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Original Article

Comparative Study on Cardiovascular Autonomic Function Tests in Type 2 Diabetes Mellitus Patients with and without Diabetic Retinopathy

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Abstract

Introduction: Autonomic dysfunction is common in diabetics and presence of cardiac autonomic neuropathy is responsible for sudden death in diabetics. Detecting subclinical Cardiac Autonomic Neuropathy (CAN) early is crucially important for treatment and for preventing potentially serious consequences of CAN.

Aims and Objectives: The aim of the study is to clinically assess cardiovascular autonomic function tests in type 2 diabetes mellitus patients and compare those with healthy normal subjects.

Method: The study included 60 type 2 diabetic patients including 30 patients without any retinopathy and 30 others with non- proliferative diabetic retinopathy(NPDR), and 60 control subjects matched for age and gender. Autonomic function tests as given by Ewing were performed on all subjects to assess the parasympathetic and sympathetic nervous activity . These tests include heart rate response to deep breathing, valsalsa ratio, 30:15 ratio, and blood pressure response to standing and sustained hand grip. Statistical analysis of the data was done using One way ANOVA (Analysis of Variance) and multiple comparisons were done using post hoc Tukey Multiple Comparison Test. Statistical significance was set at 0.05.

Results: The results of our study show that there is decrease in cardiovascular autonomic functions more in diabetic patients with NPDR as compared to diabetic patients without retinopathy.

Conclusion: We conclude that there is involvement of both cardiovasvascular sympathetic and parasympathetic nervous system in patients with type 2 diabetes mellitus. So, type 2 DM patients should be evaluated for presence of autonomic dysfunction as early as possible to prevent complications and to improve the prognosis of the disease.

Keywords: *Diabetes mellitus, Autonomic neuropathy, Autonomic function tests*

Introduction

Diabetic Autonomic Neuropathy (DAN) is one of the most important complication of diabetes. Autonomic dysfunction is common in diabetics and presence of cardiac autonomic neuropathy is responsible for sudden death in diabetics. Detecting subclinical Cardiac Autonomic Neuropathy (CAN) early is crucially important for treatment and for preventing potentially serious consequences of CAN.[1] So, the present study is directed to show the comparative effects of cardiac autonomic activity between Type 2 DM patients with and without retinopathy, and non diabetic matched controls.

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Materials and Method

The study was carried out in the Neurophysiology lab of Department of Physiology, Gandhi Medical College & associated Hamidia Hospital, Bhopal.

The study was approved by the Ethical Committee of Gandhi Medical College.

Informed consent was taken from all the participants before enrolling in the study.

Patient was provided the information about the procedure of test to be performed on him.

The study was carried out on 120 subjects, 60 Type 2 diabetes mellitus patients and 60 non diabetic healthy subjects.

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.

Inclusion criterion:

The study included following type 2 diabetes mellitus patients within age group of 40-60 years.

- 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.

Exclusion criterion:

Following patients were excluded from the study:

- Type 2 diabetes mellitus 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.
- Subjects with history of smoking, alcoholism, chronic drug intake.

Data Collection Protocol :

- The patients who satisfied the inclusion and exclusion criterion, and gave written consent were included in the study.
- Relevant information was collected using a detailed questionnaire covering all the relevant symptoms and signs pertaining to Diabetes mellitus and autonomic disturbances. On the basis of response obtained the study group was selected.
- Detailed history was obtained and recorded from the control and the diabetic groups in the prescribed proforma. It included personal details, habit of smoking, alcohol, family h/o diabetes and hypertension, all types of medications taken, h/o being diagnosed or being treated for diabetes including age of onset, duration, treatment, associated risk factors. Particular emphasis was given on symptoms of autonomic neuropathy like syncope, loss of sweating erectile dysfunctions, gastric fullness after meals, weakness, tingling and numbness .
- Confirmation of Fasting blood glucose (FBS) measurements.

FBS more than 126 mg/dl was considered diabetes mellitus as per WHO criterion.2

Occular Examination

- Ocular examination findings were noted which include determination of visual acuity by Snellen's chart and near vision chart, ocular movements, pupil reactions, and confrontational visual field screening.

