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Original Research Article

Prevalence of cardiac autonomic neuropathy in type 2 diabetes mellitus and its correlation with other microvascular complications in South Indian population

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ABSTRACT

Background: In individuals with type 2 diabetes mellitus (T2DM) the presence of Cardiac autonomic neuropathy (CAN) increases the risk of severe hypoglycaemia, cardiac arrhythmias, silent myocardial ischemia and stroke. It is also associated with increased perioperative morbidity and mortality, even with minor surgeries in these patients. The present study was conducted to assess the prevalence of CAN in T2DM patients and to investigate any possible association between CAN and micro vascular complications.
Methods: 102 T2DM patients between the age of 30 years and 70 years, who attended outpatient department of Institute of Diabetology, Rajiv Gandhi Government General Hospital and Madras Medical College, Chennai, Tamil Nadu were included. All the selected patients underwent laboratory investigations, biothesiometry, fundus examination, and CAN assessment by CANS analyser.
Results: A slight female preponderance was noted in the study, though it was statistically insignificant. Out of 102 patients, prevalence of CAN dysfunction was found in 82 (80.39%) of T2DM patients. No significant association of CAN was noted with duration of diabetes (p=0.772), HbA1c (p=0.827) and nephropathy (p=0.524). However, peripheral neuropathy (p=0.006) and retinopathy (p=0.03) were found to be significantly associated with CAN in T2DM patients.
Conclusions: Prevalence of CAN in asymptomatic South Indian T2DM population was found to be 80.39%, with equal sex distribution and was most common in the 51- 60 years age group. Diabetic neuropathy and retinopathy were the most significant microvascular complications predictive of the incidence of CAN in T2DM patients.

Keywords: Cardiac autonomic neuropathy, Micro vascular complications, South Indian population, Type 2 diabetes mellitus

INTRODUCTION

Diabetic neuropathy accounts for the most common microvascular complication of Diabetes Mellitus. Diabetic peripheral neuropathy clinically manifests as numbness of feet which may result in ulceration and infection, neuropathic pain which can be severe and disabling and autonomic neuropathy which can involve several systems.

The prevalence of neuropathy is associated with increasing age, poor glycaemic status and longer duration

of the disease. Neuropathy is often associated with other microvascular complications. Increasing height and cardiovascular risk factors (cigarette smoking, hypertension, hyperlipidaemia) are also associated with increased prevalence of neuropathy. The type of diabetes does not appear to influence its prevalence.

The onset and triggering factors for diabetic neuropathy are not very clear. Metabolic abnormalities like polyol pathway activation, depletion of myoinositol, reduction in PKC activity and a decrease in activity of nerve Na+, K+ -ATPase are brought about by diabetic state which have a negative impact in nerve perfusion, suggesting that the vascular endothelium is a major target. Diabetic neuropathy is the cause of pain, distress, suffering and poor quality of life, which, if not taken care of in the early stages, can lead to foot ulceration. Charcot's neuroarthropathy may develop in some and patients with improper care and control can end up in needless amputations.

Marchal de Calvi described peripheral anaesthesia in diabetic patients way back in 1864 and was the first to introduce the idea of diabetes being the cause rather than the result of neuropathy.[1] Almost 80 years later, R. Wayne Rundles presented a detailed description of autonomic neuropathy in diabetes in his paper on diabetic neuropathy.[2] The ANS organization and physiological control relies on its division into sympathetic and parasympathetic nervous system. Fight and flight are an important physiological response, which is mediated by sympathetic stimulation. Parasympathetic stimulation usually produces effects associated with resting and digesting. Involvement of ANS can affect cardiovascular, neurovascular, gastrointestinal and genito-urinary systems and also impair certain metabolic functions like glucose counter-regulations. Autonomic neuropathy sets in gradually and progresses slowly. The prevalence of DAN depends on the population studied and the nature of tests employed for detection of autonomic dysfunction.

