Journal of Clinical and Biomedical Sciences

Original Article

Study Of Cardiac Autonomic Neuropathy In Type 2 Diabetes Mellitus

Murthy ANLN[1], LakshmaiahV,[2] AnithaAswathanarayana[3*]

1. Postgraduate, Department of Medicine, Sri Devaraj Urs Medical College
2. Professor, Department of Medicine, Sri Devaraj Urs Medical College
3. Assistant Professor, Department of Medicine, Sri Devaraj Urs Medical College, Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar, Karnataka, India

Abstract

Background: Cardiac Autonomic Neuropathy (CAN) represents a significant cause of morbidity and mortality in diabetic patients and is associated with a high risk of cardiac arrhythmias and sudden death, possibly related to silent myocardial ischemia. Cardiac autonomic function should be assessed in most diabetic patients as it contributes to the evaluation of cardiovascular risk. The presence of CAN should lead to further awareness of possible complications and optimal control of risk factors. Knowledge of early autonomic dysfunction can encourage patient and physician to improve metabolic control and to use therapies such as ACE inhibitors and beta blockers, proven to be effective for patients with CAN. **Objectives:** 1. To assess the cardiac autonomic function in patients with Type2 Diabetes Mellitus (T2DM) for detection of CAN. 2. To evaluate the relationship between CAN and duration of diabetes, and glycemic control in Type 2 DM. **Materials and Methods:** This is a case-control study conducted in Sri DevarajUrs Medical College, Tamaka, Kolar. Sixty patients (Cases) of T2 DM aged > 40 years admitted/visiting Diabetic clinic in R.L Jalappa hospital and 60 healthy non diabetic controls matched for age and sex and satisfied the inclusion and exclusion criteria and gave informed consent for the study were included in the study. All the cases and controls have undergone standard bedside cardiac autonomic function tests. They were evaluated for glycemic control with FBS, PPBS and HbA1c levels. Cases were divided into sub-groups depending on duration of diabetes and glycemic control. The relation between CAN and duration of diabetes and glycemic control was determined by Statistical analysis. **Results:** 60 cases with diabetes and 60 controls without diabetes were included in the study. Mean age of cases was 52.38 and controls was 51.97 years. There was no significant difference in age between two groups because of matching. 36 males and 24 females were included in both cases and controls.There was no difference in sex distribution which can be attributed to matching of subjects during data collection. The mean duration of diabetes among cases was 7.28 ± 3.61 years. CAN was present in 21 (35%) of diabetic patients, 13 (21.6%) cases had early features of CAN, whereas CAN was present in 2 (3.3%) of controls and was absent in 86.6% of controls. In the study it was observed that mean age of diabetics without CAN was 48.54 ± 5.7 years, Early CAN was 52 ± 6.17 and Definitive CAN was 57.38 ± 7.2 yrs. When cases were grouped according to duration of diabetes < 5 years and >5 years, 17.6 % and 41.8% of the cases in each group respectively had CAN, which is significant. About 85.7% of the cases who had CAN have had diabetes for a duration greater than 5 years. Among cases with HbA1c levels > 7%, about 54.54% had definitive CAN and 33.3% had Early CAN. It was observed that there was significant association between increased HbA1c levels and CAN. **Conclusion:** The present study suggests Cardiac Autonomic Neuropathy is common in Diabetics compared to healthy individuals. Cardiac Autonomic Neuropathy is associated with increase in the age of the patient and duration of diabetes. Cardiac autonomic neuropathy is associated with poor glycemic control.

Key Words: Cardiac Autonomic Neuropathy, Glycemic Control, HbA1c, Autonomic Function Tests, Type 2 Diabetes Mellitus.

