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**Original article:**

# Comparative study of autonomic function tests in type 2 diabetes mellitus patients and healthy controls

**[1]Dr. Poonam S. Nandanwar, [2]Dr. Mrunal S. Phatak**

[1]Assistant Professor, Dept. of Physiology GMC, Gondia
[2]Professor & Head, Dept. of Physiology AIIMS Nagpur
Corresponding Author: Dr. Mrunal S. Phatak,Professor & Head,Dept. of Physiology,
AIIMS,Plot 2,Sector 22, Mihan, Nagpur. 441108
Email: phatakms@aiimsnagpur.edu.in



**ABSTRACT:**

**Introduction:** Chronic non-communicable diseases are the leading cause of morbidity and mortality in the world. Diabetes mellitus (DM) is one of the most common non communicable disease. Cardiac autonomic Neuropathy (CAN) is a commonly overlooked complication of type 2 DM which has major impact on cardiovascular disease ( CVD) related mortality and morbidity. Each year it is estimated that more than 17 million people die from CVD.[(1)] DM can cause dysfunction of any or every part of the autonomic nervous system, leading to a wide range of disorders like known or silent myocardial infarction (MI), cardiac arrhythmias and increased risk of sudden death[(2)].

**Methodology:** In this study Ewing's battery of autonomic function tests and heart rate variability (HRV) was done for diagnosis of CAN on 80 participants between 30-60 years of which 40 were type II diabetic patients with duration of DM more than 5 years & 40 age matched healthy control subjects.

**Observations and results :** The SBP and DBP ($p<0.001$), the delta change in SBP and DBP on standing ($p<0.01$) was more and significantly less( $p<0.001$) in sustained hand grip maneuver in cases than in controls. The resting heart rate and heart rate during deep breathing in cases and controls was not statistically significant. The $\Delta$ change in heart rate during deep breathing ($p<0.01$). and the valsalva ratio ($p<0.001$). was significantly less, whereas QTc interval was high ($p < 0.01$) in cases as compared with controls. The values of HRV namely SDNN,RMSSD,LF, HF and total power was significantly less ($p < 0.001$) in cases as compared with controls.

**Conclusions:** Ewing's tests as well as HRV were significantly deranged in diabetic patients indicating autonomic imbalance. The results are suggestive of sympathetic over activity and decline in parasympathetic activity in diabetic patients. Thus autonomic function tests should be done routinely in chronic DM patients for diagnosis of CAN.

**Key Words:** Diabetes Mellitus , Autonomic function tests , HRV

## INTRODUCTION

CVDs are the main cause of morbidity and mortality in the world.[3] The current prevalence of type 2 diabetes is 2.4% in the rural population and 11.6% in the urban population of India. . According to the World Health Organization (WHO), India had 69.2 million people living with diabetes in 2015 and estimated to reach 98 million in 2020.[4] It is estimated that almost one in six people are currently at risk of developing diabetes related complications particularly CVD. DM is most commonly associated with autonomic dysfunction. In persons with diabetes; prolonged hyperglycemia leads to degradation of the microvasculature, leading to a specific form of autonomic dysfunction termed "Diabetes Autonomic Neuropathy" .Damage to the autonomic innervations of heart can cause complications such as lethal arrhythmias and sudden cardiac death.[5] People with type 2 diabetes have a 2–4 higher relative risk for CVD. Studies in patients with type II DM have shown that arterial stiffness is associated with age, blood pressure, duration of diabetes and cardiac autonomic dysfunction.[6] CAN, especially at the early stages, can be sub-clinical and thus as the disease progresses, it becomes clinically evident.[7] CAN is very common and often overlooked complication of DM . Improving the understanding of the pathogenesis of CAN and its role in CVD offers the potential for new treatment targets that may reduce the burden of CVD in these patients.

Autonomic function tests are reliable, reproducible, simple, quick to carryout and all non invasive. In the early 1970s, Ewing et al. proposed five simple noninvasive cardiovascular reflex tests that have been applied successfully in many studies.Simple noninvasive cardiovascular reflex tests have now become the gold standard by which an autonomic neuropathy is diagnosed objectively and by which other tests are judged. The autonomic function tests specifically designed for identifying CAN requires patient cooperation and more importantly patient is unable to perform the test procedure due to co-morbidities. New methods that are non-invasive and independent of patient cooperation are easy to perform and preferable in the diagnosis of CAN.[8] Present study was done with the objective of analyzing CAN associated as a complication of type II DM. In this study autonomic function tests were done in diabetic patients and age matched healthy controls and the autonomic dysfunction was ascertained by the results of the study.