Direct ophthalmoscopy was done for the initial evaluation of the fundus occuli and to look for the status of retinopathy.

Assessment of Diabetic Cardiovascular Autonomic Neuropathy : Ewing' S Test Criterion

Baseline parameters:

The baseline parameters of subjects recorded were blood pressure and heart rate which were taken as control or baseline values. These parameters were taken before every test.

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.

1. **Parasympathetic tests :** - the tests that reflect parasympathetic activity are those that measure heart rate response to:

a. Deep breathing (DBT, deep breathing test)

b. Valsalva manouever (valsalva ratio)

c. Lying to standing (30:15 ratio)

2. **Sympathetic tests:-** These tests reflect sympathetic activity. They measure blood pressure response to :

a. Sustained handgrip exercise (HGT, hand grip test)

b. Lying to standing up (PHT, postural hypotension)

Tests for parasympathetic functions :

A. Heart rate response to deep breathing :-

In this test, heart rate changes during respiration is assessed.

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.

A normal response was a difference of 15 beats/min or more, 11-14 beats/min borderline and less than or equal to 10 beats/min was considered abnormal.

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.

Reference values :Valsalva ratio (VR)

Normal : > 1.21,

Borderline : =1.11-1.20

Abnormal : < 1.10

C. Heart rate response to standing:-

The patient was instructed about the test. The test was conducted after 10 min rest in supine position. 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.

In this test, after standing shortest R-R interval at or around 15th beat and the longest R-R interval at or around 30th beat were measured and the 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.

Reference values:-

Normal	:	> 1.04
Borderline	:	1.01- 1.03
Abnormal	:	< 1.0

1. Sympathetic Tests

A. Handgrip dynamometry/grip Test (HGT) – In this test autonomic stress is evoked by maximal voluntary contraction.

Apparatus used in this test was handgrip dynamometer (Manufactured by INCO; range max-90 kg, min 100 kg). 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.

Reference Values :

Increase in DBP : > 16 mmHg – Normal

Increase in DBP : 11-15 mmHg – Borderline

Increase in DBP : < 10 mmHg – Abnormal

B. Blood pressure response from lying to standing (orthostatic test) :

In this the test BP change is assessed from lying to standing posture.

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.

Reference Values :

Decrease in SBP < 10 mmHg – Normal

Decrease in SBP 11 - 29mmHg – Borderline

Decrease in SBP > 30 mmHg – Abnormal

Statistical methods applied:

The result were expressed as Mean+SD. One way ANOVA (Analysis of Variance) and multiple comparisons were done using post hoc Tukey Multiple Comparison Test to compare the variables between the three study groups. The mean difference was statistically significant at $p<0.05$ and non significant at $p>0.05$.

Results

Table : 1: Comparison of various autonomic function tests tests in the three study groups

TEST	GROUP 1 Mean±SD	GROUP 2 Mean±SD	GROUP 3 Mean±SD	P VALUE
DBT	13.66±5.66	11.03±4.09	18.48±3.21	F = 35.603 P < 0.01
VR	1.19±0.074	1.13±0.08	1.25±0.033	F = 42.516 P < 0.01
30:15 ratio	0.99±0.130	0.91±0.185	1.08±0.041	F = 20.484 P < 0.01
Fall in systolic BP	9.8±7.849	14.6±12.65	5.6±2.38	F = 14.297 P < 0.01
Rise in diastolic BP	15.8±4.245	12.8±4.88	18.87±3.08	F = 25.087 P < 0.01

Table : 2: Intergroup comparison of various autonomic function tests showing P value

TEST	Group-1 Vs Group-2	Group-1 Vs Group-3	Group-2 Vs Group-3
DBT	< 0.05	< 0.01	< 0.01
VR	< 0.01	< 0.01	< 0.01
30:15 ratio	< 0.05	< 0.01	< 0.01
Fall in systolic BP	< 0.05	NS	< 0.01
Rise in diastolic BP	< 0.01	< 0.01	< 0.01

Discussion

Cardiovascular autonomic function tests were used to assess autonomic neuropathy .The tests were analysed according to the criterion given by **DJ Ewing and Clarke(1982)[3]**. The observed data of these tests showed abnormal autonomic reactivity in diabetics as compared to euglycemic controls.

