Medical Journal 2008;84(990):205-10.