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Severity of Cardiovascular Autonomic Neuropathy in Type 2 Diabetes Mellitus Patients : Correlation with Duration of Diabetes

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Abstract

Introduction: Cardiovascular Autonomic Neuropathy (CAN) is one of the most overlooked complications of DM and is clinically important because of its life threatening consequences. CAN results from damage to the autonomic nerve fibers that innervate the heart and blood vessels.

Aims and Objectives The aim of the present study is to assess the correlation between severity of cardiovascular autonomic functions in type 2 DM and duration of diabetes.

Method: The study included 30 cases of type 2 diabetes mellitus without diabetic retinopathy and 30 cases of type 2 diabetes mellitus with non proliferative diabetic retinopathy (NPDR). 60 non diabetic healthy volunteers matched for age and gender were included in the study to serve as control. The study group was classified into 3 groups according to duration of diabetes. All the subjects performed five different autonomic function tests as given by Ewing's and Clarke. The score value was obtained from various tests and a scoring system was applied as recommended by Bellavere F et al (1983).[4] The results obtained were analysed statistically by one-way ANOVA and intergroup comparisons were made using post hoc Tukey multiple comparison test.

Results: The observations suggest that cardiac autonomic function declines in type 2 diabetics and CAN is more in diabetic patients with associated retinopathy The observations revealed that number of patients with autonomic dysfunction was more when duration of DM was long (>7 years) (83.3% in group 1 and 81.2% in group 2). The number of patients with CAN increased with duration of DM.Correlation between disease duration and cardiovascular autonomic score indicates significant positive correlation (r=0.5920).

Conclusion: The cardiac autonomic functions were found to be altered significantly in diabetics. Diabetic patients with longer duration of diabetes showed more severe dysfunction of cardiovascular functions. Hence, Evaluation of cardiovascular reflexes should be included as a routine in the work-up of patients of Type 2 diabetes mellitus.

Keywords: *Diabetes mellitus, Cardiovascular Autonomic Neuropathy, Autonomic function tests.*

Introduction

Neuropathy is one of the most common complications of diabetes. About half of all people with diabetes have some degree of neuropathy, which can be polyneuropathy, mononeuropthy and /or autonomic neuropathy. Cardiovascular Autonomic Neuropathy (CAN) is one of the most overlooked complications of DM and is clinically important because of its life threatening consequences[1]. CAN results from damage to the autonomic nerve fibers that innervate the heart and blood vessels and it causes abnormalities in control of heart rate and vascular dynamics[2].

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The present study was designed to assess the correlation between severity of cardiovascular autonomic functions in type 2 DM and duration of diabetes.

Materials and Method

The study was carried out on 120 subjects, 60 Type 2 diabetes mellitus patients and 60 non diabetic healthy subjects within age group of 40-60 years.

Test group : Diabetes mellitus type 2 patients were grouped as follows:

Group 1: Included 30 cases of type 2 diabetes mellitus without diabetic retinopathy.

Group 2: Included of 30 cases of type 2 diabetes mellitus with non proliferative diabetic retinopathy (NPDR).

Control group:

Group 3: 60 non diabetic healthy volunteers matched for age and gender were included in the study to serve as control.

Type 2 DM patients without retinopathy with duration of DM <10 years.

Type 2 DM patients with non proliferative diabetic retinopathy (NPDR) with duration of DM <10 years.

Following patients were excluded from the study:

Type 2 DM patients with proliferative retinopathy.

Patients with significant occular disorders including cataract, glaucoma, optic nerve disease, best corrected visual acuity <6/9 for distance, amblyopia, vitreous opacities.

Patients suffering from any cardiovascular illness or cardiac autonomic neuronal dysfunction of non-diabetic origin like hypertension.

Patients with prior history of head injury,cerebrovascular accident.

Medical conditions such as multiple sclerosis and other demyelinating disorders led to exclusion from the study.

Subjects with history of smoking, alcoholism, chronic drug intake.

Autonomic Function Tests: [3]

All the subjects performed five different autonomic function tests as given by **Ewing's and Clarke**. These tests are divided into two categories depending on the involvement of sympathetic and parasympathetic divisions of autonomic nervous system.

Tests for parasympathetic functions :

Heart rate response to deep breathing (DBD, deep breathing difference):-

In the sitting position, the subject was asked to breathe quietly and deeply at the rate of 6 breaths per minute (five seconds inspiration and five seconds expiration). After taking baseline recording, continuous ECG (Lead II) was recorded for six cycles with marker to indicate the onset of each inspiration and expiration. The maximum and minimum R-R intervals were measured during each breathing cycle and converted to beats per minute.

The result was then expressed as mean of the difference between maximum and minimum heart rate for six measured cycles in beats per minute.

B. Heart rate response to Valsalva Manouever :-

A baseline ECG (lead II) recording was taken. The subject was asked to blow into a mouthpiece connected to mercury sphygmomanometer at a pressure of 40 mm Hg for 15 sec. At the end of 15 seconds the pressure was released. After taking the baseline ECG, recording was taken during and after the maneuver. The result of valsalva ratio was expressed as the ratio of longest R-R interval after the maneuver to the shortest R-R interval during the maneuver.

