European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 03, 2022

ORIGINAL RESEARCH

A STUDY OF CARDIOVASCULAR AUTONOMIC NEUROPATHYIN ADULTS WITH DIABETES MELLITUS

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ABSTRACT

Background:Diabetes Mellitus (DM) is a major concern in India and has been described as a modern-day epidemic. It can affect nearly every organ and cause a slew of complications. Cardiac autonomic neuropathy (CAN) is a serious complication of diabetes. It is also one of the least diagnosed and understood diabetic complications. The purpose of this study was to determine the prevalence of CAN in diabetic patients and to investigate its relationship with the duration of DM and glycemic control.

Materials and Methods: 80 diabetic patients admitted to the Department of Medicine, NRI Medical College, Guntur, met the inclusion and exclusion criteria. Demographic data, history, and clinical examination were documented. All individuals were tested for CAN using 3 tests to assess parasympathetic and 2 tests to assess sympathetic function. Patients were classed as normal, early CAN, definite CAN, or severe CAN using Ewing's criteria. The duration of time for the study was one year and eight months.

Results: The prevalence of CAN in the studied population was 60%. In individuals with CAN, the duration of diabetes was substantially longer, and HbA1c was much greater than in patients with normal cardiac autonomic function. There was a significant connection between CAN and DM duration (r=0.54435) and glycemic control as determined by HbA1c levels (r=0.665925), but not with age. The normal CAN score was 29 (36.25 percent), the early CAN score was 30, the definite CAN score was 9, and the severe CAN score was 12. (15 percent). Background retinopathy (68 percent), proliferative retinopathy (31%), and various retinopathies were identified in CAN patients (19.6 percent) Number 11 maculopathy (19.6 percent) 11. Clinical Presentation Characteristics of Patients Patients with severe CAN and impaired cardiac autonomic function developed diabetic foot 35.55 percent of the time, cataracts 57.14 percent of the time, muscle wasting 14% of the time, and tingling 90% of the time.

Conclusion: CAN is a common and widespread consequence of diabetes that is asymptomatic in the early stages. As a result, it is recommended that every diabetic patient be diagnosed for CAN.

Keywords: Diabetes Mellitus, CAN, HbA1c, retinopathy.

INTRODUCTION

The World Health Organization (WHO) has issued a warning that the number of diabetes in India could more than double by the year 2030, increasing from 32 million at the present time to 80 million.[1]Diabetes mellitus patients, whether they have type 1 or type 2 diabetes, are at a greater risk of developing cardiovascular disease (CVD) , which is responsible for more than 60 percent of the death rate among diabetic patients.[2-4] People who have type 2 diabetes have a risk of mortality from coronary heart disease that is three times higher than the risk of death from CVD in people who do not have diabetes. People who have diabetes are more likely to have a cluster of cardiovascular disease risk factors, all of which contribute to an increased risk of cardiovascular disease. These risk factors include obesity, hypertension, dyslipidemia, physical inactivity, and cardiovascular autonomic neuropathy (CAN). CAN is one of the consequences of diabetes that is underdiagnosed, and it is also one of the key risk factors for cardiovascular disease in those who have diabetes.[2]This condition is referred to as a dysfunction of the nerve that is innervated by the autonomic nervous system (ANS), which is responsible for regulating the heart and blood vessels. In patients with type 2 diabetes, the prevalence of CAN has been reported to be between 31 and 73 percent, whereas in patients with type 1 diabetes, the prevalence has been reported to be between 17 and 66 percent. This variance in prevalence can be partially attributed to the use of a variety of research approaches and diagnostic procedures. There is a correlation between the existence of CAN in patients who have diabetes and an increased risk of dying from cardiovascular disease over a period of five years. Resting tachycardia, postural hypotension, exercise intolerance, silent myocardial ischemia or infarction, and left ventricular systolic and diastolic function are symptomatic symptoms that are related with the existence of CAN.[2,3]DM is a deadly disease. It can affect almost every organ and cause a myriad of complications. Cardiac autonomic neuropathy (CAN) is an important complication of DM. It is also among the most under diagnosed and least understood diabeticcomplications.[4-6]

There are many reasons why the evaluation of CAN is important:

- CAN is a common complication that may be disabling and dangerous.
- Studies have demonstrated that CAN not only causes symptoms like exercise intolerance and orthostatic hypotension, but it is also implicated in increased intraoperative cardiovascular lability, silentmyocardial ischemia, increased risk of mortality and sudden cardiac death.
- CAN may be present at the time of diagnosis of DM. It may develop even before features of somatic peripheral neuropathy manifest.
- CAN may be entirely asymptomatic in some patients.
- Intensive therapy can slow the progression and delay the appearance ofabnormal autonomic function tests
- Subclinical autonomic neuropathy can be detected early using autonomicfunction tests
- There are standardized methods to evaluate CAN using simple bedside testswhich may easily be performed in resource poor settings.

