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A comparative study on the status of autonomic function in recently detected type 2 Diabetes after maintaining two months of sustained euglycemia

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Abstract:
***Background**: Cardiac autonomic neuropathy (CAN) is a serious and common complication of Diabetes. Hyperglycemia is the leading cause of the initiation of this pathogenic process, even though the pathogenesis of Diabetic CAN is multifactorial. The present study aims to estimate the effect of reduced fasting blood sugar (FBS), post prandial blood sugar (PPBS) and glycated hemoglobin (HbA1c) levels on the cardiac autonomic function in recently detected cases of diabetes.*
***Materials and methods:** The study was done on 100 recently detected cases of type 2 Diabetes. A series of autonomic function tests were done according to Ewing's criteria on the patients to determine cardiac autonomic neuropathy and percentage of patients showing abnormal result were calculated. FBS, PPBS and HbA1c were also estimated. Statistical analysis was done by applying Student's t test.*
***Results**: The mean differences for all the variables like E: I ratio, 30:15 ratio, Sustained hand grip test and drop in systolic blood pressure were found to be statistically significant ($p < 0.05$) except valsalva ratio as compared to values at the time of enrollment. Mean differences for FBS and PPBS were found to be statistically significant ($p < 0.05$) while that for HbA1c was statistically not significant($p > 0.05$) after maintaining 2 months of sustained euglycemia. It was observed that patients with improved autonomic functions had significant reductions in FBS as well as PPBS levels while reduction in HbA1c levels was not significant.*
***Conclusion**: At the end of study, patients with improved autonomic functions had significant reductions in FBS as well as PPBS levels while reduction in Hba1c levels was not significant. Therefore, all the recently detected type-2 Diabetes patients should be routinely assessed for CAN as early intervention may reduce the morbidity.*
***Keywords**: cardiac autonomic neuropathy, diabetes mellitus, fasting blood sugar, post prandial blood sugar*

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I. Introduction

The prevalence of type 2 Diabetes mellitus (DM) is rising much more rapidly, presumably because of increasing obesity, reduced activity levels as countries become more industrialized, and the ageing of the population.[1] Diabetes currently affects 72.94 million Indians which is around 10.4 % of the adult population.[2]

Diabetic autonomic neuropathy is a serious and common complication of diabetes.[3] Diabetes-related complications usually do not appear until the second decade of hyperglycemia. Because type 2 Diabetes mellitus (DM) often has a long asymptomatic period of hyperglycemia before diagnosis, many individuals with type 2 DM have complications at the time of diagnosis.[1,4] The vascular complications of DM are categorised into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications (coronary heart disease, peripheral arterial disease, cerebrovascular disease). The microvascular complications of both type 1 and type 2 DM result from chronic hyperglycemia. [4]

The clinical symptoms of Diabetic neuropathy generally do not appear early, until long duration after the onset of disease. CAN is often an underdiagnosed complication of diabetes mellitus (DM) and is associated with increased mortality and morbidity. Identifying patients with CAN is important as early initiation of intensive interventions targeting lifestyle, glycemic control, and cardiovascular risk factors can slow the progression of neuropathy and may be reversed if diagnosed soon after onset.[5] Therefore, present study was conducted to see the effect of reduced FBS, PPBS and Hba1c levels on the status of autonomic functions when compared to the same group of patients after maintaining two months of sustained euglycemia.

II. Material And Methods

The study was a type of cross sectional study conducted in Jawaharlal Nehru Institute of Medical Sciences (JNIMS), Imphal East, Manipur, India in time period from September 2017 to August 2019. A total of 100 recently diagnosed type-2 diabetes (less than 6 months) patients between the age group of 40 - 65 years including both males and females attending the Endocrine outpatient department and Diabetic clinic were recruited for the study. The diagnosis of DM was based on the criteria given by American Diabetes Association 2016.[6] Alcoholic patients were excluded from the study. Patients having uncontrolled hypertension, chronic obstructive pulmonary disease or thyroid disorder were also excluded from the study.

