Section: General Medicine

Original Research Article

A CROSS-SECTIONAL OBSERVATIONAL STUDY OF CARDIAC AUTONOMIC NEUROPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ITS ASSOCIATION WITH PERIPHERAL NEUROPATHY

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ABSTRACT

Background: The subsequent Message contains a number of Medical Acronyms. Each acronym shall be identified in bold print within the Message. No new acronyms will be used. The first three lines contain the phrase "Diabetes Mellitus (DM)" as the acronym for Diabetes Mellitus (DM). However, in this instance, as it is being used to refer to a specific type of Diabetes Mellitus (T2DM), it shall appear in Parenthesis After, i.e. T2DM.The last two lines of the article are the references to those who have diabetes. Therefore, their First Names have also been changed to include only the Initials. Individuals with (T2DM) may suffer from a life-threatening condition known as Cardiac Autonomic Neuropathy (CAN). CAN may lead to significant cardiovascular problems and also death. CAN typically exists along with other diabetic conditions, including diabetic peripheral neuropathy (DPN). The same underlying pathologic processes (chronic hyperglycemia, increased oxidative stress, and microvascular dysfunction) lead to both CAN and DPN. The diagnostic process to identify CAN includes the assessment of cardiac autonomic function to include sympathetic and parasympathetic stimulation. The relationship of CAN and DPN must be identified and the risks assigned to each to ensure timely treatment of patients with CAN. The Complete Medical Report/Final Medical Report on the Diabetes Diagnosis is currently pending; however, as there is not yet any documented association between CAN and DPN's cardiovascular conditions, early diagnosis of CAN is critical to support the risk assessment and provide timely care of patient(s) with CAN. **Objectives:** To determine the prevalence of cardiac autonomic neuropathy in patients with type 2 diabetes mellitus and to evaluate its association with peripheral neuropathy.

Materials and Methods: The present study was conducted in an academic tertiary care center. Over a year, 185 individuals (aged between 35-70) diagnosed with T2DM were enrolled through the outpatient and inpatient departments by means of simple random sampling methods. The evaluation of cardiac autonomic neuropathy (CAN) was accomplished through standard tests for cardiovascular autonomic reflexes (CARs): heart rate variability during deep breathing; Valsalva manoeuvre; heart rate (HR) adjustment to the upright position (30:15 ratio); and blood pressure (BP) adjustment to the upright position and sustained handgrip (SHG). Peripheral neuropathy (PN) was assessed via clinical examination and the Neuropathy Disability Score (NDS), along with testing of vibration perception threshold (VPT) and monofilament testing. In addition, information on the demographic, clinical, and biochemical parameters of the participants was collected as well.

Results: A study involving 185 subjects found that one-third of those individuals had definite CAN (33.5%), one-fifth had early CAN (18.4%), one-seventh had the most severe form of CAN (14.6%), and one-third exhibited normal autonomic function (33.5%). neuropathy was present in 70.8% of studied subjects. There was a significant, strong relationship between CAN status and peripheral neuropathy ($\chi^2 = 121.104$, df = 3, $p < 0.001$), with all subjects having Definite or Severe CAN demonstrating some degree of peripheral neuropathy, while the majority of subjects with Normal Autonomic Function demonstrated low NDS scores for PNNs. There was a statistically significant correlation between increased age and diabetes duration with increased severity of CAN.

Conclusion: Autonomic neuropathy affecting the heart is common among individuals suffering from Type 2 Diabetes Mellitus (T2DM) and is closely associated with peripheral neuropathy. Frequently, both conditions appear together; consequently, the routine examinations of all patients diagnosed with T2DM should include assessing for signs/symptoms of both forms of neuropathy so as to identify them at an earlier point to reduce cardiovascular complications through appropriate intervention.

Keywords: Cardiac autonomic neuropathy; Type 2 diabetes mellitus; Peripheral neuropathy; Neuropathy Disability Score; Vibration perception threshold; Autonomic function tests; Cross-sectional study.