Early detection of autonomic dysfunction could identify patients at risk for adverse outcomes and may facilitate medical practitioners and patients to improve glycemic control and decrease morbidity.[6,7]

Aims and Objectives

1. To study the prevalence of cardiovascular autonomic neuropathy in diabetic patients admitted to Department of General Medicine, NRI Medical College, Guntur, AP.
2. To study the association between cardiovascular autonomic neuropathy in diabetic patients and:
   - Duration of DM
   - Glycemic control- HbA1c
   - QTc interval

MATERIALS & METHODS

Source of data:

Diabetic patients admitted in the Department of Medicine, NRI Medical College, Guntur, AP.

Method of collection of data:

80 diabetic patients who were admitted in the Department of Medicine, NRI Medical College were included. Patients were selected after fulfilling the following inclusion and exclusion criteria.

Inclusion criteria:

1. Diabetic patients of age more than 18 years
2. Duration of DM of at least 5 years
3. Patients giving written informed consent

Exclusion criteria:

1. Chronic renal failure
2. Ischemic heart disease
3. Use of beta-blockers
4. Serum electrolyte abnormalities
5. Asthma or severe chronic obstructive pulmonary disease
6. Use of drugs that prolong QT interval
7. Non complying patients who do not consent to participate in the study

A proforma was used to record each patient's demographic information, as well as their comprehensive medical history, their physical examination, and their fundus examination performed with direct ophthalmoscopy. In looking through patient case files and hospital records, we found that investigations such as FBS, PPBS, RFT, serum electrolytes, HbA1c, urine routine, ECG, and 2D-ECHO were performed on each and every patient. The CAN was evaluated in each patient by performing the 3 tests of parasympathetic function and the 2 tests of sympathetic function that are described in the following section.

RESULTS

80 diabetic patients admitted from November 2019 to May 2021 in the Department of Medicine, NRI Medical College, Guntur were included in this cross-sectional study.

The mean age of the 80 patients studied was 50.32± 8.6 years. The oldest patient was 69 years, and the youngest patient was 22 years old.

Table 1: Age Distribution of Patients

Age groups	Normal		Early CAN		Definite CAN		Severe CAN	
	Number	%	Number	%	Number	%	Number	%
<29	0	0	2	6.67	1	1.11	0	0.00
30-40	1	3.4	5	16.67	1	1.11	1	8.33
40-50	8	27.59	9	30	2	2.22	2	16.67
50-60	14	48.27	10	33.33	4	4.44	6	50
60-70	6	20.6	3	10	1	1.11	2	16.66
70-80	0	0	1	3.33	0	0	1	8.33
>80	0	0	0	0	0	0	0	0.00
Mean ± SD	53.65 ± 10.26		46.90 ± 9.76		49.4 ± 10.2		52.15 ± 8.32	

85% of the patients in the study were aged between 40 to 70 years with the maximum number of patients (n=43) in the age group of 50-60 years.

In this study, out of 80 diabetic patients, there were 47 who were male.

Table 2: Gender distribution of patients

	Mal e		Female	
	Number	%	Number	%
Normal	16	37.2	13	35.13
Early CAN	18	41.86	12	32.43
Definite CAN	4	9.3	5	13.51
Severe CAN	5	11.64	7	18.91
Total	43	100	37	100

43 of males and 37 % of females had normal cardiac autonomic function.11.64% of males and 18.91% of females had severe CAN.

