

Original Research Article

To study the impact of glycemic control over cardiac autonomic neuropathy in type 1 and type 2 diabetics patients using bedside tests at a tertiary care hospital

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ABSTRACT

Background: Cardiac autonomic neuropathy a serious complication of diabetes and is often overlooked. It is associated with higher cardiovascular mortality and poor quality of life in diabetic individuals. The Glycemic control has been well established as the risk factor for all the diabetes related microvascular and macrovascular complications. This stresses importance of role of glycemic control over CAN in Type 1 and Type 2 Diabetics in order to stop further progression to advanced and irreversible stages. The objective was to study the impact of various demographic and other clinical factors over prevalence of CAN in type 1 and type 2 diabetic patients who are asymptomatic for CAN using bedside tests

Methods: A case control comparative clinical study was undertaken comprising of 100 diabetic patients, both type 1 and type 2 with duration from 5-10 years and >10 years. The tests which were performed are deep breathing test, heart rate response to standing, hand grip test, cold pressor test, BP response to standing. Depending on these tests, patients were categorised as patients with cardiac autonomic neuropathy and without cardiac autonomic neuropathy.

Results: The prevalence of cardiac dysautonomia was 68%. Type 2 diabetics had higher prevalence of cardiac dysautonomia than type 1 diabetics ($p=0.025$). Significant correlation was observed between cardiac autonomic neuropathy and poor glycemic status (type 1 $p<0.001$; type 2 $p<0.001$). The mean HbA1c in patients with and without CAN in type 1DM was 9.16 ± 0.81 and 7.21 ± 0.56 and in type 2 DM was 9.15 ± 1.72 and 7.15 ± 0.53 respectively. Similarly, presence of other microvascular complications increased the prevalence of CAN in both types of diabetes mellitus.

Conclusions: Cardiac autonomic neuropathy is a common complication in long standing diabetes. Present results suggest that glycemic status of the diabetics is undoubtedly an important factor for the onset of cardiac dysautonomia which in turn account for high prevalence of cardiac mortality in diabetic patients. All asymptomatic diabetic patients should be evaluated for the presence of autonomic neuropathy and glycemic status should be controlled to prevent the further progression of CAN.

Keywords: Autonomic Function test, Autonomic neuropathy, Cardiac dysautonomia, Glycemic control, Prevalence, Type 1 Diabetes mellitus, Type 2 Diabetes mellitus

INTRODUCTION

The metabolic dysregulation associated with diabetes mellitus causes secondary pathophysiologic changes in multiple organ system that impose tremendous burden on

individual with diabetes and on health care system.¹ The global figure of people suffering from diabetes is estimated to rise from current estimate of 150 million to 300 million in 2025. Among this the greatest increase will be in India; from 19 million in 1995 to 578 million in

2025.² Diabetic neuropathy occurs in approximately 50% of individuals with long standing type 1 and type 2 diabetes mellitus. Diabetic autonomic neuropathy can affect cardiovascular (CV), gastrointestinal, genitourinary, sudomotor and metabolic system.³ The risk of developing autonomic dysfunction in DM depends on duration of the disease and the degree of glycemic control. Clinical symptoms of autonomic neuropathy generally do not occur until long after the onset of diabetes.⁴

Cardiovascular autonomic neuropathy (CAN) is one of the most clinically significant complications of DM, but one of the least frequently evaluated. The prevalence of borderline or definite CAN is 8.5 to 16.8% among type 1 diabetic patients and 12.2% to 22.2% among type 2 diabetic patient respectively.⁵

CAN is associated with higher cardiovascular morbidity and mortality rates and poor quality of life in diabetic individuals.⁶ The mortality at 5 to 7 years of CAN will be in the order of 50%.⁷

In this study an attempt has been made to study the utility of the bedside autonomic function evaluation tests in analysing the prevalence of asymptomatic autonomic dysfunction in both type 1 and type 2 diabetics who have not developed overt target organ dysfunction.

METHODS

The study was conducted at the department of medicine, K.R. Hospital, Mysore, Karnataka, India for a period of one year. One hundred patients of both type 1 and type 2 diabetics from outpatients and inpatients were included in the study. In each type of diabetes, the study population was sub grouped as per the duration of diabetes i.e. <10 years and >10 years. Thirty healthy controls were also subjected the tests.