INTRODUCTION

T2DM, also referred to as Type 2 diabetes mellitus, is currently a worldwide concern with an increasing number of new cases occurring each year and also carries a heavy burden of long-term complications.[1] Among these complications of diabetes mellitus, the most frequently seen and disabling consequence of diabetic neuropathy is a diabetic neuropathic condition commonly referred to as diabetic neuropathy of the autonomic nervous system.[2] While diabetic peripheral neuropathy (DPN) is very commonly diagnosed for its sensory and motor symptoms, the existence of cardiac autonomic neuropathy (CAN) frequently goes undetected and usually has significant effects on clinical outcomes.[3] The cardiac autonomic nerve fibers innervate both the heart and blood vessels, resulting in alterations of heart rate control and vascular dynamics. The clinical significance of cardiac autonomic neuropathy lies in its associated risk of increased cardiovascular morbidity and mortality.[4] For patients with CAN, there is an increased risk of developing resting tachycardia, exercise intolerance, orthostatic hypotension, silent myocardial ischemia, and sudden cardiac death.[5] In addition, CAN is associated with perioperative cardiovascular instability and the poor prognosis of patients with diabetes. Despite the serious consequences of CAN, it typically does not become apparent until the patient's condition has progressed to the stage of symptomatic dysfunction.[6] To determine whether a patient has CAN, standardized cardiovascular autonomic reflex tests must be performed in a structured way on an ongoing basis. Diabetic peripheral neuropathy is one of the most common complications of T2DM and is a major reason for the development of foot ulcers, infections and non-traumatic lower-limb amputations.[7].In assessing the development of diabetic peripheral neuropathy, clinicians use various methods to evaluate diabetic peripheral neuropathy such as the Neuropathy Disability Score (NDS), vibration perception threshold (VPT) and monofilament testing. The pathophysiological mechanisms that result in the progression of both CAN and DPN are similar, including chronic hyperglycemia, oxidative stress, advanced glycation end-products, and microvascular ischemia, indicating that both CAN and DPN may occur concurrently and progress at a similar rate.[8] Several studies have evidenced that when one form of diabetic neuropathy is present it is more likely that at least one other form will also be present; both forms may be the result of the same underlying and systemic process that affects many parts of the nervous system.[9] Currently, in many clinical settings, screening for autonomic neuropathy is not as common as screening for peripheral neuropathy; this difference is especially evident in resource-challenged countries. Because of the lack of routine screening and evaluation for autonomic neuropathy, there is a significant missed opportunity for early risk stratification and early intervention in patients with features of peripheral neuropathy.[10] Standardized cardiovascular autonomic reflex tests that can be used to diagnose and stage CAN include heart rate variability with deep breathing, the Valsalva maneuver, heart rate response to standing, and blood pressure response to standing as well as sustained handgrip exercise.[11] Implementing these autonomic function tests along with existing methods used for peripheral neuropathy assessment allows for a complete assessment of the degree and severity of diabetic neuropathy involvement.[12] Due to the overwhelming burden of diabetes and the associated complications, along with the serious potential side effects of an unknown or unrecognized level of autonomic dysfunction, there is a clear need for research studies that assess the prevalence and degree of cardiac autonomic

neuropathy and how it correlates with peripheral neuropathy among patients with type 2 diabetes mellitus.[13]

The present study was conducted to determine the prevalence of cardiac autonomic neuropathy among patients with type 2 diabetes mellitus and to evaluate the association of cardiac autonomic neuropathy with diabetic peripheral neuropathy through the use of standardized autonomic function tests and peripheral neuropathy assessment tools.

MATERIALS AND METHODS

Study design and setting

A prospective cross-sectional observational design was developed in the Department of General Medicine within a Teaching Hospital. A one year study was developed to assess the prevalence of cardiac autonomic neuropathy (CAN) in type 2 diabetic patients and whether there was a relationship between the occurrence of CAN and diabetic peripheral neuropathy.

Study population

A screening process was conducted to determine eligibility for participation among patients who had Type 2 Diabetes Mellitus (T2DM) at both outpatient and inpatient hospital settings. One hundred eighty-five (185) Individuals between 35 and 70 years of age that met all inclusion criteria and signed an Informed Consent form were accepted and received as participants into this trial.