***Corresponding Author**
Dr. AnithaAswathanarayana
Assistant Professor, Department of Medicine.
Sri Devaraj Urs Medical College, SDUAHER,
Tamaka, Kolar, Karnataka, India
E-mail: anithasdumc@gmail.com

Introduction

Diabetes Mellitus affects an estimated 250 million worldwide. WHO reported that total diabetics in India in 2000 was 31.7 million and

this number is likely to increase to 79.4 million by 2030. According to the Indian Council of Medical Research-Indian Diabetes study, a national diabetes mellitus study, India currently has 62.4 million people with diabetes mellitus. [1] Chronic hyperglycemia is a major initiator of micro vascular complications of Diabetes. Micro vascular complications comprise neuropathy, retinopathy and nephropathy. Neuropathy includes both peripheral and autonomic neuropathy.Cardiac autonomic neuropathy (CAN) is one of the major complications of diabetes mellitus. It is also the most under diagnosed and least understood.[2] CAN represents a significant cause of morbidity and mortality in diabetic patients and is associated with a high risk of cardiac arrhythmias and sudden death, possibly related to silent myocardial ischemia. Poor glycemic control plays an important role in the development and progression of diabetic cardiac autonomic neuropathy, and studies have shown that reduced cardiovascular autonomic function is associated with increased morbidity and mortality.Clinical symptoms of autonomic neuropathy generally do not occur until long after the onset of diabetes. Subclinical autonomic dysfunction can, however, occur within a year of diagnosis in type 2 diabetes patients and within two years in type 1 diabetes patients.[3] Cardiac autonomic function should be assessed in most diabetic patients as it contributes to the evaluation of cardiovascular risk.

The presence of CAN should lead to further awareness of possible complications and optimal control of risk factors. Knowledge of early autonomic dysfunction can encourage patient and physician to improve metabolic control. This study is undertaken to assess the cardiac autonomic function in patients with T2 DM and to evaluate the relationship between CAN and duration of diabetes, and glycemic control.

Materials and Methods

The study group included 120 subjects, 60 T2DM patients as cases, who were admitted in R.L Jalappa Hospital attached to SDUMC, Kolar or attending Diabetic Clinic attached to the hospital and 60 healthy non diabetic volunteers as controls, who were matched for age and gender with the cases. Cases were divided into two sub-groups based on the duration of diabetes, i.e, Group 1 with duration of diabetes </= 5yrs and Group 2 duration of diabetes > 5yrs. Cases were also divided in two sub-groups based on the glycemic control , i.e, Group 1 with HbA1c levels < 7% (T2DM patients with good glycemic control) and Group 2 with HbA1c levels > 7% (T2DM patients with poor glycemic control).

Inclusion Criteria (for cases):

1. T2 DM patients aged > 40yrs who gave informed consent for the study.

Exclusion Criteria (for cases):

1. Patients with cardiac rhythm abnormalities and atrioventricular conduction abnormalities.
2. Patients on drugs known to cause cardiac rhythm abnormalities and atrioventricular conduction abnormalities.
3. Patients with coexisting organic heart disease.
4. Patients who were smokers and alcoholics.

Inclusion Criteria (for controls):

1. Healthy non diabetic individuals aged > 40 years.
2. HbA1c levels less than 6%.

Exclusion Criteria (for controls):

1. Subjects with cardiac rhythm abnormalities and atrioventricular conduction abnormal
2. Subjects on drugs known to cause cardiac rhythm abnormalities and atrioventricular conduction abnormalities.
3. Subjects with coexisting organic heart disease.
4. Subjects who were smokers and alcoholics.

All the cases and controls who fulfilled the inclusion and exclusion criteria and have given consent to the study were subjected to detailed clinical examination which included bedside tests for cardiovascular autonomic neuropathy. All the cases and controls have undergone the following investigations for

evaluation of glycemic control, i.e, FBS, PPBS and HbA1c. Later, the cases were divided into groups based on duration of diabetes and also according to glycemic control. The relationship between CAN and duration of diabetes and glycemic control was evaluated by statistical analysis. The glycosylated Hb level is estimated by cat-ion exchange resin method.

Autonomic Function Tests. [4,5]

1. Lying to standing test (LST) – Change inSystolic Blood Pressure (SBP). Blood pressure was recorded in the upper arm by sphygmomanometer in supine position at rest and again recorded 1 minute after standing. The postural fall in systolic blood pressure was taken as a difference between systolic pressure in supine and systolic pressure on 1 min. after standing.