## AIMS AND OBJECTIVES

The present study was undertaken to study and compare the variation in autonomic function tests indicating the activity and reactivity of the ANS in diabetic patients and healthy controls. The duration of diabetes was more than 5 years so the study aimed to evaluate presence of CAN in long standing DM.

## MATERIAL & METHODS

The present study was carried out in the Department of Physiology, Indira Gandhi Government medical college, Nagpur. Study was approved by Institutional Ethics committee. The sample size was calculated to 40 per group considering the mean ±S.D. of parameters with α error 5% & power 80%. Eighty participants both males & females of age group 30-60 yrs were selected & divided into two equal groups of 40 each. Case group of 40 patients with duration of type II DM of more than 5 yrs were recruited from diabetic OPD. Control group of 40 non diabetic age & height matched participants from non teaching staff in and around the college.

All the participants having heart disease, hypertension, pregnancy, chronic renal failure, endocrine disorder, alcoholics, smokers, athletes, sports persons, yoga practitioners & those consuming drugs affecting ANS were excluded. Informed consent was obtained from all participants. Participants were asked to refrain from beverages containing caffeine & alcohol for 24 hrs before recording. All investigations were carried out between 10 am to 1 pm in optimum environmental conditions in quiet surrounding. After 5 minutes of mandatory rest ECG was recorded in lead II in supine position with the help of computerized polygraph( Medicaid Systems, Ambala) & only artifact free section was selected. The ECG record was exported to Kubois software from which HRV parameters i.e. The square root of the mean of the sum of the squares of differences between adjacent NN interval (RMSSD), standard deviation of all NN intervals (SDNN), high frequency (HF), low frequency (LF) in $ms^2$ & total power of HRV were recorded. After this the resting heart rate & delta change in heart rate during deep breathing, blood pressure in supine position & changes during standing & sustained hand grip maneuver were recorded & valsalva ratio & corrected QT interval was calculated.

The data was analyzed using statistical software STATA version 13.1. Variables were presented as mean ±SD. Continuous variables (age, height , weight, W/H ratio, heart rate, SBP, DBP, delta change in blood pressure & heart rate) were compared between diabetic patients & control subjects by performing unpaired t-test for normalized data. Wilcoxon Rank Sum test was performed to compare non- normalized variables (RMSSD, SDNN, LF, HF, LF/HF & total power) between diabetic patients & control subjects. $P< 0.05$ was considered as statistically significant.

**OBSERVATION & RESULTS**

**Table 1: Group wise comparison of anthropometric parameters & glycemic status**

| **Variables** | **Control group (n=40) Mean ± SD** | **Cases group (n=40) Mean ± SD** | **p value** |
|---|---|---|---|
| Age (yrs) | 48.12 ± 6.03 | 50.02 ± 6.78 | 0.189 |
| BMI ($Kg/m^2$) | 23.53 ± 2.31 | 28.65 ± 4.34 | 0.000*** |
| W/H Ratio | 0.86 ± 0.05 | 0.92 ± 0.07 | 0.000*** |
| FBG (mg/dl) | 86.07 ± 9.43 | 178.25 ± 29.64 | 0.000*** |
| PMBG (mg/dl) | 122.2 ± 11.74 | 272.6 ± 27.92 | 0.000*** |
| GHb (%) | 4.94 ± 0.94 | 8.02 ± 0.7 | 0.000*** |

****p < 0.001 – statistically very highly significant, p> 0.05 – statistically not significant*

The difference in mean age between the two groups was not significant (p<0.05). The BMI, W/H Ratio, FBG,PMBG and GHb values were significantly higher in cases than controls (p<0.001).