Inclusion criteria

- Patients diagnosed with type 2 diabetes mellitus
- Age between 35 and 70 years
- Both male and female patients
- Willingness to participate and provide informed written consent

Exclusion criteria

- Patients with known cardiovascular diseases such as ischemic heart disease, arrhythmias, or heart failure
- Patients with conditions known to affect autonomic function (e.g., Parkinson's disease, chronic alcoholism)
- Patients on drugs known to interfere with autonomic function (e.g., beta-blockers, tricyclic antidepressants)
- Patients with acute illness or severe systemic disease at the time of evaluation
- Patients with other causes of peripheral neuropathy unrelated to diabetes

Sample size calculation

The sample size was calculated based on the expected prevalence of cardiac autonomic neuropathy among patients with type 2 diabetes mellitus, using the standard formula for estimating sample size in prevalence studies:

$$n = \frac{Z^2 \times p \times q}{d^2}$$

Where:

- n= required sample size
- Z= standard normal deviate corresponding to 95% confidence level (1.96)
- p= anticipated prevalence of cardiac autonomic neuropathy in T2DM (based on previous studies)
- q= 1 − p
- d= absolute precision (allowable error)

After analyzing previously published prevalence statistics and using a 95 percent confidence interval for adequate levels of precision, the minimum sample size needed to properly evaluate these data points was computed. The initial estimate to determine the proper sample size was based on the need to improve precision when creating estimates and an understanding of potential errors due to exclusions or incompleteness in patient data. The final total number of patients included in study evaluation was one hundred eighty-five patients.

Data collection and clinical evaluation

A comprehensive clinical assessment was performed on all patients included in the study. This included a review of the patient's demographic information, the length of time they have had diabetes, the type of therapy they receive for diabetes, and any significant medical conditions in the past that may relate to diabetes. All patients had a comprehensive physical examination performed and appropriate anthropometric and BP measurements taken.

Assessment of cardiac autonomic neuropathy

Cardiac autonomic function was assessed using standardized cardiovascular autonomic reflex tests:

- Heart rate response to deep breathing
- Heart rate response to standing (30:15 ratio)
- Valsalva maneuver
- Blood pressure response to standing
- Blood pressure response to sustained handgrip

Based on the results of these tests, CAN was classified into stages (normal, early, definite, and severe) according to standard criteria.

Assessment of peripheral neuropathy

Peripheral neuropathy was evaluated using a combination of:

- Detailed neurological examination
- Neuropathy Disability Score (NDS)
- Vibration perception threshold (VPT) testing
- Monofilament testing

Patients were categorized according to the presence and severity of peripheral neuropathy based on these assessments.

Laboratory investigations

Laboratory tests relevant to this study which were performed included fasting and post-prandial plasma glucose, HbA1c (glycosylated hemoglobin), creatinine concentration (mg/dl), lipids (triglycerides and total cholesterol), and routine biochemistry tests if documented in the medical record at the time of testing.

Statistical Analysis

Statistical software was used to analyze data entered into a spreadsheet. Continuous variables were

expressed as either means ± SD or medians where appropriate, while categorical variables were expressed as either frequency or percentage. Chi-square tests were utilized to evaluate the association between categorical variables. A p-value of less than 0.05 was considered statistically significant.

Ethical considerations

Prior to conducting this study, Institutional Ethics Committee Approval was obtained. All Participants provided Written Informed Consent prior to being included in the study. Patient's confidentiality was maintained throughout the course of the study.

RESULTS

Study population and baseline characteristics

A total of 185 patients with type 2 diabetes mellitus were included. The age ranged from 35 to >65 years, with the largest proportion in the 55–65 years group (31.4%). Males constituted 51.4% (n = 95) and females 48.6% (n = 90) of the cohort. Duration of diabetes was <5 years in 35.1%, 5–10 years in 31.9%, 10–15 years in 22.7%, and 15–20 years in 10.3% of patients

Prevalence and grading of cardiac autonomic neuropathy

Based on cardiovascular autonomic reflex tests, patients were classified into four groups: normal autonomic function (n = 62, 33.5%), early CAN (n = 34, 18.4%), definite CAN (n = 62, 33.5%), and severe CAN (n = 27, 14.6%). Thus, nearly two-thirds of the study population had some degree of cardiac autonomic neuropathy

Peripheral neuropathy and its association with CAN

Peripheral neuropathy, assessed using the Neuropathy Disability Score (NDS), was present in 131 patients (70.8%), while 54 patients (29.2%) had low NDS scores (0–2). All patients with definite CAN (62/62) and severe CAN (27/27) had NDS scores in the 3–10 range, indicating moderate to severe peripheral neuropathy. In contrast, 80.6% (50/62) of patients with normal autonomic function had low NDS scores. A strong and statistically significant association was observed between CAN status and peripheral neuropathy ($\chi^2 = 121.104$, df = 3, $p < 0.001$)