2. Normal: ≤ 10 mmHg. Borderline: 11 – 20 mmHg. Abnormal: ≥ 20 mmHg. Handgrip test (HGT) - Change in Diastolic Blood Pressure (DBP). Resting systolic blood pressure was recorded. Subjects were asked to maintain handgrip in other arm at 30 % of maximum voluntary pressure for up to 5 minutes. Systolic pressure was recorded each minute. The difference between the resting systolic pressure and maximum systolic pressure during sustained handgrip was considered for the interpretation. Normal: ≥ 16 mmHg. Borderline: 11 – 15 mmHg. Abnormal: ≤ 10 mmHg.

3. Cold Pressor test (CPT) - Change in DBP The cold pressor test was evaluated by immersion of subjects left hand (up to wrist) in cold water at 8 0C for 2 min. in recumbent position. Blood pressure was measured before immersion and 1 min. after immersion of hand. In normal persons immersing of hands in ice water raises the systolic pressure by 15 – 20 mmHg and the diastolic pressure by 10 – 15 mmHg. Normal: ≥ 16 mmHg. Borderline: 11 – 15 mmHg. Abnormal: ≤ 10 mmHg.

4. Deep breathing test (DBT) - delta heart rate. With subject sitting, ECG was recorded in lead II throughout the period of deep breathing. Subject breaths deeply and evenly at 6 breaths per minute (5 sec. in, 5 sec. out) for 3 cycles (30 sec.). The onset of inspiration and expiration were marked on ECG paper. The maximum and minimum R-R interval were measured during expiration and inspiration respectively in each cycle. The heart rate difference during each cycle was measured and average of the 3 differences was considered. Normal: ≥ 15 beats / min. Borderline: 11 – 14 beats / min. Abnormal: ≤ 10 beats / min.

5. Valsalva maneuver (VM) - Valsalva Ratio (VR). The quantitative Valsalva maneuver was performed by blowing with open glottis into a mouthpiece connected to mercury column of a sphygmomanometer. Subjects/patients were asked to maintain 40–50mmHg pressure for 15 sec. The ECG was recorded for 15 sec. during and 30 sec. after the maneuver. Valsalva ratio was calculated by using the following formula.

Valsalva ratio = Longest R-R interval after maneuver. Shortest R-R interval during maneuver.

Normal:> 1.21. Borderline: 1.11-1.20. Abnormal: < 1.10.

6. Lying to standing test (30:15 ratio).
The ECG limb leads were attached and ECG was recorded in lead II. Subject stands from supine position as quickly as possible. The 30: 15 ratio i.e. ratio of longest R-R interval around 30th beat after standing to shortest R-R interval about 15th beat after standing were considered .

Normal: ≥ 1.04. Borderline: 1.01-1.03. Abnormal: ≤ 1.01.

After the subjects have undergone the above mentioned six autonomic functions tests, the presence of CAN was determined by the following criteria.

Normal = all test normal or one test borderline.
Early CAN = one test abnormal or two test borderline.

Definite CAN = two tests abnormal.
The relationship between CAN, duration of diabetes and glycemic control was determined .by Statistical Analysis.

Statistical analysis:

Data collected was entered into Microsoft excel data sheet and was analyzed using EPI info Version 7 software. Qualitative data was represented in the form of frequencies, proportions and Chi-square test was the test of significance. Quantitative data was represented as Mean, Standard Deviation and Student's t test (Independent t test) and ANOVA (Analysis of Variance) were the tests of significance. p value <0.05 was considered as statistically significant.

Results

60 cases with diabetes and 60 controls without diabetes were included in the study. Mean age of cases was 52.38 and controls was 51.97 years respectively. There was no significant difference in age between two groups because of matching.In the study there were equal no of females and males in both cases and controls. There was no difference in sex distribution. This can be attributed to matching of subjects during data collection.