Diabetic autonomic neuropathy (DAN) is often associated with diabetic peripheral sensory neuropathy. It is frequently under-diagnosed during clinical evaluation. The severity of autonomic dysfunction ranges from asymptomatic to severe disability. Common manifestations are decreased pupillary size and reduction in light response due to sympathetic denervation, episodic nocturnal diarrhea, constipation and gastric atony, orthostatic hypotension, dizziness, resting tachycardia, cardiac arrhythmia and silent myocardial infarction. Genitourinary system dysfunction presents with bladder atonia, distention, recurrent infections and impotence Patients suffering with DAN have a much-increased risk of development of renal infections and unexplained cardiorespiratory arrest, with a higher mortality rate.

Cardiac autonomic neuropathy (CAN) can be considered as one of the most overlooked, least understood, less commonly evaluated and serious complication of diabetes mellitus that has a very significant impact on quality of life and survival in individuals who suffer with diabetes.[3] Systemic hypertension, distal symmetrical peripheral neuropathy, retinopathy and persistent poor glycaemic status are in general major risk factors in the development of cardiac autonomic neuropathy in both Type 1 and Type 2 Diabetes Mellitus.[4]

This study aims to assess the prevalence of CAN among patients with T2DM of varying duration and correlate any possible influences of age, duration of diabetes, hypertension, coexistent peripheral neuropathy, nephropathy and/or retinopathy on occurrence of cardiac autonomic neuropathy in native south Indian population.

METHODS

The present descriptive study was conducted at the Institute of Diabetology, Rajiv Gandhi Government General Hospital and Madras Medical College, Chennai, Tamil Nadu over a period of six months from September 2014 to February 2015. 102 T2DM patients without any symptoms related to cardiac autonomic neuropathy, irrespective of duration of diabetes, of age ≥30 years and ≤70 years who attended outpatient department were included in the study after obtaining approval from Institutional ethics committee.

Exclusion criteria

- Their age was <30 years and >70 years
- They had type 1, gestational or secondary diabetes mellitus
- They were on pacemakers or on anti-arrhythmic drugs
- They had any self-reported neurological or cardiac diseases
- They had symptoms related to cardiac autonomic neuropathy
- They had co-morbid illness
- There was use of drugs like anti-histamines, anti-tussives, antidepressants or diuretics

After obtaining informed consent from the 102 patients, complete history was recorded according to a questionnaire, patients were advised to abstain from smoking and drinking coffee at least one hour before the test and they were subjected to clinical examination and investigations including renal function tests, plasma glucose, HbA1c, urine protein creatinine ratio, cardiac autonomic neuropathy testing, biothesiometry and fundus examination of the eye. Serum and urine creatinine were done by Jaffe's method. Plasma glucose was assessed by glucose oxidation method, HbA1c by high pressure liquid chromatography (HPLC) and Urine proteins were determined by turbidimetric method using 3% sulphosalicylic acid.

Cardiac autonomic neuropathy testing was performed by Cardiac Autonomic Neuropathy System (CANS) analyser

(Figure 1). (Figure 1 taken at Institute of Diabetology, Rajiv Gandhi Government General Hospital and Madras Medical College, Chennai, Tamil Nadu, India. CANS analyser is an important tool to measure and diagnose autonomic dysfunction using R-R intervals of ECG and automatic BP measurements. The test procedure is guided by computer software and both cardiac sympathetic and parasympathetic autonomic functions are analysed. Quantitative tests to assess autonomic function show less advancement than those used to assess the functions and deficits of motor and sensory nerves.