The patients were also given time to consider participation and written consent was taken from the participants after clearance from the Ethical Committee of the Institute. They were asked to come to the department by 9 am after having light breakfast. The procedure of all the tests and purpose was properly explained. All the tests were done before 12 noon.

All the patients were tested under similar laboratory conditions. The patients were allowed to familiarize to the experimental and environmental conditions of the laboratories. Cardiovascular Autonomic Function Test was done by utilising "Ewing's battery of tests". Fasting sample collected in sodium fluoride vial between 8 to 9 am and FBS estimation was done using glucose oxidase peroxidase method using Vitro's instrument For Hba1c calculation, sample was collected in EDTA vial and analysis was done using Fast Ion Exchange Resin Separation Method

Cardiovascular parasympathetic assessment was done by

(i) Deep breathing test

Breathing cycles were repeated in order to get 6 complete cycles (i.e; each cycle consisting of 5 seconds inspiration followed by 5 seconds expiration) and a continous ECG was recorded throughout the test. Difference between the maximal and minimal heart rate during inspiration and expiration respectively, averaged for 6 cycles(ΔHR) was calculated. E: I ratio was calculated as ratio of longest R-R interval and shortest R-R interval averaged over 6 cycles.

(ii) Heart rate response to standing

The test was conducted after 10 mins of supine rest. Patient was told to attain the standing posture within 3 seconds and readings were taken. A continuous lead II ECG was taken till 30th beat after standing and 30 : 15 ratio was calculated. Ratio of longest R-R interval at or around 30th beat and the shortest R-R interval at or around the 15th beat was calculated.

Both sympathetic and parasympathetic assessment was done by :

Valsalva manoeuvre

The patient was instructed to blew into a mouth piece attached to a sphygmomanometer while keeping expiratory pressure at 40 mmHg for 15 seconds by looking at marker in sphygmomanometer and then release the pressure. A continous lead II ECG was recorded. Valsalva ratio was calculated by formula longest R-R interval during phase IV / shortest R-R interval during phase II.

Cardiovascular sympathetic assessment was done by

(ii) Blood pressure response to standing

Blood pressure (BP) was recorded in supine position and then within 3 secs after standing. The postural fall in BP measured immediately after standing was taken as the difference between systolic BP lying and the systolic BP standing.

(ii) **Sustained Hand grip test (SHGT)**

After recording the basal blood pressure (BP), the subject was asked to grip a hand dynamometer (INCO) three times with his / her dominant hand using maximal effort, at an interval of two minutes each. All the three readings on the dynamometer were noted and 30% of the mean maximal voluntary capacity was calculated. The patient was then asked to grip the dynamometer at 30% of his/ her maximum voluntary capacity for up to a maximum of 5 minutes.Blood pressure was measured on the contralateral arm. Difference between diastolic blood pressure (DBP) just before release of handgrip and before starting handgrip was taken as the measure of response.

Patients were defined as dysfunction of both system (parasympathetic and sympathetic) if valsalva ratio was abnormal or any test of parasympathetic system was abnormal and any test of sympathetic system was borderline or any test of parasympathetic system was borderline and any test of sympathetic system was abnormal or any test of parasympathetic system was abnormal and any test of sympathetic system was abnormal.[7]

Patients were defined as having abnormality of parasympathetic system alone if one or more of the parasympathetic tests was abnormal, while rest of the tests were normal.[7]
Patients were defined as having abnormality of sympathetic system alone if one or more of the sympathetic tests was abnormal, while rest of the tests were normal.
Patients were defined as borderline if both or either of thesympathetic or parasympathetic tests was borderline, while all the other tests including valsalva ratio were normal.[7]

Statistical Analysis:
The data was analysed using Statistical Package for the Social Sciences (SPSS) version 20. Descriptive statistics were expressed in terms of mean ± SD and percentage. Analytical statistics was done by applying student's paired t test and p value was calculated. "p value" less than 0.05 was taken as significant.