Exclusion criteria

- Postural dizziness with vasovagal syncope or syncope due to other causes except hypoglycemic attacks.
- Vasodilators for any disease like peripheral vascular disease or hypertension.
- Chronic alcoholism and alcohol dependency.
- Alpha blockers and beta blockers.
- Overt renal failure.
- Antihypertensive medication.
- Patients with clinically overt peripheral neuropathies.
- Heart failure.
- Anemia (Hb% of <11gm% in men and <10gm% in women).
- Overt autonomic neuropathy.

Patients were enquired about symptoms of autonomic neuropathy like syncope, fainting, palpitations, fullness

of stomach, nausea, vomiting of partially digested food, bouts of nocturnal diarrhea, constipation, urinary incontinence, dribbling of urine, retention of urine, impotence, sweating abnormalities like hyperhidrosis or anhidrosis of hand and foot and gustatory sweating. The bedside tests were performed after instructing them to abstain from caffeine drinks and smoking. Informed consent was obtained from the participants.

Deep breathing test, sustained handgrip test, cold pressor test, immediate heart rate response to standing, and blood pressure response to standing, were performed as per the AFT laboratory guidelines, AIIMS.⁸ The results were subdivided into normal (all test normal), early CAN (one or more tests borderline) and definite CAN (one test abnormal).

Statistical methods

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. The following assumptions on data is made

- Dependent variables should be normally distributed.
- Samples drawn from the population should be random, cases of the samples should be independent.

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Student t-test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven's test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

RESULTS

The study group included 49 Type 1 diabetics, 51 Type 2 diabetic patients and 30 healthy controls. The mean age of type 1 diabetics and type 2 diabetics was 26.76±6.49 yrs (14-45 years) and 56.22±7.42 (32-70 years) respectively. Majority of the type 1 diabetics belonged to 3rd decade (53%). Among the type 2 diabetics nearly ½ of them belonged to 6th decade (49%).

We took 5 healthy controls from each decade starting from 2nd to 7th decade with a mean age of 40.27±16.71 years (range: 11-70 years). There was male preponderance in type 1 diabetics (M:F=2.2:1) and mild female preponderance in type 2 diabetics (M:F=0.96:1). In type 1 diabetes mellitus, 29 (59.2%) were with duration of less than 10 years and 20 (40.8%) had diabetes for more than 10 years. In type 2 diabetes

mellitus, 25 (49.1%) were with duration of less than 10 years and 20 (50.9%) had diabetes for more than 10 years.

All type 1 DM patients were on insulin therapy at onset, at 5 years and at 10 years. In type 2 DM patients at 5 yrs all were on OHA's, however in patients with >10 years of duration, 4 were exclusively on insulin and remaining 21 were on OHA's. The mean BMI among type 1 was 19.43±2.86. The mean BMI in type 2 diabetics was 26.63±3.03. The overall glycemic control between type 1 and 2 diabetics was evaluated with HbA1C. The mean HbA1C did not differ between type 1 (8.34±1.21) and type 2 diabetics (8.72±1.75) (p=0.218).

Table 1: Demographic variables and clinical features of autonomic dysfunction in the study.

Variable	Type-1	Type-2	Control
Age (years)	26.73±6.49	56.22±7.42	41.78±16.35
Gender			
Male (%)	33 (67.3)	25 (49)	26 (86.71)
Female (%)	16 (32.7)	26 (51)	4 (13.3)
Family history			
Diabetes (%)	7 (14.3)	23 (45)	5 (16.7)
Cardiac death (%)	8 (16.3)	17 (33.3)	7 (23.3)
Habits			
Smoking (%)	15 (30.6)	21 (41.2)	15 (50)
Alcohol (%)	8 (16.3)	20 (39.2)	17 (56.7)
Clinical autonomic dysfunction			
Skin changes (%)	7 (14.3)	25 (49)	-
Nail changes (%)	4 (8.2)	3 (5.9)	-
Hair loss (focal) (%)	10 (20.4)	25 (49)	-
Foot (ulcer) (%)	0	0 (0)	-
Pedal edema (%)	0	1 (1.9)	-
Sweating abnormalities (%)	5 (10.2)	17 (33.3)	-

Table 2: Prevalence of cardiac autonomic neuropathy among type 1 and type 2 diabetics in the study population.