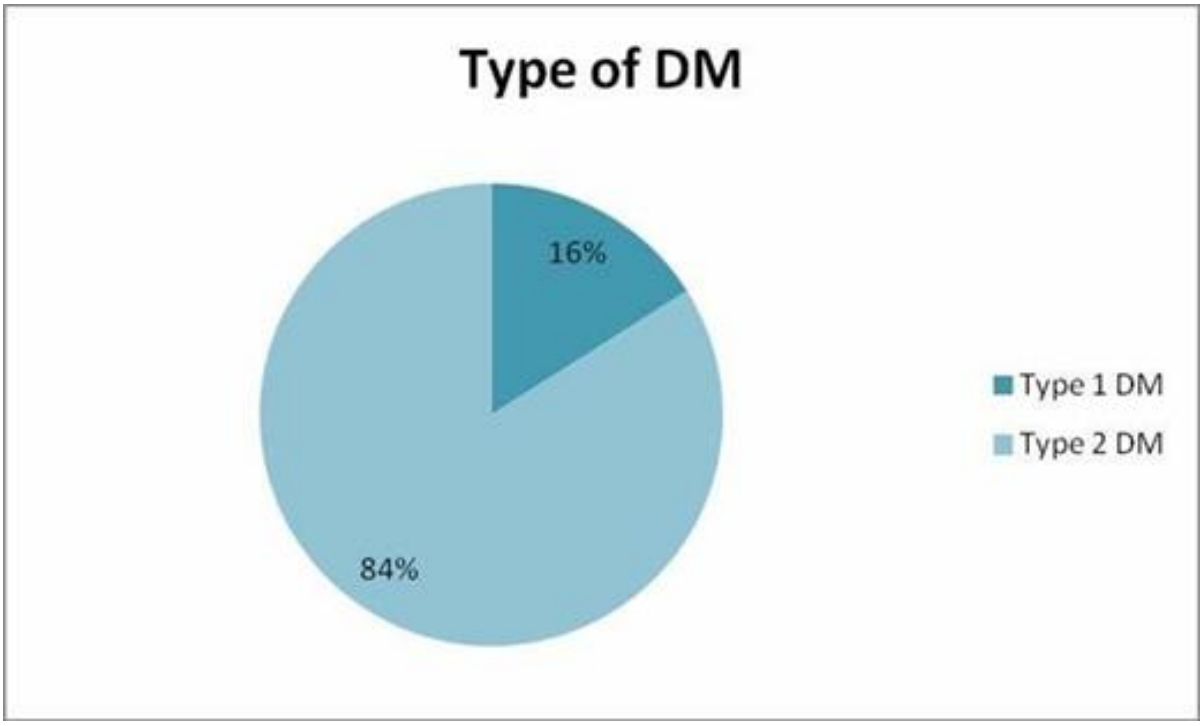

Figure 1: Type of DM in the study population

84% of the patients in the study had type 2 DM.
All 80 patients underwent each of the 5 tests for CAN. 42 patients had abnormal R-R interval during deep breathing while only 5 had abnormal SBPresponse to standing. 77 patients had a normal standing 30:15 ratio.

Table 3: Results of the 5 tests for CAN

Test for CAN	**Number of patients (N=80)**		
	Normal	**Borderline**	**Abnormal**
The R-R interval during deepbreathing	41	12	27
The Valsalva Ratio	42	26	12
The standing 30:15 ratio	65	3	12
SBP response to standing	58	19	3
DBP response to sustained handgrip	42	19	19

The mean duration of DM in this study was 8.12 ± 2.23 years. The shortestduration of DM was 5 years and the longest duration of DM was 18 years.

Table 4: Comparison of duration of DM among patients with normal and abnormal cardiac autonomic function

	Duration of diabetes in yearsMean ± SD
Normal	6.23 ± 0.95
Early CAN	6.43 ± 1.62
p-value	0.21
Normal	6.18 ± 0.92
Definite CAN	8.45 ± 0.94

p-value	<0.001
Normal	6.18 ± 0.92
Severe CAN	12.2 ± 3.21
p-value	<0.001

Duration of DM among patients with definite and severe CAN, was significantly higher than those with normal cardiac autonomic function (p <0.001). Duration of DMshowed an increasing trend across the groups of patients with early, definite andsevere CAN.
9.43 ± 2.51 g/dl was the mean HbA1c level of the patients in this study. Thelowest value was 6.4 g/dl and the highest was 16g/dl.