III. Results

Table-1: Demographic and Biochemical characteristics of patients

Variables	Range	Mean ± SD
Age (Years)	40 - 65	52.77 ± 8.33
Weight (Kg)	46 - 82	61.86 ± 7.49
Height (cm)	140 - 172	154.41 ± 7.51
BMI (kg/m^2)	20.11 - 34.07	25.67 ± 3.30
FBS (mg/dl)	88 - 423	250.87 ± 79.36
PPBS (mg/dl)	174 - 664	352.77 ± 54.74
HbA1c(%)	5.90 - 17	9.22 ± 1.8

'n' : number of patients, BMI : body mass index, FBS: Fasting blood sugar, PPBS: Post prandial blood sugar, HbA1c: Glycated hemoglobin

Table 1 shows the demographic and biochemical characteristics of the patients. Age of patients was in the range of 40 to 65 years with mean of 52.77±8.33. Similarly, weight was in the range of 46 to 82(61.86±7.49) Kgwhile height was in the range of 140 to 172(154.41±7.51)cms. BMI of the patients was between 20.11 and 34.07 kg/m^2 with mean of 25.67±3.30. The fasting and postprandial blood sugar were in the range of 88 to 423 (250.87 ± 79.36)mg/dl and 174 to 664(352.77 ± 54.74)mg/ dl respectively. Glycated hemoglobin levels were in the range of 5.90 to 17 % with mean of 9.22± 1.8.

Table 2: The values of variables of the autonomic function tests:

Variables	Range	Mean ± SD
Basal systolic BP (mm Hg)	102 - 156	125.8 ± 13.54
Basal diastolic BP (mm Hg)	72 - 94	85.46 ± 6.79
Basal heart rate (bpm)	55 - 97	70 ± 2.24
E:I ratio (HR response to deep breath)	1.04 - 1.48	1.12±0.09
30:15 ratio (HR response to standing)	0.95 - 1.2	1.01±0.04
ΔHR (bpm)	6 - 20	12±5.07
BP response to standing (mm Hg)	4 - 30	10.11±7.20
SHGT (BP response to sustained hand grip) (mm Hg)	2 - 30	10.58±5.59
Valsalva ratio	1.1 - 1.46	1.23±0.08

ΔHR : heart rate variability, bpm: beats

Table 2 shows the variables of autonomic function test .The mean basalsystolic and diastolic BP of patients were 125.8±13.54(102 to 156) mmHg and 85.46±6.79(72 to 94)mm Hg respectively. The mean basal heart rate was 70 ± 2.24 (55 - 97) bpm. Mean E:I ratio was 1.12±0.09 (1.04-1.48 while mean 30:15 ratio was 1.01±0.04 (0.95 - 0.12). Similarly, mean ΔHR was 12±5.07(6-20) bpm while mean BP response to standing was 10.11±7.20 (4 - 30) mmHg. Mean of SHGT was 10.58±5.59 (2-30) mmHg while that of valsalva ratio was 1.23±0.08(1.1-1.46) respectively.

Table 3: Status of autonomic function tests at the time of enrollment (n = 100)

AFT variables	Normal (%)	Borderline (%)	Abnormal (%)
HR variation during deep breathing (δHR) (bpm)	18(18)	31(31)	51 (51)
HR response to deep breathing (E:I ratio)	40 (40)	-	60 (60)
HR response to standing (30:15 ratio)	24 (24)	36 (36)	40 (40)
BP response to standing (mm Hg)	65 (65)	32 (32)	3 (3)
BP response to sustained hand grip (mm Hg)	24 (24)	18 (18)	58 (58)
HR response to valsalvamanoeuvre (Valsalva ratio)	64 (64)	-	36 (36)

n = Total Number of patients, bpm = beats per minute

Table 3 shows status of autonomic function test of all the patients at the time of enrollment. All the tests were done on 100 patients. E: I ratio was most common abnormality seen, which was abnormal in 60% patients, while least common abnormality was BP response to standing seen in only 3% cases. Most common borderline abnormality was seen in HR response to standing (36% patients).