Table 1. Cardiac autonomic neuropathy in Cases and Controls

		Groups		
		Cases	**Controls**	**Total**
Cardiac autonomic Neuropathy (CAN)	**Absent**	26	52	78
	Definite CAN	21	2	23
	Early CAN	13	6	19
Total		60	60	120

Table 2. Glycemic status among Cases and Controls.

		N	Mean	Std. Deviation	t value	p value
FBS	**Cases**	60	132.77	42.399	7.499	<0.0001**
	Controls	60	89.10	15.385		
PPBS	**Cases**	60	176.68	59.595	7.732	<0.0001**
	Controls	60	114.27	18.935		
HbA1c	**Cases**	60	7.30	1.139	11.16	<0.0001**
	Controls	60	5.47	0.566		

Table 3. Mean Age in Cardiac autonomic neuropathy

		N	Mean	Std. Deviation	F	p value
Age	**Definitive CAN**	21	57.38	7.290	11.105	0.0001**
	Early CAN	13	52.00	6.178		
	Absent	26	48.54	5.715		
	Total	60	52.38	7.420		

Table 4. Sympathetic tests in Cardiac autonomic neuropathy

		N	Mean	Std. Deviation	F value	p value
LST- ΔSBP (in mm Hg)	**Definitive CAN**	23	12.78	6.082	41.330	<0.0001**
	Early CAN	19	8.74	4.544		
	Absent	78	5.53	1.585		
	Total	120	7.43	4.447		
HGT-ΔDBP(in mm Hg)	**Definitive CAN**	23	14.00	4.758	16.502	<0.0001**
	Early CAN	19	16.37	3.483		
	Absent	78	17.96	1.970		
	Total	120	16.95	3.307		
CPT-ΔDBP(in mm Hg)	**Definitive CAN**	23	15.35	5.006	7.263	<0.0001**
	Early CAN	19	18.37	3.218		
	Absent	78	18.17	2.525		
	Total	120	17.66	3.407		

Table 5. Para sympathetic tests in Cardiac autonomic neuropathy

		N	Mean	Std. Deviation	F value	p value
DBT	**Definitive CAN**	23	13.65	5.749	15.657	<0.0001**
	Early CAN	19	16.68	6.856		
	Absent	78	19.85	3.875		
	Total	120	18.16	5.392		
VR	**Definitive CAN**	23	1.09	0.288	4.112	0.019**
	Early CAN	19	1.42	0.607		
	Absent	78	1.45	0.573		
	Total	120	1.38	0.551		
LST (30:15) R	**Definitive CAN**	23	1.014	0.055	14.397	<0.0001**
	Early CAN	19	1.067	0.051		
	Absent	78	1.086	0.057		
	Total	120	1.069	0.061		

Discussion

Diabetic autonomic neuropathy (DAN) is among the least recognized and understood complications of diabetes, despite its significant negative impact on survival and quality of life in people with diabetes.Cardiac autonomic neuropathy (CAN) encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics.

This study was undertaken to assess the cardiac autonomic function in patients with T2 DM and to evaluate the relationship between CAN and duration of diabetes, and glycemic control. In this study, 60 cases (patients with T2DM) and 60 controls (healthy volunteers) have undergone the previously described autonomic function tests, investigations for glycemic control and the data obtained was statistically evaluated.

In this study, the mean age of cases was 52.38 years and controls was 51.97 years. There was no significant difference in age between two groups because of matching. In the study it was observed that mean age of diabetics without CAN was 48.54 ± 5.7 years, Early CAN was 52 ± 6.17 and Definitive CAN was 57.38 ± 7.2 yrs. There was a statistically significant relationship (p value - 0.0001) between CAN and increasing age among the diabetics. There were 24 females and 36 males in both cases and controls. There was no significant difference in sex distribution. This canbe attributed to matching of subjects during data collection.