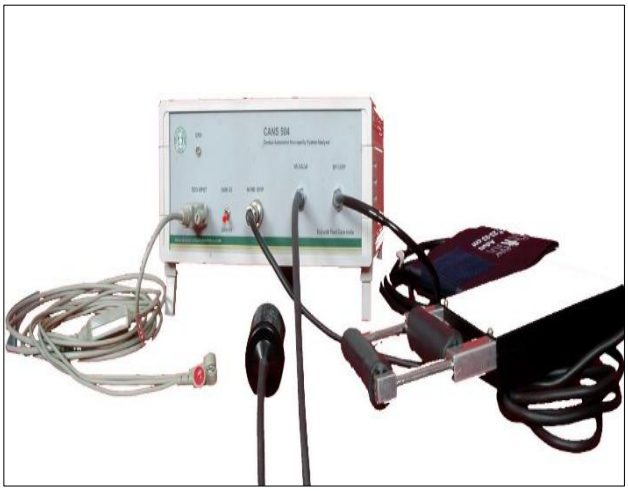

Figure 1: CANS Analyzer, a computer software aided device which helps perform tests like heart rate, blood pressure and ECG to assess cardiac sympathetic and parasympathetic nervous system function.

In this study, the parasympathetic function tests included:

- Resting heart rate
- Heart rate response to deep breathing
- Heart rate response to standing

Sympathetic system analysis included:

- Blood pressure response to standing
- Blood pressure response to sustained hand grip

The cardiac autonomic dysfunction was classified as:

- Early-Grade I abnormality of any two of the above parameters or one Grade I and one Grade II dysfunction
- Definite or Mild-Grade II abnormality of any two parameters or two Grade II and one Grade I dysfunction
- Moderate -three or more Grade II parameters abnormal

Authors have look for reduced variability (less of a change in heart rate), a sign that the patient's heart response, as provided by the body's autonomic control center is not adequate. At least two tests must be performed in order for the test to be conclusive. Sometimes one test result may be abnormal, but the second test result turns out normal. This is because some heart rate variability tests are more sensitive to earlier autonomic nervous system dysfunction than others. This is also due to the fact that test results are based on a combination of activities within the body, which are influenced differently in each patient. As a general rule, more the abnormal results, more severe is the affliction to the autonomic nervous system.

Statistical analysis

All the data was expressed in number and percentages. Data was analysed using XLStat. Statistical significance was set at $p<0.05$. All statistical analyses were conducted by using the SPSS version 17.0.

RESULTS

The present study comprised of 102 subjects of which 49 were males and 53 were females. A total of 82 (80.39%) were found to have CAN dysfunction of varying degrees. 75.7% males and 84.61% females were detected to have CANS dysfunction. Early CAN dysfunction was detected in 18 of 49 males (36.73%) and 18 of 53 females (32.69%). Definite CAN dysfunction was seen in 13 males (26.53%) and 23 females (43.4%) and moderate CAN was detected in 6 males (12.2%) and 4 females (7.69%) as given in Table 1. No statistically significant association was seen between the sexes and prevalence of CAN ($p=0.173$).

When authors have compared age of patients with CAN dysfunction, we found that in the age group of 31 to 40 years, out of 4 males 50% had no CAN dysfunction and 50% had CAN dysfunction. Of 12 females, 3 (25%) had no CAN dysfunction and 9(75%) had CAN dysfunction. In 41 to 50 years age group, of 13 males 6(46.15%) had no CAN dysfunction and 7(53.86%) had CAN dysfunction. Among the 13 females 2(15.38%) had no CAN dysfunction and 11 (84.62%) had CAN dysfunction.

In 51 to 60 years age group, of the 20 males 2(10%) had no CAN dysfunction and 18(90%) had CAN dysfunction. Of 23 females 3(13.04%) had no CAN dysfunction and 20(86.96%) had CAN dysfunction. In 61 to 70 years age group, of 12 males 2(16.66%) had no CAN dysfunction and 10(83.33%) had CAN dysfunction. All 5 females (100%) in this group had varying degrees of CAN dysfunction (Table 2).

Table 3 presents the relation of duration of diabetes with CAN dysfunction. There was a total of 24 patients with less than 1 year of diabetes. Among these, 6 (25%) had no CAN dysfunction and 18 (75%) had CAN dysfunction. In the 30 subjects with duration of diabetes between 1 to 5 years 5 (16.66%) had no CAN dysfunction and 25 (83.33%) had CAN dysfunction.