Table 4: Status of Autonomic function tests after 2 months of euglycemia(n = 100)

AFT variables	Normal (%)	Borderline (%)	Abnormal (%)
HR variation during deep breathing (δHR)	32 (53.33)	11 (18.33)	17 (28.33)
HR response to deep breathing(E:I ratio)	28(46.6)	-	32 (53.3)
HR response to standing (30: 15 ratio)	19 (31.66)	25 (41.66)	16 (26.66)
Drop in SBP after 2 min of standing	39 (65)	20(33.33)	1 (1.66)
BP response to sustained hand grip test (SHGT)	21 (35)	15(25)	24 (40)
Valsalva ratio	47 (78.33)	-	13 (21.66)

n: number of patients followed up after 2 months of euglycemia.

Table 4 shows AFT status after 2 months of euglycemia. All the tests were repeated on same group of patients. Most common AFT abnormality was found in E:I ratio which was abnormal in 53.3% patients while BP response to standing was least common abnormality seen in 1.66% patients. Most common borderline abnormality was seen in HR response to standing (41.66% patients).

Table 5: Mean values of AFT variables at the time of enrollment and after 2 months of euglycemia

AFT Variables	At the time of enrollment (Mean ± SD)	After 2 months of euglycemia (Mean ± SD)	p value
HR variation during deep breathing, δHR (bpm)	12 ± 5.07	18.09 ± 9.91	.001
HR response to deep breathing (E:I ratio)	1.12 ± 0.09	1.18 ± 0.05	.001
HR rate response to standing (30:15 ratio)	1.01 ± 0.04	1.03 ± 0.06	.001
BP response to standing (mm Hg)	10.11 ± 7.20	8.15 ± 6.4	.03
BP response to sustained hand grip , (mm Hg)	10.58 ± 5.59	13.25 ± 8.21	.004
Valsalva ratio	1.23 ± 0.087	1.27 ± 0.138	.07

$p< 0.05$ was taken significant , bpm: beats per minute

Table 5 shows mean values of AFT variables at the time of enrollment and after 2 months of euglycemia. Comparison has been made for all the patients that followed up after maintaining euglycemia. All the values are shown in mean ± SD. Except valsalva ratio, the mean differences for all the variables like E: I ratio, 30:15 ratio, SHGT and drop in SBP were found to be statistically significant ($p < 0.05$).

Table 6: Comparison of baseline values of FBS, PPBS, HbA1c at the time of enrollment vs values after 2 months of euglycemia

Variable	At the time of enrollment	After 2 months of euglycemia	p value
FBS (Mean ± SD) (mg/dl)	220.23 ± 62.58	102.27 ± 6.79	.001
PPBS (Mean ± SD) (mg/dl)	332.69 ± 50.46	148.33 ± 12.27	.001
HbA1c (Mean ± SD) (%)	9.67 ± 1.87	9.01 ± 1.02	.076

$p < 0.05$ was taken significant , FBS: fasting blood sugar, PPBS: post prandial blood sugar, HbA1c: Glycated hemoglobin

Table 6 has shown the comparison for FBS and PPBS (at the time of enrollment vs after 2 months of euglycemia). Similar comparison has been done for HbA1c (at the time of enrollment vs 2 months of euglycemia).Values are shown in mean ± SD . Comparison has been done for all the patients that followed after maintaining euglycemia. Mean differences for FBS and PPBS were found to be statistically significant ($p < 0.05$) while that for HbA1c was statistically not significant($p > 0.05$).

Table 7: Distribution of sympathetic and parasympathetic reactivity at the time of enrollment vs after 2 months of euglycemia

Group	At the time of enrollment n = 100(%)	After 2 months of euglycemia n = 60 (%)
No dysfunction	18 (18)	12(20)
Parasympathetic dysfunction alone	13(13)	7(11.66)
Sympathetic dysfunction alone	9 (9)	5(8.33)
Both dysfunction	56 (56)	27(45)
Borderline	4(4)	9(15)

IV. Discussion

Although very common and serious, autonomic dysfunction is a frequently overlooked complication of diabetes.[8] Intraoperative and perioperative cardiovascular instability, abnormal blood pressure profile, orthostatic hypotension, silent myocardial infarction and stroke are some of the most deleterious manifestations of autonomic neuropathy which are associated with significant morbidity and mortality.[8] Recent studies strongly recommend screening for autonomic neuropathy in patients with diabetes since the progression of cardiovascular denervation is partly reversible or can be slowed down in the early stages of the disease.[9]