Table 5: Comparison of HbA1c levels among patients with normal and abnormal cardiac autonomic function

	HbA1c in g/dlMean ± SD
Normal	7.62 ± 0.53
Early CAN	8.57 ± 2.8
p-value	<0.0001
Normal	7.54 ± 0.56
Definite CAN	11.2 ± 1.45
p-value	<0.0001
Normal	7.62 ± 0.55
Severe CAN	13.72 ± 1.2
p-value	<0.0001

HbA1c levels among patients with abnormal cardiac autonomic function, including early, definite and severe CAN, were significantly higher than those with normal cardiac autonomic function (p <0.0001). HbA1c levels showed an increasing trend across the groups of patients with early, definite and severe CAN.

Table 6: Comparison of age among patients with normal and abnormal cardiac autonomic function

	Age in yearsMean ± SD
Normal	53.32 ± 10.2
Early CAN	45.8 ± 9.1
p-value	0.1254
Normal	53.21 ± 10.4
Definite CAN	49.8 ± 10.2
p-value	0.3932
Normal	53.13 ± 10.02
Severe CAN	52.18 ± 8.45
p-value	0.9909

There was no statistically significant difference in the mean age of patientswith normal and early or definite or severe cardiac autonomic dysfunction.

Table 7: Clinical Features of Patients with Normal and Abnormal Cardiac Autonomic Function

Clinical Feature	Normal% (N=29)	Early CAN% (N=30)	Definite CAN% (N=09)	Severe CAN% (N=12)
Resting Tachycardia	0	5.5	0.00	40.1
Exercise Intolerance	0	2.4	8.2	35.45
Lightheadedness On Standing Up	0	8.5	20.00	28.50
Constipation	0	2.9	8.2	14.29
Diarrhea	0	0.00	0.00	7.14
Fecal Incontinence	0	0.00	0.00	0.00
Post Meal Distension	0	2.45	0.00	7.14
Hypoglycemia Unawareness	0	5.86	0.00	0.00
Decreased Pupil Size	0	0.00	0.00	0.00
Delayed/Absent Pupillary Reflex	0	0.00	0.00	0.00
Erectile Dysfunction	0	0.00	0.00	6.7
Incomplete Bladder Emptying	0	0.00	0.00	12.56
Hesitancy	0	0.00	0.00	7.14
Weak Stream Or Dribbling	0	0.00	0.00	7.12
Anhidrosis	0	2.9	8.22	7.14
Gustatory Sweating	0	0.00	0.00	0.00
Heat Intolerance	0	0.00	8.02	7.14
Dry Skin	0	0.00	8.25	28.8
Feet Feel Cold	0	0.00	16.67	28.7
Dependent Edema	0	0.00	8.33	7.14
Bullous Formation	0	0.00	0.00	0.00
Tingling	8	58.55	80.00	90.5
Numbness	5	38.24	91.55	80.00
Burning	4	26.4	91.67	82.67
Pain	0	5.88	50.00	64.29
Muscle Wasting	0	8.85	41.6	14.22
Diminished Vibration Sense	5	52.25	100.00	100.00
Diminished Sense of Pain AndTemp	2.5	26.47	8.24	85.71
Loss Of Ankle Jerk	5	35.22	66.65	100.00
Clawing Of Toes	7.5	50.00	50.00	14.02
Callus At Pressure Points	4	47.00	41.61	71.43
Decreased Vision	12	50.00	66.67	100.00
Diabetic Foot	0	2.14	0.00	35.55

Cataract	2	38.24	25.00	57.14
Background Retinopathy	3	52.35	41.05	50.00
Proliferative Retinopathy	0	0.00	12.65	57.35
Maculopathy	0	0.00	6.5	64.02

All patients with severe CAN had symptoms of numbness and decreased vision on history and diminished vibration sense and loss of ankle jerk on examination. In the study population, 'tingling' was the most common complaint (58 %) followed by 'decreased vision' (50%). The most common finding on examination was 'diminished vibration sense' (52.25%).

Table 8: Comparison of fundus examination between patients with normalcardiac autonomic function and CAN

Fundus examination	**Normal**		**CAN**		
	N=29	**%**	**N= 51**	**%**	**p-value**
BackgroundRetinopathy	2	6.89	31	60.78	<0.05
ProliferativeRetinopathy	0	0	10	19.60	0.1146
Maculopathy	0	0	10	19.60	0.1146

The presence of retinopathy was higher in patients with CAN than in patients with normal cardiac autonomic function but not significant.