Table 1: Relationship between sex and presence of CAN.

Sex	Presence of CAN				Total (n=102) %	p value
	Normal n (%)	Early n (%)	Definite n (%)	Moderate n (%)		
Male	12 (24.5)	18 (36.73)	13(26.53)	6 (12.2)	49 (75.7)	0.173
Female	8 (15.1)	18 (32.69)	23 (43.4)	4 (7.69)	53 (84.61)	

Table 2: Relationship between age and presence of CAN.

			CANS Dysfunction				Total	P value
			Normal	Early	Definite	Moderate		
Age in years	30-40	Count	5	7	3	1	16	0.013
		% within age in years	31.3%	48.3%	18.8%	6.3%	100%	
		% with CANS dysfunction	25%	19.4%	8.3%	10%	15.7%	
		Count	8	12	6	0	26	
		% within age in years	30.8%	46.2%	23.1%	0%	100%	
		% with CANS dysfunction	40%	33.3%	16.7%	0%	25.5%	
		Count	5	13	21	4	43	
		% within age in years	11.6%	30.2%	48.8%	9.3%	100%	
		% with CANS dysfunction	25%	36.1%	58.3%	40%	42.2%	
		Count	2	4	6	5	17	
		% within age in years	11.8%	23.5%	35.3%	29.4%	100%	
		% with CANS dysfunction	10%	11.1%	16.7%	50%		
Total		Count	20	36	36	10	102	
		% within age in years	19.6%	35.3%	35.3%	9.8%	100%	
		% with CANS dysfunction	100%	100%	100%	100%	100%	

Table 3: Relationship between duration of diabetes and presence of CAN.

Duration of diabetes (in years)	Normal n (%)	CAN n (%)	Total (n=102)	P value
<1	6 (25)	18 (75)	24	0.772
1-5	5 (16.66)	25 (83.33)	30	
6-10	4 (15.38)	22 (84.62)	26	
11-15	4 (30.76)	9 (69.24)	13	
>15	1 (11.11)	8 (88.89)	9	

Table 4: Relationship between glycaemic status (HbA1c) and presence of CAN.

Glycaemic status (HbA1c)	Presence of CAN				Total (n=102)	P value
	Normal n (%)	Early n (%)	Definite n (%)	Moderate n (%)		
≤7	5 (18.5)	10 (37.0)	9 (33.3)	3 (11.1)	27	0.827
7.1-8	7 (24.13)	10 (34.48)	11 (37.93)	1 (3.44)	29	
8.1-9	2 (12.2)	6 (36.5)	5 (31.25)	3 (18.75)	16	
9.1-10	3 (27.2)	3 (27.2)	4 (36.36)	1 (9.09)	11	
>10	3 (15.78)	7 (36.8)	7 (36.8)	2 (10.52)	19	

Table 5: Relationship between diabetic nephropathy and presence of CAN.

Nephropathy	Normal n (%)	CAN n (%)	Total (n=102)	P value
Present	2 (11.77)	15 (88.23)	17	0.301
Absent	18 (21.2)	67 (78.8)	85	

In 6 to 10 years duration cohort, we had 26 patients, out of which 4 (15.38%) had no CAN dysfunction and 22 (84.62%) had CAN dysfunction. In 11 to 15 years diabetes duration group, out of a total of 13 patients, 4

(30.76%) had no CAN dysfunction and 9 (69.24%) had CAN dysfunction.