In this study it was observed that Cardiac Autonomic Neuropathy was present in 21 (35%) of the diabetic patients, 13 (21.6%) cases had early features of CAN and in 26 (43.3%) cases CAN was absent. Whereas CAN was present in 2 (3.3%) of controls and was absent in 86.6% of controls. This observation was statistically significant

The mean duration of diabetes in cases was 7.28 + 3.61 years. It was observed that with increase in duration of diabetes there was increase in the risk of CAN among diabetics. This observation was found to be statistically significant between the groups and within the groups (p value = 0.001). This finding was in agreement with many of the previous studies which were conducted for finding the prevalence of CAN. Mohan et al[8] studied an increase in prevalence of CAN with duration of diabetes. In this study it was observed that Mean RHR was more among diabetics, SBP and DBP was high in diabetics compared to non-diabetics which was statistically significant. Resting tachycardia and a fixed heart rate are characteristic late findings in diabetic patients with vagal impairment.[9]

In Lying to Standing Test, to evaluate the sympathetic component, the mean fall in SBP in subjects with Definite CAN was 12.78 + 6.02 mm Hg,which when compared to 5.53 + 1.58 mm Hg in subjects without CAN, was statistically significant(p value - <0.0001). The mean increase in the DBP in Hand Grip Test was 15.8 + 3.91mm Hg in Cases which was low when compared to 18.1 + 2.00 mm Hg in controls. This finding was statistically significant when diabetic patients were compared to healthy volunteers. Blood pressure response to sustained handgrip was significantly reduced in diabetics. Increase in DBP to sustained handgrip was highly significant between controls and well controlled diabetics, controls and poorly controlled diabetics also between well controlled and poorly controlled diabetics.Popovic et al studied effect of sustained hand grip on BP variation in 90 subjects and observed an abnormal BP variation in type II Diabetics than compared to other groups.[10]

The mean increase in the DBP in Cold Pressor Test was 17.15 + 3.50 in Cases which was lower when compared to 18.17 + 3.25 mm Hg in Controls and was statistically significant.In study done by Sayinal P.S, Sozen T, Ozdogan M entitled “Cold pressor test in diabetic autonomic neuropathy” in 1994, the CPT was applied to a group of diabetic patients (n=33) and control group (n=15), the mean systolic cold pressor response in diabetic patients was found similar to controls (9 ± 1.4 vs 10.6 ± 1.2 mmHg).[11]

In this study, about 43.5% of the subjects who had CAN, had an abnormal Deep Breathing Test and in 96.2% of the subjects having normal DBT, CAN was absent. This was statistically significant. DBT was significantly decreased ($p<0.0001$) in both the diabetic groups when compared to controls. This shows that there is progressive parasympathetic dysfunction in diabetics but it is more in poorly controlled diabetics. In this study, 60.9% of the subjects with CAN, had abnormal valsalva ratio and in 88.7% of the subjects having normal VR, CAN was absent. About 34.8% of CAN subjects had abnormal LST (30:15) Ratio and 94.4% of normal LST (30:15) R test CAN was absent. Spallone V et al performed cardiovascular autonomic function test in 35 normotensive diabetic subjects by measuring HRV from lying to standing, using 24 hour ECG recording and found significant variation in HRV from lying to standing ($P< 0.02$).

In 85.71 % of the cases with Definite CAN, HbA1c levels were greater than 7% (Poorly Controlled T2 DM) when compared to 14.29 % who had HbA1c levels less than 7%, which was significant. Sustained hyperglycemia levels leads to vascular and metabolic complications resulting in severe autonomic dysfunction. In the poorly controlled diabetics (HbA1c > 7%) long-standing hyperglycemia induced pathological changes intrinsic to neurons[13] may be the probable cause for the noticed autonomic dysfunction in our study. J.M.Pappachan, J.Sebastian, et al,[14] in their study, also showed that incidence of diabetic autonomic neuropathy increased with increasing duration and poor glycemic control. Early observations by researchers that near normal glycemic control seems to be the most effective way to delay the onset of CAN and arrest its progression. Hence it is important in emphasizing tight glycemic control for individuals with autonomic dysfunction with re-education of the patient with regard to need for regular monitoring and hypoglycemia.