Association between age and CAN

There was a clear age-related increase in CAN severity. In the 35–45 years group, 78.3% (36/46) had normal autonomic function and only 4.3% (2/46) had definite CAN. In contrast, in patients aged >65 years, 46.7% (14/30) had definite CAN and only 10.0% (3/30) had normal autonomic function. This association between age group and CAN status was statistically significant ($\chi^2 = 66.345$, df = 9, $p < 0.001$)

Association between duration of diabetes and CAN

Duration of diabetes showed a strong relationship with CAN severity. Among patients with <5 years duration of diabetes, 80.0% (52/65) had normal autonomic function and only 7.7% (5/65) had definite CAN. In contrast, among those with 10–15 years duration, 52.4% (22/42) had definite CAN and 40.5% (17/42) had severe CAN, with no patients having normal autonomic function. This association was highly significant ($\chi^2 = 138.766$, df = 9, $p < 0.001$)

Gender distribution and CAN

Among females (n = 90), 30.0% had definite CAN, 16.7% early CAN, 41.1% normal autonomic function, and 12.2% severe CAN. Among males (n = 95), 36.8% had definite CAN, 20.0% early CAN, 26.3% normal, and 16.8% severe CAN. There was no statistically significant association between gender and CAN status ($\chi^2 = 4.620$, df = 3, $p = 0.202$)

Neuropathy Disability Score (NDS) and CAN

All patients with definite CAN and severe CAN had NDS scores in the 3–10 range, whereas the majority of patients with normal autonomic function had NDS scores 0–2. Early CAN patients predominantly showed intermediate to high NDS scores. The association between NDS category and CAN status was highly significant ($\chi^2 = 121.104$, df = 3, $p < 0.001$)

Diastolic blood pressure response to handgrip and CAN

Blunted diastolic blood pressure (DBP) rise to handgrip (≤10 mmHg) was predominantly observed in patients with severe CAN (94.4%). In contrast, patients with normal and early CAN mostly exhibited DBP rises of 10–15 mmHg. The association between DBP handgrip response and CAN severity was statistically significant ($\chi^2 = 105.182$, df = 9, $p < 0.001$)

Vibration perception threshold (VPT) and CAN

Left foot VPT: Higher VPT values were strongly associated with more severe CAN. Among patients with definite CAN, 71.0% had VPT ≥20 V, and all patients with severe CAN had VPT ≥15 V. In contrast, patients with normal autonomic function were clustered at lower VPT values (≤10 V). This association was highly significant ($\chi^2 = 149.617$, df = 12, $p < 0.001$)

Right foot VPT: A similar graded relationship was observed. Among patients with definite CAN, 77.4% had VPT ≥20 V, and among those with severe CAN, 92.6% had VPT ≥20 V, whereas 74.2% of patients with normal autonomic function had VPT of 5–10 V. This association was also highly significant ($\chi^2 = 174.265$, df = 15, $p < 0.001$)

Orthostatic systolic blood pressure fall and CAN

The magnitude of systolic blood pressure fall on standing increased with CAN severity. Patients with definite CAN predominantly had falls of 15–20 mmHg (74.2%), while those with severe CAN frequently exhibited large drops, with 48.1% showing 25–30 mmHg falls and 29.6% showing >30 mmHg falls. This association between orthostatic SBP fall and CAN status was highly significant ($\chi^2 = 162.674$, df = 15, $p < 0.001$).

A total of 185 patients with type 2 diabetes mellitus were evaluated for cardiac autonomic neuropathy and peripheral neuropathy. The study population

included a wide age range with nearly equal gender distribution and varying durations of diabetes. Cardiac autonomic neuropathy was categorized into normal, early, definite, and severe stages based on standardized autonomic function tests. Peripheral neuropathy was assessed using the Neuropathy Disability Score and vibration perception threshold measurements. A strong and statistically significant association was observed between cardiac autonomic neuropathy and peripheral neuropathy. Increasing age and longer duration of diabetes were associated with greater severity of autonomic dysfunction. The detailed distributions and associations are presented in the following tables.

Table 1: Age distribution of study participants (n = 185)

Age group (years)	Number of patients	Percentage (%)
35–45	46	24.9
45–55	51	27.6
55–65	58	31.4
>65	30	16.2
Total	185	100.0

Table 1 shows the age-wise distribution of patients included in the study.