On comparing age of the study groups, the statistical difference of mean between diabetic patients and controls was not significant (p>0.05). So, the different study groups appear to be comparable statistically.

Tests Reflecting Parasympathetic Nervous Activity

Deep Breathing Test

In our study, on comparing the statistical difference of mean of ***Deep Breathing Test*** by using ANOVA, statistically significant difference of mean was observed in study groups with p < 0.01. On intergroup comparison of DBT in all the three groups using post hoc comparison test , comparing group 1 vs group 2 , group 1 vs group 3 and group 2 vs group 3 , the p values were <0.05, <0.01 and <0.01 respectively which were statistically significant.

The findings of our study are consistent with the results of **Krishna BH et al. (2014)[4],** they found that normal variation of heart rate during breathing may have a noticeable reduction and sometimes complete absence of variation of heart rate in diabetic patients.

A study conducted by **Prasad HB et al. (2014)[5]** showed that heart rate variation on DBT was the most abnormal test in all CAN assessing tests.

NagalaxmiV et al. (2016)[6]also suggested that there is predominance of involvement of parasympathetic system in diabetics first and also supported the evidence found in the present study that the DBT involvement occurs in type 2 diabetes mellitus.

In accordance to these studies, our study also suggests that heart rate variation is affected more in diabetic patients.

Valsalva Ratio

On comparison of heart rate during ***Valsalva Ratio*** in the three study groups by using ANOVA, p<0.01 which is statistically significant.

On intergroup comparison in diabetic patients, p <0.01 which is statistically significant.On comparing diabetics with control group p <0.01 which is statistically significant.

Krishna BH et al. (2014)[4] stated that during strain period of valsalva test, heart rate increases and blood pressure decreases but in diabetic patients the rise in heart rate during strain and decrease in heart rate during relaxing phase is decreased. Our findings are consistent with these findings.

Nazeema K et al. (2010)[7] reported similar findings.

HR-Lying to Standing Test

On comparison of heart rate from ***lying to standing (30:15 ratio)*** in the three study groups by using ANOVA, we found p<0.01 which is statistically significant.

On intergroup comparison in diabetic patients, p <0.01 which is statistically significant. On comparing diabetics with control group p <0.01 which is statistically

significant.

Mohapatre D et al. (2012)[8] stated that diabetic patients have lower 30:15 ratio in comparison to controls.

Gupta S et al. (2017)[9] found abnormal HR response on standing in diabetic patients.

Tests Reflecting Sympathetic Nervous Activity

Postural Hypotension Test

Blood pressure response from lying to standing was evaluated in diabetic patients and controls. The mean and SD of PHT in different groups is shown in **TABLE 1**

Fall in systolic blood pressure on standing was statistically significant between groups 1 and 2 ($p<0.05$, S). Highly significant difference of mean was found between groups 2 and 3 ($p<0.01$). However, no significant difference of mean was found between groups 1 and 3 ($p>0.05$). Blood pressure response was significantly reduced in diabetics.

The results in our study correlated with the study conducted by **Endukuru CK et al. (2015).**[10]

Hand Grip Test

In our study it was observed that mean value of ***increase in DBP during the sustained hand grip*** was significantly lower in diabetics in comparison to control group. Our results for HGT show highly significant difference between different groups ($p<0.01$).

The findings of the present study are in conformity with study done by **Datta S et al. (2005)**[11] on patients with varying severity of diabetic retinopathy. They found significant difference in DBP on handgrip test between normal controls and diabetics with retinopathy.

Hassan ZF et al. (2014)[12] found abnormal blood pressure response to sustained hand grip in diabetic patients.

Conclusion

It may be concluded that diabetes has an effect on Cardiovascular Autonomic Functions**.** The observations in the present study suggest the presence of autonomic dysfunction in diabetics. Both parasympathetic and sympathetic cardiovascular responses were altered. The decrease in cardiovascular autonomic functions is more in diabetic patients with NPDR as compared to diabetic patients without retinopathy.

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

Source of Funding: None

Conflicts of interest: Nil

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