Table 9: Comparison of clinical features of peripheral neuropathy betweenpatients with normal cardiac autonomic function and CAN

Clinical Feature ofPeripheral Neuropathy	**Normal**		**CAN**		**p-value**
	n(N=29)	**%**	**n(N=51)**	**%**	
Tingling	3	10	40	78.43	<0.001
Numbness	2	5	31	60.78	<0.001
Burning	2	5	32	62.74	<0.001
Pain	0	0	12	23.52	<0.001
Muscle Wasting	0	0	10	19.60	<0.0053
Diminished Vibration Sense	2	5	38	74.5	<0.001
Diminished SenseofPain And Temp	1	2.5	19	37.25	<0.001
Loss Of Ankle Jerk	2	5	31	60.78	<0.001
Clawing Of Toes	0	0	14	27.45	<0.001
Callus At Pressure Points	0	0	09	17.64	<0.00521

The presence of clinical features of peripheral neuropathy was significantlyhigher in patients with CAN than in patients with normal cardiac autonomic function.

DISCUSSION

The cardiac autonomic function of 80 diabetic patients admitted to NRI Medical College, Guntur were studied. 60 of them had abnormal cardiac autonomic function as assessed by Ewing's criteria. The normal CAN scores were 29 (36.25 percent), the early CAN scores were 30, the definite CAN scores were 09 (11.25 percent), and the severe CAN scores were 12. (15 percent). According to the findings of Dhumad et al., cardiac autonomic neuropathy can be broken down into four distinct stages. These stages are determined by Ewing's criteria. 14: Normal: when all the cardiovascular autonomic tests were negative and consisted of 67 patients (47.18 percent); Early: when one of the three HR tests was abnormal and consisted of 19 patients (13.38 percent); Definite: when two HR tests were abnormal and included 20 (14.08 percent); and Severe: when two HR tests and one or both BP tests were abnormal and consisted of 36 patients. Severe: when two HR tests and one or both BP tests were abnormal and (25.35 percent).[8]

CAN patients' retinopathies were broken down as follows: background retinopathy (68 percent), proliferative retinopathy (31), and other retinopathies (19.6 percent) Maculopathy, number 11 (19.6 percent) 11. Characteristics of the Patients' Clinical Presentation Patients with severe CAN who had abnormal cardiac autonomic function were found to have diabetic foot 35.55 percent of the time, cataracts 57.14 percent of the time, muscle wasting 14 percent of the time, and tingling 90 percent of the time. The study conducted by Ekta K in New Delhi found a prevalence that was higher than the one found in this study.[10] The findings of this study are comparable to those found in Pappachan JM6, most likely due to the fact that both studies were carried out at hospitals attached to medical institutions in South India and the demographics of the patients who participated may have been comparable.[8,9] It is possible for prevalence to vary depending on a number of factors, including the kind and number of tests that were performed, the instruments that were used to carry out the test, where the research was carried out (in the community, a clinic, or a tertiary referral centre), and the geographic region that the research was carried out in.[10] The duration of diabetes mellitus among patients who had normal (6.23 0.95 years) and those who had definite CAN (8.45 0.94 years, p-value 0.001) was shown to differ significantly from one another in this study. The duration of diabetes mellitus in patients with severe CAN was considerably longer (12.46 3.41 years) compared to patients with normal cardiac autonomic function (p-value 0.001) This is consistent with the findings of Valensi P7, who found that the duration of diabetes was considerably longer in patients with CAN (9.3 +/- 0.9 years) (p 0.01) than it was in those whoseparasympathetic tests were normal. This finding is analogous to the findings of Valensi P7. There was not a statistically significant difference in the duration of diabetes between individuals who had early CAN (6.53 1.92 years) and patients who had normal autonomic function (6.088 0.97) (p- value = 0.229). Glycemic control, as measured by HbA1c levels, was found to differ significantly (p value 0.0001) among patients who were classified as having normal (7.64 0.58) and early CAN (8.87 2.08), patients who were classified as having normal and definite CAN (11.08 1.71), and patients who were classified as having normal and severe CAN (13.72 1.2) in this study. This is very similar to the observation made by Valensi P34, who found that the HbA1c level was higher in patients with CAN than in those who had three normal parasympathetic tests (9.95 +/- 0.35 percent versus 8.17 +/- 0.42 percent, p 0.005).[12] This finding supports the hypothesis that CAN is associated with a