C. Heart rate response to standing:-

With the subject lying gently in the supine position baseline blood pressure, heart rate was recorded. The subject was then asked to stand unaided (without support i.e. not leaning against the wall). ECG (Lead II) was recorded continuously. The point of standing was marked on ECG paper.

Heart rate response expressed as the 30:15 ratio was calculated as the ratio between the longest R-R interval at or around the 30th beat and the shortest R-R interval at or around the 15th beat.

Sympathetic Tests

Handgrip dynamometry/grip Test (HGT) –After recording baseline heart rate and blood pressure in sitting position the maximum voluntary contraction was determined using the dominant hand. The subject was then asked to maintain the handgrip with dominant hand at 30% of maximum force for 4 minutes. The changes in blood pressure during handgrip were recorded on contralateral arm .

Change in diastolic blood pressure is calculated as the difference between highest DBP during the tests and basal DBP.

Blood pressure response from lying to standing (orthostatic test) : The blood pressure was recorded after 5 minutes of rest in supine position. The subject was instructed to attain standing posture without any support within 3 seconds and blood pressure was recorded within 30 seconds of standing up, then at 1st, 2nd, 3rdand 5th minutes. The difference in systolic blood pressure between supine and standing BP levels is taken as the measure of postural blood pressure change.

NORMAL AND ABNORMAL VALUES OF VARIOUS CARDIOVASCULAR REFLEX TESTS [3]

Type of Tests	Cardiovascular Reflex Tests	Variables	Normal	Borderline	Abnormal
Parasympathetic Tests	Valsalva Maneuver	Valsalva Ratio	≥ 1.21	1.11-1.20	≤ 1.10
	HR Response to Standing	(30:15 ratio)	≥ 1.04	1.01-1.03	≤ 1.00
	HR response to deep breathing	DBD (beats/min)	≥ 15	11-14	≤ 10
Sympathetic Tests	Handgrip Test	Increased DBP (mm of Hg)	≥ 16	11-15	≤ 10
	Orthostatic Hypotension	Fall in SBP (mm of Hg)	≤ 10	11-29	≥ 30

CARDIAC AUTONOMIC NEUROPATHY SCORING

1. Categorization as per Ewings and Clarke criterion:-[3]

The participants are subjected to five non-invasive autonomic function tests as recommended by Ewing's criterion .

For grading of cardiovascular autonomic function, results are classified into normal, borderline and abnormal (scores 0, 0.5 and 1 respectively).

Overall scores are categorized as:

Normal: all five tests normal or one borderline.

Early involvement: one of the three heart rate tests abnormal or two borderline.

Definite involvement: two or more of the heart rate tests abnormal.

Severe involvement: two or more of the heart rate tests abnormal plus one or both blood pressure tests abnormal or both borderline.

Categorization as per Bellavere' s criterion

Bellavere F et al. (1983)[4] have given a scoring system to determine severity of CAN. According to this , score 0, 1 and 2 are assigned for each test as shown below :

0: normal result

1: borderline result

2: **abnormal result**

Therefore, a total score of 0-10 was obtained for each patient who underwent the standard battery of all five tests.

CAN Scoring System :-

The score value was obtained from various tests

and a scoring system was applied as recommended by Bellavere F et al (1983).[4]

The sum of the score obtained from each test determines the degree of autonomic involvement. Classification of patients was done according to the total score.

CAN Scoring System : Grading of Cardiac Autonomic Neuropathy

CAN Score	Categories
0-1	No autonomic neuropathy
2-4	Early autonomic neuropathy
5-10	Severe autonomic neuropathy

The results obtained were analysed statistically by **one-way ANOVA** and intergroup comparisons were made using **post hoc Tukey multiple comparison test** to compare the variables between the groups.

Results

Table : 1: Distribution of patients according to can scoring system

CAN Score	Categories	Group -1 (n=30)		Group -2 (n=30)	
		No. of Patients	%	No. of Patients	%
0-1	No CAN	13	43.3%	8	26.6%
2-4	Early CAN	10	33.3%	9	30%
5-10	Severe CAN	7	23.3%	13	43.3%
Total		**30**		**30**	

TABLE : 2: Comparison of mean of can score in the study groups

Groups	Mean±SD	P Value
Group-1	2.9±2.91	F = 43.712 P < 0.01
Group-2	5.0±3.698	
Control	0.20±8.408	

TABLE : 3: INTERGROUP comparison of mean can score BETWEEN different groups

	Group-1 Vs Group-3	Group-2 Vs Group-3	Group-1 Vs Group-2
P Value	< 0.01	< 0.01	< 0.01

The above table shows that there was a significant increase in autonomic score in groups 1 and 2 when compared to group 3.

Autonomic score were significantly increased in both the diabetic groups (P<0.01).