As shown in Table 4, a total of 27 patients had HbA1c of less than 7%. In this group with good glycaemic control, only 5 (18.51%) had no CAN dysfunction whereas 10 (37.03%) had early CAN, 9 (33.3%) had definite and 3 (11.11%) had moderate CAN dysfunction. Among the 29 patients with HbA1c between 7.1 to 8%, 7 (24.13%) had no CAN dysfunction but 10 (34.48%) had early, 11 (37.93%) definite and 1 (3.44%) had moderate CAN dysfunction. In the cohort with 8.1 to 9 HbA1c there were 16 patients. Of these, 2 (12.2%) had no CAN dysfunction, 6(36.5%) had early, 5 (31.25%) had definite and 3 (18.75%) had moderate CAN dysfunction. In the 9.1 to 10 HbA1c group, out of 11 patients, 3 (27.2%) had no CAN dysfunction, 3 (27.2%) early, 4 (36.36%) definite and 1 (9.09%) moderate CAN dysfunction.19 patients had HbA1c >10%, of which 3 (15.78%) had no CAN dysfunction, 7 (36.8%) early, 7 (36.8%) definite and 2 (10.52%) moderate CAN dysfunction.

Table 6: Relationship between diabetic neuropathy and presence of CAN.

Neuropathy	Normal n (%)	CAN n (%)	Total (n=102)	P value
Present	3 (7.1)	39 (92.85)	42	0.006
Absent	17 (28.3)	43 (17.6)	60	

Table 7: Relationship between diabetic retinopathy and presence of CAN.

Retinopathy	Normal n (%)	CAN n (%)	Total (n=102)	P value
Present	3 (10.7)	25 (89.28)	28	0.034
Absent	17 (22.9)	57 (77.02)	74	

Diabetic nephropathy was detected in 17 patients who were enrolled in this study. Among the patients with nephropathy, 15(88.23%) had CAN dysfunction. 85 patients were without nephropathy but CAN dysfunction was present in 67 (78.8%) (Table 5) 60 patients had no neuropathy detected by biothesiometry. Of these 17(28.3%) had no CAN dysfunction and 43 (17.6%) had varied degrees of CAN dysfunction. A total of 42 patients were diagnosed with peripheral neuropathy, out of which 3 (7.1%) had no CAN dysfunction, whereas 39(92.85%) had varying degrees of CAN dysfunction as presented in Table 6.

As given in Table 7, 74 patients had no retinopathy. Among them, 17 (22.9%) had no CAN dysfunction whereas 57 (77.02%) had some degree of CAN dysfunction. A total of 28 patients were diagnosed with different stages of retinopathy and in this cohort, there were 3 (10.7%) with no CAN dysfunction and 25 (89.28%) with varying degrees of CAN dysfunction.

DISCUSSION

When there is damage of autonomic fibres innervating the heart and coronaries, there occur certain abnormalities not only of heart rate control but also of vascular dynamics.[4] It was believed that autonomic neuropathy had little if any contribution and correlation to peripheral neuropathies which commonly affect diabetes patients. More than forty years back, in order to assess cardiovascular reflex, the following five simple and non-invasive tests were proposed.

- Heart rate variation during deep breathing
- Immediate heart rate response to standing
- Heart rate response to valsalva manoeuvre
- Blood pressure response to standing
- Blood pressure response to sustained handgrip

These tests have been utilized successfully in a number of studies and for assessment of patients with features suggestive of autonomic dysfunction. It is mandatory to rule out end organ damage before subjecting the patient to these tests. They are valid, specific and significant time-tested procedures to diagnose autonomic neuropathy noninvasively. Technological advances in the past decade have made it possible to identify autonomic dysfunction in early stages with the help of objective standardized measures. This allows earlier intervention, when there is still a possibility to reverse the condition.

Information regarding the frequency of CAN in diabetic population is limited. The prevalence rates range from 1% to 90% according to various studies which used different endpoints. It may be present at the stage of prediabetes itself. It has poor prognosis and at times presents with orthostasis, exercise intolerance, postural hypotension, enhanced intra-operative and perioperative cardiovascular instability and increased incidence of silent myocardial infarction, ischemia and sudden death.[5] Age, obesity and duration of smoking are known risk factors for reduced heart rate variability in T2DM.