**Table 2 : Group wise comparison of blood pressure in supine & delta change in blood pressure on standing and sustained hand grip test maneuver.**

| **Variable** | | **Control Group (n=40) Mean ± SD** | **Cases Group (n=40) Mean ± SD** | **p value** |
|---|---|---|---|---|
| Blood pressure Supine (mmHg) | SBP | 120.75 ± 6.89 | 129.6 ± 6.69 | 0.000*** |
| | DBP | 80.1 ± 3.89 | 83 ± 3.97 | 0.001** |
| Δ change in blood pressure on standing (mmHg) | SBP | - 2.45 ± 3.08 | - 15.2 ± 6.59 | 0.000*** |
| | DBP | - 1.85 ± 1.94 | - 10.1 ± 3.32 | 0.000*** |
| Δ change in blood pressure during hand grip test (mmHg) | SBP | 13.5 ± 4.63 | 9.95 ± 4.18 | 0.000*** |
| | DBP | 12.5 ± 3.41 | 5.65 ± 2.78 | 0.000*** |

****p<0.001 – statistically very highly significant. **p <0.01 -statistically highly significant.*

The SBP and DBP ( p<0.001), the delta change in SBP and DBP on standing (p<0.01) was significantly more in cases group as compared to control group. The delta change in SBP and DBP in sustained hand grip maneuver was significantly less in cases than in controls( p<0.001).

**Table 3 : Group wise comparison of delta change in resting heart rate during deep breating, valsalva ratio & QTc**

| **Variable** | **Control Group (n=40) Mean ± SD** | **Cases Group (n=40) Mean ± SD** | **p value** |
|---|---|---|---|
| RHR beats / min | 78.57 ± 13.48 | 84.05 ± 13.09 | 0.069 |
| HRDB (beats / min) | 92.17 ± 10.71 | 88.12 ± 10.11 | 0.086 |
| Δ HRDB (beats / min) | 13.6 ± 6.10 | 5.92 ± 3.23 | 0.000*** |
| VR | 1.67 ± 0.19 | 1.34 ± 0.13 | 0.000*** |
| QTc (ms) | 385.15 ± 33.03 | 409.75 ± 39.79 | 0.003** |

****p< 0.001 –statistically very highly significant, **p < 0.01- statistically highly significant*

The increase in resting heart rate and heart rate during deep breathing in cases group as compared to control group was not statistically significant. The Δ change in heart rate during deep breathing ($p<0.01$). and the valsalva ratio ($p<0.001$). was significantly less in cases group than in controls. The QTc interval was significantly high ($p < 0.01$) in cases group as compared with control group.

**Table 4: Group wise comparison of heart rate variability parameters**

| **Parameter** | **Control Group (n=40) Mean ± SD** | **Cases Group (n=40) Mean ± SD** | **Z value** | **p value** |
|---|---|---|---|---|
| SDNN | 63.36 ± 28.56 | 36.28 ± 15.42 | 5.148 | 0.000*** |
| RMSSD | 34.57 ± 29.85 | 15.87 ± 7.3 | 5.341 | 0.000*** |
| LF ($ms^2$) | 681.05 ± 626.82 | 206.35 ± 214.19 | 4.499 | 0.000*** |
| HF ($ms^2$) | 104.57 ± 83.42 | 39.07 ± 37.67 | 4.504 | 0.000*** |
| Total power ($ms^2$) | 2519.42 ± 1597.78 | 1123.1 ± 836.33 | 4.686 | 0.000*** |

****p < 0.001 –statistically very highly significant, p > 0.05 – not significant*

The values of SDNN, RMSSD LF, HF and total power was significantly less ($p < 0.001$) in cases as compared with controls.

**DISCUSSION:**

Autonomic neuropathy can involve multiple systems including cardiovascular, gastrointestinal, genitourinary, sudomotor, and metabolic syndrome Autonomic neuropathy is among the least recognized and understood complication of DM, despite its significant negative impact on survival and quality of life in people with diabetes. It impairs the ability to conduct activities of daily living, and increases the risk of death. It also accounts for a large portion of the cost of care.The metabolic disorders of diabetes lead to diffuse and widespread damage of peripheral nerves and small vessels. Diabetes can cause dysfunction of any or every part of the autonomic nervous system, leading to a wide range of disorders. And these are serious: among the most troublesome and dangerous of the conditions linked to autonomic neuropathy are known or silent myocardial infarction (MI), cardiac arrhythmias, ulceration, gangrene, and nephropathy. Autonomic neuropathy is also associated with an increased risk of sudden death. One of the most overlooked complications of diabetes is CAN [(9).]