Table 2: Gender distribution of study participants (n = 185

Gender	Number of patients	Percentage (%)
Female	90	48.6
Male	95	51.4
Total	185	100.0

Table 2 shows the gender-wise distribution of the study population.

Table 3: Duration of diabetes mellitus among study participants (n = 185)

Duration of diabetes (years)	Number of patients	Percentage (%)
<5	65	35.1
5–10	59	31.9
10–15	42	22.7
15–20	19	10.3
Total	185	100.0

Table 3 shows the distribution of patients according to duration of diabetes.

Table 4: Distribution of cardiac autonomic neuropathy status (n = 185)

CAN status	Number of patients	Percentage (%)
Normal	62	33.5
Early CAN	34	18.4
Definite CAN	62	33.5
Severe CAN	27	14.6
Total	185	100.0

Table 4 shows the overall distribution of patients according to CAN status.

Table 5: Association between CAN status and peripheral neuropathy (NDS categories)

CAN status	No PN (NDS 0–2)	Yes PN (NDS 3–10)	Total
Definite CAN	0	62	62
Early CAN	4	30	34
Normal	50	12	62
Severe CAN	0	27	27
Total	54	131	185

Table 5 shows the association between CAN status and presence of peripheral neuropathy.

Table 6: Distribution of CAN status by age group

Age group (years)	Definite CAN	Early CAN	Normal	Severe CAN	Total
35–45	2	8	36	0	46
45–55	22	10	12	7	51
55–65	24	12	11	11	58
>65	14	4	3	9	30
Total	62	34	62	27	185

Table 6 shows the relationship between age groups and severity of CAN.

Table 7: Distribution of CAN status by duration of diabetes mellitus

Duration of diabetes (years)	Definite CAN	Early CAN	Normal	Severe CAN	Total
<5	5	7	52	1	65
5–10	27	20	10	2	59
10–15	22	3	0	17	42
15–20	8	4	0	7	19
Total	62	34	62	27	185

Table 7 shows the association between duration of diabetes and CAN severity.

Table 8: Neuropathy Disability Score (NDS) categories by CAN status

NDS category	Definite CAN	Early CAN	Normal	Severe CAN	Total
0–2	0	4	50	0	54
3–10	62	30	12	27	131
Total	62	34	62	27	185

Table 8 shows the distribution of NDS categories across different CAN stages.

Table 9: Diastolic blood pressure rise to handgrip by CAN status

DBP rise (mmHg)	Definite CAN	Early CAN	Normal	Severe CAN	Total
5–10	1	0	0	17	18
10–15	37	20	33	8	98
15–20	17	11	24	2	54
20–25	7	3	5	0	15
Total	62	34	62	27	185

Table 9 shows the distribution of DBP response to sustained handgrip across CAN categories.

Table 10: Vibration perception threshold (Left foot) by CAN status

VPT Left (V)	Definite CAN	Early CAN	Normal	Severe CAN	Total
<5	0	0	2	0	2
5–10	0	4	48	0	52
15–20	26	19	12	3	60
20–25	17	7	0	12	36
25–30	19	4	0	12	35
Total	62	34	62	27	185

Table 10 shows the distribution of left foot VPT values across CAN stages.

Table 11: Vibration perception threshold (Right foot) by CAN status

VPT Right (V)	Definite CAN	Early CAN	Normal	Severe CAN	Total
<5	0	0	2	0	2
5–10	0	4	46	0	50
10–15	0	1	3	1	5
15–20	17	21	11	1	50
20–25	31	7	0	12	50
25–30	14	1	0	13	28
Total	62	34	62	27	185

Table 11 shows the distribution of right foot VPT values across CAN stages.