The present study is unique as we have not only estimated the prevalence of asymptomatic cardiac

autonomic neuropathy in T2DM population but also correlated it with HbA1c, age of patients, gender, duration of diabetes and associated microvascular complications like diabetic neuropathy, nephropathy and retinopathy.

In this study the overall prevalence of CAN in the South Indian T2DM population was found to be 80.39%. Of this 34.31% had early CAN dysfunction, 33.33% had definite CAN dysfunction and 9.80% had moderate CAN dysfunction. During history taking and physical examination all these patients who were included in the study were asymptomatic in relation to cardiac autonomic neuropathy. In a study by Zoppini et al, the prevalence of possible CAN and definite CAN has been reported to be 15.3% and 1.8% respectively in patients with newly diagnosed T2DM.[6]

In the study population, CAN dysfunction is almost equal in prevalence among both the genders but there was a statistically insignificant female preponderance. The most common age group affected was 51-60 years among males (90%) and 61-70years in females (100%). No significant association was seen with duration of diabetes (p=0.772), nephropathy (p=0.524) and HbA1c (p=0.827), though a single HbA1c value may not depict the glycaemic control throughout the course of the disease. Neuropathy (p=0.006) and retinopathy (p=0.03) were significantly associated with CAN in patients with type 2 diabetes.

Severe CAN was not included in the diagnostic tests because patients are symptomatic at this stage and our study was conducted on asymptomatic individual. For similar reasons, the percentage of patients with moderate degree of CAN was lesser than those with early and definite CAN and duration of diabetes did not significantly correlate with presence of CAN.

Research done by Krolewski et al, who correlated CAN with retinopathy in type 1 DM found a strong correlation of CAN with diabetic retinopathy but diabetic nephropathy correlated weakly.[7] Another study by Spallone et al showed relationship between autonomic neuropathy, 24 hours BP profile and nephropathy in normotensive T1DM patients and DAN was significantly associated to increased urinary albumin excretion.[8] Basu et al from eastern India studied 50 patients with T2DM and their study revealed 54% prevalence and it was strongly associated with retinopathy and microalbuminuria.[9] Study by Hyuang et al, confirmed retinopathy as the most significant risk factor in predicting the presence of CAN in patients with type 2 diabetes. His findings also revealed that younger patients with diabetes are more affected than older oneEURODIAB study found age, poor glycaemic status, high systolic BP, neuropathy and retinopathy to be significant risk factors for CAN dysfunction.[10,11]

CONCLUSION

The findings of the study help to conclude that increasing age, neuropathy, and retinopathy were the most significant microvascular complications associated with CAN in patients with type 2 diabetes. CAN was not significantly associated with duration of diabetes, HbA1c and nephropathy. Almost equal distribution of the disease was seen among both the genders.

This study helps us understand that CAN dysfunction appears much before patients manifest its signs and symptoms, hence CANS testing should be mandatory and started early to insist better metabolic control. As the problem is associated with other microvascular complications, further deterioration should be prevented. Age has a significant association with CAN hence elderly people with diabetes need regular CANS evaluation. Considering the vast implications of cardiac autonomic neuropathy in the progression and complication of diabetes, perhaps the most important thing we can do for our patients with diabetes is to make them aware of autonomic neuropathy, to let them know whether they have it, and to help them keep blood sugar levels in an acceptable range. Doing so not only helps reduce the risk of heart disease, but also lowers the risk of retinopathy, nephropathy and neuropathy. Diabetic autonomic neuropathy has been called a "silent killer," because few patients realize that they suffer from it, and yet its effects can be so lethal. With a brief, 15-minute test that can be administered in the office and some relatively modest interventions, the influence of DAN on the other complications of diabetes such as neuropathy, nephropathy and retinopathy can be minimized. Limitations of the study should be acknowledged. We understand that the cohort was not large enough to represent the whole population and larger studies involving more subjects are needed to confirm the findings of our present study.

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