The observations suggest that cardiac autonomic function declines in type 2 diabetics and CAN is more in diabetic patients with associated retinopathy.

Table : 4: Distribution of cases with respect to duration of diabetes and cardiac autonomic neuropathy

Duration of DM	Group-1 (n=30)					Group-2 (n=30)				
	Total	CAN				Total	CAN			
		PRESENT		ABSENT			PRESENT		ABSENT	
		N	%	N	%		N	%	N	%
0-3	13 (43.33%)	4	30.7%	9	69.2%	4 (13.33%)	1	25%	3	75%
4-6	11 (36.66%)	8	72.7%	3	27.2%	10 (33.33%)	8	80%	2	20%
7-10	6 (20%)	5	83.3%	1	16.6%	16 (53.33%)	13	81.2%	3	18.7%
Total	**30**	**17**		13		30	22		8	

The observations revealed that number of patients with autonomic dysfunction was more when duration of DM was long (>7 years) (83.3% in group 1 and 81.2% in group 2). The number of patients with CAN increased with duration of DM.

Table 5: **Pearson's correlation between duration of dm and cardiovascular autonomic function tests score**

Parameter	Total CAN Score
Duration of DM	r = 0.5920
	p = < 0.001

Correlation between disease duration and cardiovascular autonomic score indicates significant positive correlation.

Discussion

In the present study grading of CAN was done on the basis of scoring system as recommended by Bellavere F et al. (1983)[4] as normal (score 0-1), early autonomic neuropathy (score 2-4) and severe autonomic neuropathy (score 5-10).

TABLE 1 shows distribution of patients according to CAN scoring system.

33.3% patients had early CAN and 23.3% had severe CAN in group1 while the number of patients with early CAN was 30% and 43.3% had severe CAN in group 2.

It is observed that majority of the patients with severe CAN (score 5-10) were in group 2 (43.33%, 13/30) whereas number of patients with no CAN (score 0-1) was more in group 1 (13/30, 43.33%) as compared to group 2 (26.66%, 8/30).

Our findings are in conformity with the findings of **Smith SE et al. (1981)**[5] and **Krolewski AS et al. (1992).**[6] They suggested that severity of autonomic neuropathy is more in patients with associated diabetic retinopathy.

Nayak UB et al. (2013)[7] in their study found 40% of patients had no CAN, 20% had early CAN and rest 20% had severe CAN.

Mathur CP et al. (2006)[8] reported 58% CAN among diabetics including 20% had early CAN**,** 30% having definite CAN & 8% had severe CAN. Another study by **Ahire C et al. (2014)**[9] reported severe CAN as 20%. Early and definite cardiac dysautonomia was present in 33.3% and 23.3% respectively.

Mean and SD of autonomic score in the study groups are shown in TABLE 2. There was significant increase in autonomic score in diabetics group when compared to controls ($p< 0.01$) (TABLE 3) . Our results are consistent with previous studies.

Similar findings were reported by **Nayak UB et al. (2013)**.[7] They found mean CAN score as 2.04 in diabetic patients. **Roy TM et al. (1989)**[10]found the mean CAN score in diabetic males to be 2.11.Similar observations were reported by **Noronha JL et al. (1981)**[11]

Basu AK et al (2010)[12] found retinopathy in 10% of the study population who also had CAN.

TABLE 4 shows that the percentage of patients affected by CAN was increased with a longer duration of diabetes.

Most of the patients with longer duration of diabetes (>7 yrs) had CAN (5/6, 83.3 % in group 1 ; 13/16 , 81.2 % in group 2)..

A similar finding was obtained by **David CL et al. (2012)**[13] who reported an increase in CAN prevalence as the duration of diabetes is prolonged.

The relation of CAN prevalence with diabetes duration could be explained by the prolonged exposure to the metabolic abnormalities as the duration of diabetes increases **(Vinik AI et al. , 2003)**.[14] Furthermore, increased concentration of oxidative stress may also play a role **(Schmidt MI et al. , 2005; Hoeldtke RD et al. , 2011)**.[15,16]

TABLE 5 shows correlation of total CAN score with duration of diabetes. In the present study, a **positive correlation** between duration of DM and presence of cardiac autonomic neuropathy was found which was significant ($r= 0.5920$; $p < 0.001$).

We observed that CAN was associated with increase in duration of DM. A moderate correlation between duration of diabetes and CAN was found in our study.

Similar observations were reported by **Toyry JP et al. (1996)**.[17]

Nayak UB et al. (2013)[7], **Noronha JL et al. (1981)**[11] found increasing CAN score with duration of diabetes but their observation was not statistically significant.

Conclusion

Duration of diabetes affects the occurrence of cardiovascular autonomic dysfunction. Diabetic patients with longer duration of diabetes showed more severe dysfunction of cardiovascular functions. Hence, Evaluation of cardiovascular reflexes should be included as a routine in the work-up of patients of Type 2 diabetes mellitus.

Ethical Clearance: The study was approved by the Ethical Committee of Gandhi Medical College, Bhopal

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Conflicts of Interest: Nil

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