Table 1 shows that the largest proportion of patients belonged to the 55–65 years age group with 58 patients (31.4%), followed by the 45–55 years group with 51 patients (27.6%), while 46 patients (24.9%) were aged 35–45 years and 30 patients (16.2%) were older than 65 years. Table 2 shows that males constituted 95 patients (51.4%) and females 90 patients (48.6%), indicating an almost equal gender distribution. Table 3 shows that 65 patients (35.1%) had diabetes duration of less than 5 years, 59 patients (31.9%) had 5–10 years, 42 patients (22.7%) had 10–15 years, and 19 patients (10.3%) had 15–20 years duration. Table 4 shows that 62 patients (33.5%) had normal autonomic function, 34 patients (18.4%) had early CAN, 62 patients (33.5%) had definite CAN, and 27 patients (14.6%) had severe CAN. Table 5 shows that peripheral neuropathy was present in 131 patients (70.8%) and absent in 54 patients (29.2%), with all patients with definite CAN (62/62) and severe CAN (27/27) having peripheral neuropathy, while 50 of 62 patients (80.6%) with normal autonomic function had no peripheral neuropathy. Table 6 shows that in the 35–45 years age group, 36 of 46 patients (78.3%) had normal autonomic function, whereas in those older than 65 years, 14 of 30 patients (46.7%) had definite CAN and only 3 of 30 patients (10.0%) had normal autonomic function, indicating increasing CAN severity with age. Table 7 shows that among patients with diabetes duration less than 5 years, 52 of 65 patients (80.0%) had normal autonomic function, whereas among those with 10–15 years duration, 22 of 42 patients (52.4%) had definite CAN and 17 of 42 patients (40.5%) had severe CAN, with no patients showing normal autonomic function. Table 8 shows that 54 patients (29.2%) had NDS scores of 0–2 and 131 patients (70.8%) had NDS scores of 3–10, with all patients with definite and severe CAN falling into the 3–10 category. Table 9 shows that a DBP rise of 10–15 mmHg was the most common response, observed in 98 patients (53.0%), while a blunted response of 5–10 mmHg was predominantly seen in patients with severe CAN, affecting 17 of 27 patients (63.0%). Table 10 shows that higher left foot VPT values were more frequent in patients with definite and severe CAN, with 43 of 62 patients (69.4%) with definite CAN and 24 of 27 patients (88.9%) with severe CAN having VPT values of 20 V or more. Table 11 shows a similar pattern for right foot VPT, with 45 of 62 patients (72.6%) with definite CAN and 25 of 27 patients (92.6%) with severe CAN having VPT values of 20 V or more, while 46 of 62 patients

(74.2%) with normal autonomic function had VPT values of 5–10 V.

DISCUSSION

This study used a cross-sectional observational design to examine the prevalence of Cardiac Autonomic Neuropathy (CAN) in patients with T2DM and determine if there is a relationship between CAN and Peripheral Neuropathy (PN). Cardiac autonomic neuropathy was found to have a high prevalence in this patient population, with approximately two-thirds of patients within this cohort presenting with some degree of autonomic dysfunction. Furthermore, the presence of CAN was found to statistically significantly correlate with the incidence of Peripheral Neuropathy, further demonstrating the close pathophysiological relationship between these two common complications of diabetes mellitus.[14]

It was found that 33.5% of patients had definite CAN while 14.6% of patients had severe CAN. In contrast, only one-third of patients displayed normal autonomic function. This means that a substantial burden of subclinical and clinical autonomic involvement exists in patients with T2DM presenting to a tertiary medical centre. Furthermore, many patients could already have advanced autonomic dysfunction at the time they seek routine medical care; thus there is a need for improved and routine screening for autonomic function.[15]

The association between CAN and Peripheral Neuropathy is dramatic; all patients with definite or severe CAN also exhibited symptoms of Peripheral Neuropathy. Conversely, the vast majority of patients exhibiting normal autonomic function displayed low Neuropathy Disability Scores.The hypothesis that diabetic neuropathy is a widespread process that impacts several areas of the nervous system, with evidence of additional pathways being added to previously identified pathways for every area of the nervous system affected by neuropathy, continues to be supported by the findings from this study. The high correlation observed between the areas involved in the findings of this study supports the use of clinical evaluation of the autonomic nervous system for individuals who have documented evidence of peripheral neuropathy.[16,17]

Age and duration of diabetes were identified as significant contributors to the severity of Clinical Autonomic Neuropathy (CAN). Increased age was found to be related to higher rates of definite and severe forms of CAN, compared to younger people who had been diagnosed with and exhibited evidence of normal autonomic function.[18] A similar relationship was found for patients with diabetes diagnosed for more than 10 years compared to patients diagnosed for less than 10 years – patients with longer durations of diabetes demonstrated significant differences in the severity of the CAN with virtually no patients exhibiting normal autonomic function. These findings fall in line with previous studies that have shown that the cumulative effects of long-standing hyperglycemia and metabolic stress adversely affect the nerve structure and function, leading to the development and progression of diabetic neuropathy.[19]