CAN	Type I DM (n=49)		Type II DM (n=51)		Total DM (n=100)	
	No.	%	No.	%	No.	%
No CAN	21	42.9	11	21.6	32	32.0
Early CAN	2	4.1	4	7.8	6	6.0
Definite CAN	26	53.1	36	70.6	62	62.0

The overall prevalence of CAN in present study was 68%. CAN was more prevalent among type 2 (78%) compared to type 1 (57.1%). The early CAN was less prevalent in both type 1 (4.1%) and type 2 (7.8%). However, definite CAN was seen in 70.6% of type 2 diabetics and 53.1% of type 1. Although we have included even single borderline test as early CAN,

present study showed that nearly 2/3rd (68%) of asymptomatic diabetics showed abnormal autonomic tests. The lower socioeconomic status showed higher association with the presence of CAN (p=0.001 in type 1 diabetics and 0.004 in type 2 diabetics).

However, presence of cardiac death among family members (p=0.009), poor glycemic control (p<0.001), presence of other microvascular changes such as microalbuminuria (p=0.026), and diabetic retinopathy (p<0.001) showed higher association with the presence of CAN among type 2 diabetics. There was no statistically significant correlation between presence of CAN with the duration of the diabetes.

DISCUSSION

In the current study an attempt was made to look for correlation between various demographic factors, duration of diabetes, glycemic control, and with the presence of other microvascular complications such as microalbuminuria, retinopathy and prolonged QTc interval.

Kempler et al showed that age, duration of diabetes, glycemic control, presence of other microvascular complications at the time of evaluation for autonomic neuropathy showed stronger correlation among European type 1 diabetics.⁹ Khoharo HK et al showed that duration of the diabetes had stronger correlation with the presence of CAN among Asian type 1 diabetics.¹⁰

Chen HT et al found statistically significant correlation between duration of diabetes, age of the study population, glycemic control, presence of other microvascular complications such as retinopathy, microalbuminuria, prolonged QTc interval had stronger relationship with CAN among Asian type 2 diabetics.¹¹ Aggarwal S et al reported significant correlation between the glycemic control and cardiac dysautonomia (p<0.001).¹²

In the present study similar observations were made with respect to glycemic control and presence of other microvascular complications at the time of evaluation for CAN. Although the number of study population was smaller we had included both forms of diabetes and compared with the healthy controls which has given statistical strength to the study.

The lower socioeconomic status which will in turn influence the glycemic control was found to be significantly associated with the presence of CAN among both type 1 (p<0.001) and type 2 diabetics (p=0.004). similarly, presence of cardiac deaths among family members of the type 2 diabetics (p=0.009) also showed probable genetic predisposition for the development of CAN among type 2 diabetics, the factor which needs to be further evaluated in future studies.

Table 3: Correlation of variables with or with cardiac autonomic Neuropathy (CAN) in Type I DM and II DM.