Conclusions

1. Cardiac Autonomic Neuropathy is common in Diabetics compared to healthy individuals.
2. Cardiac Autonomic Neuropathy is associated with increase in the age of the patient and duration of diabetes.
3. Cardiac autonomic neuropathy is associated with poor glycemic control.

References

1. Anjana RM, Pradeepa R, Deepa M, et al. ICMR-INDIAB Collaborative Study Group: Prevalence of diabetes and prediabetes in rural and urban India: Phase 1 results of the Indian Council of Medical Research-INdiaDIABetes (INDIAB) study. Diabetologia 2011; 54:3022-3027.
2. Maser RE, Lenhard MJ, DeCherney GS. Cardiovascular autonomic neuropathy: the clinical significance of its determination. Endocrinologist 2000; 10: 27–33.
3. Pfeifer MA, Weinberg CR, Cook DL, Reenan A, Halter JB, Ensinck JW, et al. Autonomic neural dysfunction in recently diagnosed diabetic subjects. Diabetes Care 1984; 7: 447–453.
4. Ewing DJ. Autonomic function testing (clinical) – Michael Poon's Shrine of neurology. 1985, 1988 in www.Autonomic function testing.html. (accessed on 4/8/14).
5. EktaKhandelwal, Ashok Kumar Jaryal, Kishore Kumar Deepak. Pattern and Prevalence of Cardiovascular Autonomic Neuropathy in Diabetics visiting a Tertiary Care Referral Centre in India. Indian J PhysiolPharmacol 2011;55: 119-127.
6. Aaron I. Vinik, Raelene E. Maser, Braxton D. Mitchell, Roy Freeman, "Diabetic Autonomic Neuropathy". Diabetes Care May 2003; 26 :1553-1579.
7. J.M.Pappachan, J.Sebastian, B.C. Bino, et al, Cardiac Autonomic Neuropathy in Diabetes Mellitus: prevalence, risk factors and utility of Corrected QT interval in the ECG for its Diagnosis, Kottayam Medical College, South India. Melaka Manipal Medical College, Malaysia. 88. Rundle RW. "Diabetic neuropathy". Medicine (Baltimore) 1945; 24: 111-160.
8. Mohan V et al. Autonomic Neuropathy in NIDDM and fibrocalculus pancreatic diabetes in south India, Diabet Med 1996; 13: 1038-1043.
9. Hage FG, Iskandrian AE. Cardiovascular imaging in diabetes mellitus. J NuclCardiol 2011; 18: 959–965.

10. Popovic S, TodorovicDilas L, Pantelinac P. The role of autonomic cardiovascular neuropathy in pathogenesis of ischemic heart disease in patients with diabetes mellitus. Med Pregl. 2006 Mar-Apr; 59(3-4):118-23.

11. Sayinal P.S, Sozen T, Ozdogan M. cold pressor test in diabetic autonomic neuropathy. Diabetes. Res. Clin. Pract. 1994; 26 (1) : 21- 28.

12. Bhatia S. G. Sainani S.G. Nayak N. J and Diwate P.G. Valsalvamanoeuvre as a test of autonomic neuropathy in diabetes mellitus. Jr.Asso.Phys.Ind.1976; 24 : 89-93.

13. Peters AL. Peters MB. Davidson DL, Schriger V, Hasselblad. A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated hemoglobin levels. Meta-analysis Research Group on the Diagnosis of Diabetes Using Glycated Hemoglobin Levels J. Am. Med. Assoc., 1996; 276 :1246–1252.

14. 102. J.M.Pappachan, J.Sebastian, B.C. Bino, et al, Cardiac Autonomic Neuropathy in Diabetes Mellitus: prevalence, risk factors and utility of Corrected QT interval in the ECG for its Diagnosis, Kottayam Medical College, South India. Melaka Manipal Medical College, Malaysia. 88. Rundle RW. "Diabetic neuropathy". Medicine (Baltimore) 1945; 24: 111-160.