higher HbA1c level. A link that is statistically significant (r=0.668195) was discovered between HbA1c and CAN when using Pearson's method for analysing correlations (as assessed by autonomic function score). In contrast, Ekta K did not detect a significant association between HbA1c level and autonomic impairment in their research.[10] This finding contradicts Ekta K's findings.The QTc interval and CAN did not have an association that was statistically significant (r = 0.07267). (as assessed by autonomic function score). Patients who had normal autonomic function and CAN did not significantly differ from one another in terms of their mean QTc interval. In contrast to this, the research conducted by Veglio M found that there was a statistically significant link between the QTc duration and the DAN score of autonomic cardiovascular test findings (r = 0.34, p 0.0001).[13]

All of the patients in this study underwent a comprehensive evaluation of their clinical characteristics, which included both a history and an examination. As signs of CAN, doctors looked for tachycardia at rest, sensitivity to physical activity, and feeling lightheaded when standing up. Surprisingly, 88 percent of patients with early CAN and 83 percent of patients with definitive CAN did not have any symptoms associated with the condition. If only their history and a general physical examination had been considered, it's possible that cardiac autonomic dysfunction would not have been detected in them or identified. Only Ewing's tests were able to conclusively determine that these patients had CAN. This leads one to believe that in its early stages, CAN may not exhibit any symptoms at all, and as a result, it may be ignored if one does not look for it properly. It is important to note that early CAN can be quickly picked up by performing straightforward bedside procedures. Patients who are now in these stages would certainly benefit substantially from improved glycemic control and tighter monitoring in the hopes that this will allow for a delay inthe progression of CAN. In this study, it was also shown that once severe CAN sets in, patients are more likely to be symptomatic, with 79 percent of patients with severe CAN experiencing symptoms of CAN. This was one of the observations that was made regarding the relationship between severe CAN and symptomatology.

Patients diagnosed with CAN were more likely to experience hypoglycemia unawareness than patients whose autonomic functioning was normal. However, there were only two patients that exhibited this characteristic; hence, there was insufficient evidence to arrive at any conclusion. One other intriguing finding was that a considerably larger percentage of patients diagnosed with CAN exhibited clinical signs of peripheral neuropathy as compared to those whose cardiac autonomic function was normal. On examination, numbness was present in all of the patients with severe CAN, along with decreased vibration sensitivity and loss of ankle jerk.[12] The history of these patients also revealed numbness. Patients diagnosed with CAN had an increased risk of having vision problems when compared to patients whose autonomic function was normal. Patients diagnosed with CAN had a higher prevalence of retinopathy compared to patients who did not have CAN; however, this difference did not reach statistical significance. Vision loss was a symptom experienced by every patient diagnosed with severe CAN. It is unknown if peripheral neuropathy and retinopathy both serve as risk factors for CAN or whether all three conditions belong to the same spectrum of diabetic microvascular consequences.

This was a cross-sectional study, and the data was collected from the records kept at the hospital and the laboratory. Patients were not followed up to determine whether or how

rigorous control of glycemic levels delays or reverses the advancement of CAN. In clinical practise, it is not uncommon to come across conditions such as the intake of alcohol, chronic renal failure, ischemic heart disease, the use of beta-blockers, serum electrolyte abnormalities, and asthma or severe chronic obstructive pulmonary disease. Due to the fact that these were part of the criteria for excluding participants from the study, a significant number of diabetes individuals were unable to take part. History, clinical examination, and direct ophthalmoscopy were utilised in order to diagnose peripheral neuropathy and retinopathy; however, a nerve conduction study and fundus fluorescein angiography would have been more sensitive diagnostic tools. It is likely that early peripheral neuropathy and retinopathy were not picked up by the patient's medical professionals.[13]

CONCLUSION

The patient's age did not have a significant correlation with cardiac autonomic dysfunction; however, the length of time the patient had diabetes and their HbA1c level did. CAN is a common complication that was found to have a prevalence of sixty percent in one study. The early stages of CAN do not manifest any symptoms. As a result, it is recommended that a diagnostic for CAN be performed on every diabetic patient.

Acknowledgement

The author is thankful to Department of General Medicine for providing all the facilities to carry out this work.

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