Objective measures of peripheral nerve impairment, including VPT and NDS demonstrated a strong relationship with autonomic dysfunction in patients with definite and severe CAN. Patients with definite and severe CAN demonstrated higher values for VPT in both feet and exhibited higher categories of NDS classification than patients with normal autonomic function who mainly clustered at lower values for VPT and NDSThe diagnostic evidence of autonomic neuropathy and peripheral nerve damage associated with autonomic nerve dysfunction and damage due to the combined effects of long-term diabetes is further supported by the concurrent deterioration of the function of both somatic and autonomic nerves, thereby suggesting that shared mechanisms of disease and progressive damage to the autonomic and peripheral nerves are present in long-term diabetes.[20,21]

Autonomic function tests that assess the degree of sympathetic dysfunction (e.g., diastolic blood pressure response to sustained handgrip and orthostatic drop in systolic blood pressure) in patients with increasing CAN grade show progressively more abnormal autonomic function with increasing severity of CAN.[22] In patients with severe autonomic nerve dysfunction, for example, there was markedly blunted diastolic blood pressure response to handgrip and significantly greater than 20mmHg drop in their systolic blood pressure while standing, reflecting significant progressive sympathetic nerve dysfunction. Further, the clinical consequences of the above-mentioned abnormalities include, but are not limited to, exercise intolerance, postural symptoms, and increased cardiovascular risk.[23,24]

Our finding of no significant relationship between CAN and sex indicates that both men and women with type 2 diabetes mellitus experience similar risk for developing autonomic neuropathy, and that other variables, such as age, duration of disease, and overall severity of neuropathic involvement, have a greater impact on the risk for developing CAN.[25]

Overall, the findings of this study suggest, in part, the prevalence of cardiac autonomic neuropathy in patients with type 2 diabetes and the strong association between cardiac autonomic neuropathy and the presence and degree of peripheral neuropathy. The strong relationships between CAN and age, duration of diabetes and throughout neuropathic assessment demonstrate that there is a need to incorporate both autonomic function and peripheral function into assessments performed as part of routine care for individuals with type 2 diabetes.

While the ability of the study to assess the temporal relationship between peripheral and autonomic neuropathy is limited due to the cross-sectional

design of the study, the above-mentioned findings provide clinical evidence supporting the association and burden of these two disorders in patients with diabetes in a qualified tertiary care setting.

CONCLUSION

A high rate of cardiac autonomic neuropathy among persons with newly diagnosed type 2 diabetes was demonstrated in this cross-sectional observational study. The rate of those who had cardiac autonomic neuropathy was found to be nearly two-thirds of the participants. Additionally, there was a strong, statistically significant relationship found between cardiac autonomic neuropathy and peripheral neuropathy. Therefore, it is common for patients with diabetes to exhibit both autonomic involvement as well as somatic nerve damage. The degree or severity of cardiac autonomic neuropathy was found to increase with increased age, longer duration of diabetes, and higher Neuropathy Disability Scores and elevated vibration perception thresholds. These results demonstrate the importance of routine and systematic assessments for cardiac autonomic neuropathy in individuals with long-standing diabetes and/or evidence of peripheral neuropathy to facilitate the detection of cardiac autonomic neuropathy as early as possible, improve risk stratification, and provide patients with more comprehensive/definitive treatment for diabetic neuropathic complications.

Limitations

This research has some limitations. A cross-sectional study cannot show the timing or cause behind why cardiac autonomic neuropathy and peripheral neuropathy occur together. The data collected came from only one facility which could limit the ability to apply what was learned in this study to other hospitals or groups of people. The study used standard tests to assess the autonomic nervous system and the presence of peripheral neuropathy but did not include more advanced testing methods such as cardiac sympathetic fibre imaging or nerve conduction studies. Additionally, other important confounding factors, such as variations in blood sugars over time or how medications were treated were not analyzed separately. Although there are limitations on the research performed, it provides valuable information about the magnitude of both forms of neuropathy and how they relate to one another for patients with diabetes type 2.

To summarize, patients with diabetes type 2 have a high incidence of cardiac autonomic neuropathy, and that cardiac autonomic neuropathy is correlated with the presence of peripheral neuropathy therefore establishing the need for more routine screenings to assist in identifying patients with CAN before there are significant health risks related to CAN.

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