Data of present study shows increase in BMI & W/H ratio ( Table 1) due to excess weight gain and central obesity as Type II DM is associated with obesity, insulin resistance impairing carbohydrate utilization and storage.[9] There was a significant increase in glycated hemoglobin indicating poor control of blood sugar in the cases.

In cases of type II DM , we have observed more fall in the systolic as well as diastolic blood pressure on standing from the supine position as compared to controls. During sustained hand grip we have observed a lesser increase in the systolic as well as diastolic blood pressure in cases than controls (Table 2). This might be because of autonomic dysfunction in cases, causing damage to the efferent sympathetic vasomotor fibers innervating the heart & blood vessels. This may have resulted in the impairment of the baroreflex mediated vasoconstriction and tachycardia.[10] . The activity of autonomic nervous system is crucial in moment to moment regulation of heart rate and blood vessel resistance. In diabetic autonomic neuropathy the heart rate and vascular tone are not adjusted to maintain the blood flow to organs like brain. There is impaired baroreflex mediated vasoconstriction and tachycardia.

The decreased valsalva ratio in Type II DM patients ( Table 3) may be due to decreased baroreceptor sentitivity.[11] The cardiovascular responses to Valsalva maneuver are complex. Bradycardia elicited by overshoot of blood pressure is mediated by vagus nerve and tachycardia seen during the maneuver is due to removal of vagal tone or sympathetic mechanisms. QTc prolongation in diabetic patients (Table 3) is an indicator of sympathetic dysfunction. There is an association of prolonged QTc interval with cardiac dysautonomia in DM. QTc prolongation has linear correlation with the degree of CAN [12] .In present study we found that HRV parameters like SDNN (ms), RMSSD (ms), LF ($ms^2$), HF ($ms^2$) and total power ($ms^2$) was significantly decreased in cases as compared to controls ( Table 4).A reduction in time domain parameters of HRV carries negative prognostic value for autonomic neuropathy. This also precedes the clinical expression of autonomic neuropathy. SDNN is a global index of HRV and reflects long term components for variability whereas RMSSD reflects short term component. It reflects alterations in autonomic tone that are predominantly mediated by vagus nerve ([13] . The efferent vagal activity is a major contributor to the HF component. LF component is considered as a marker of sympathetic modulation. LF/HF ratio reflects sympathovagal balance or sympathetic modulations. Thus, the initial manifestation of this neuropathy is likely to involve both efferent limbs of the autonomic nervous system.[14]

In our study we have found out that both the activity and reactivity tests for autonomic function are deranged. Patients with long duration of type II DM have CAN with involvement of both, sympathetic and parasympathetic components of autonomic nervous system. If one could identify the contributing factors, early detection of CAN and prompt intervention would be clinically meaningful for the prevention of adverse cardiovascular outcomes in patients with type II DM. Early detection of Autonomic Neuropathy would suggest the need for an aggressive approach in the management of diabetes mellitus to reduce mortality and morbidity in these patients. Hence autonomic function tests and HRV can be used as routine testing protocol in diagnosis , management and prognosis of Type II DM patients.

More studies are needed to evaluate the exact time of initiation of CAN in diabetics. Also larger sample size studies should be done to formulate regression equations for various populations.

## Abbreviations:

**CAN-** cardiac autonomic neuropathy
**HRV-** heart rate variability
**DM-**diabetes mellitus
**QTc**- corrected QT interval
**SDNN -** standard deviation of all NN intervals
**HF-** high frquency
**LF-** low frequency
**BMI-** body mass index
**W/H-** waist hip ratio
**FBG-** fasting blood glucose
**PMBG-** post meal blood glucose
**GHb**- glycated haemoglobin
**SBP-** systolic blood pressure
**DBP-** diastolic blood pressure
**RHR-** resting heart rate
**HRDB-** heart rate during deep breathing
**VR-** valsalva ratio
**RMSSD-** The square root of the mean of the sum of the squares of differences between adjacent NN interval

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