Variables	Total number of patients (n=49)	CAN in type I DM		P-value	Total number of patients (n=51)	CAN in type II DM		P-value
		Absent (n=21)	Present (n=28)			Absent (n=11)	Present (n=40)	
Age in years	26.76±6.49	25.29±5.76	26.86±6.88	0.172	56.22±9.81	56.09±9.81	56.25±6.78	0.951
Gender								
Male	33 (67.3%)	14 (66.7%)	19 (67.9%)	0.930	25 (49%)	4 (36.4%)	21 (52.5%)	0.343
Female	16 (32.7%)	7 (33.3%)	9 (32.1%)		26 (51%)	7 (63.6%)	19 (47.5%)	
Income								
Up to 2000	7 (14.3%)	1 (4.8%)	6 (21.4%)	<0.001**	21 (41.2%)	0 (0%)	21 (52.5%)	0.004**
2001-5000	28 (57.1%)	7 (33.3%)	21 (75%)		21 (41.2%)	7 (63.6%)	14 (35%)	
5001-10000	12 (24.5%)	11 (52.4%)	1 (3.6%)		6 (11.8%)	3 (27.3%)	3 (7.5%)	
>10000	2 (4.1%)	2 (9.5%)	0 (0%)		3 (5.9%)	1 (9.1%)	2 (5%)	
Occupation								
Unskilled	4 (8.2%)	2 (9.5%)	2 (7.1%)	0.955	6 (11.8%)	0 (0%)	6 (15%)	0.776
Semi Skilled	16 (32.7%)	6 (28.6%)	10 (35.5%)		6 (11.8%)	2 (18.2%)	4 (10%)	
Skilled	12 (24.5%)	5 (23.8%)	7 (25%)		5 (9.8%)	1 (9.1%)	4 (10%)	
Professional	2 (4.1%)	1 (4.8%)	1 (3.6%)		1 (2%)	0 (0%)	1 (2.5%)	
House Wife	6 (12.2%)	3 (14.3%)	3 (10.7%)		26 (51%)	6 (54.5%)	20 (50%)	
Not Working	9 (18.4%)	4 (19%)	5 (17.9%)		7 (13.7%)	2 (18.2%)	5 (12.5%)	
F/O Diabetes Mellitus								
Absent	42 (85.7%)	18 (85.7%)	24 (85.7%)	1.000	28 (54.9%)	7 (63.6%)	21 (52.5%)	0.734
Present	7 (14.3%)	3 (14.3%)	4 (14.3%)		23 (45.1%)	4 (36.4%)	19 (47.5%)	
Family H/O cardiac deaths								
Absent	41 (83.7%)	19 (90.5%)	22 (78.6%)	0.438	34 (66.7%)	11 (100%)	23 (57.5%)	0.009**
Present	8 (16.3%)	2 (9.5%)	6 (21.4%)		17 (33.3%)	0 (0%)	17 (42.5%)	
Smoking								
Non smoker	34 (69.4%)	13 (61.9%)	21 (75%)	0.325	30 (58.8%)	7 (63.6%)	23 (57.5%)	0.750
Current smoker	15 (30.6%)	8 (38.1%)	7 (25%)		11 (21.6%)	2 (18.2%)	3 (7.5%)	
Past smoker	0 (0%)	0 (0%)	0 (0%)		10 (19.6%)	2 (18.2%)	8 (20%)	
Alcohol								
Never drinker	41 (83.7%)	17 (81%)	24 (85.7%)	1.000	31 (60.8%)	8 (72.7%)	23 (57.5%)	0.154
Current drinker	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	0 (0%)	
Past drinker	2 (4.1%)	1 (4.8%)	1 (3.6%)		2 (3.9%)	0 (0%)	2 (5%)	
Social drinker	6 (12.2%)	3 (14.3%)	3 (10.7%)		18 (35.3%)	3 (27.3%)	15 (37.5%)	
BMI (kg/m²)	19.43±2.86	19.10±3.05	19.69±2.74		26.64±3.01	25.52±3.17	26.94±2.92	0.165
Duration of DM	9.87±3.85	9.36±3.23	10.25±4.27		9.70±3.37	8.68±3.08	9.98±3.43	0.264
HbA1c	8.33±1.20	7.2±0.56	9.16±0.81		8.72±1.75	7.15±0.53	9.15±1.72	<0.001**
Urine for Micro albumin (mg)	45.57±63.13	17.43±2.84	66.68±77.47		68.02±84.81	18.16±2.69	81.74±91.25	0.026*
QTc Interval (msec)	419.06±42.68	396.83±26.53	435.71±45.23		429.94±43.07	406.64±36.03	436.35±43.01	0.041*
Retinopathy	7 (100.0%)	0	7 (25%)		27 (100.05)	0	27 (±67.5)	<0.001*

CONCLUSION

Cardiac autonomic dysfunction is not uncommon among asymptomatic type 1 and type 2 diabetic patients. Most of the studies including the current study had shown stronger correlation with poor socioeconomic status, glycemic control and presence of other microvascular damage among diabetics. Cautious and sincere attempts is needed to tackle these factors in a country like ours which has fast increasing diabetic individuals which might affect the all-round progress of the nation.

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