In this study, we observed that the prevalence of CAN among recently detected type 2 diabetes is 78%. Thirteen percent (13%) of the patients had parasympathetic dysfunction alone, 9% had sympathetic dysfunction alone, 56% had both dysfunction, 4% had borderline dysfunction and 18% patients had normal results.Our study also showed E: I ratio as the most sensitive test followed by sustained hand grip test and heart rate variability during deep breathing. We also observed in our study that 60 % of patients had abnormal E: I ratio. Similarly 56% had abnormal BP response to sustained hand grip test, 40% had abnormal heart rate response to standing(30:15) ratio, 36% had abnormal valsalva ratio and 3% were having abnormal BP response to standing.

After 2 months of sustained euglycemia, the prevalence of CAN was reduced from 78% to 65% in the present study. Patients with parasympathetic dysfunction only was reduced from 13 % to 11.66% , sympathetic dysfunction only was reduced from 9% to 8.33%, combined dysfunction was reduced from 56 % to 45%, borderline was increased from 4% to 15% and patients who were having no dysfunction increased from 18 to 20%. (Table 7) All the parameters of Ewing's test (E:I ratio, 30;15 ratio, δHR , BP response to standing, SHGT) were showing significant improvement except valsalva manoeuvre after attaining 2 months of euglycemia (table- 5) .

We also observed that there was statistically significant decrease in fasting and postprandial blood sugar in follow up patients as compared to baseline values at the time of enrollment (Table-6). However, HbA1c level was showing decreasing trend which was not statistically significant. This could be due to the fact that normal life of red blood cell is around 3 months so glycated cell takes longer time to return to normal levels.

Study from Jyotsana et al[10] has revealed that there was overall improvement in cardiac autonomic function in recently detected type 2 diabetes patients who were put on treatment for glycemic control. The group of patients who showed improvement in cardiac autonomic function had more reduction in glycated hemoglobin levels compared to those who did not show improvement though this change in glycated hemoglobin level was not significant. Parasympathetic and sympathetic dysfunction were present respectively in 58.25%, 74.75% (baseline), 46.97%, 81.25% (6 months) and 38.3%, 68.09% (12 months).

Manzella et al[11] have studied on 120 overweight type 2 diabetic patients who were treated by placebo (*n* =60) plus diet or metformin (850 mg twice daily) (*n* = 60) plus diet for 4months, to evaluate the effect of metformin treatment on the cardiac autonomic nervous system.They found that Metformin treatment, but not placebo treatment, was associated with a decrease in fasting plasma glucose and insulin levels. They also reported metformin treatment was also associated with a significant improvement in cardiac sympathovagal balance but not in mean arterial BP. In contrast , previous studies have reported use of metformin can worsen the neuropathy as it affects the vitamin B_{12}. [12]

Larsen et al [13] in their study followed up 39 patients with type 1 diabetes and yearly measurement of HbA1c was done. At 18 years, follow up HRV measurement was done in all patients. They found that mean HbA1c during 18 years was associated with cardiac autonomic function. Cardiac autonomic function was found to be preserved in the group with HbA1c $\leq$ 8.4% whereas cardiac autonomic function was impaired in group with HbA1c $\geq$ 8.4%.

The pathogenesis of autonomic neuropathy is complex and multifactorial. Hyperglycemia-induced activation of the polyol pathway cause direct neuronal damage and activation of protein kinase C leading to vasoconstriction and decreased neuronal blood flow. Other mechanisms involved are increased oxidative stress, increased free radical production, dysfunction of nitric oxide production, immune mechanisms, and neurotrophic growth factors deficiency.[14] Accumulation of advanced glycosylation end products in the neuronal blood vessels leads to nerve hypoxia and altered nerve function.[15] Neuronal apoptotic processes are precipitated by endoplasmic reticulum stress induced by hyperglycemia, along with impaired nerve perfusion, dyslipidemia, alterations in redox status, low-grade inflammation and disturbance in calcium balance.[16]

Recent studies have supported the theory that hyperglycemia also impairs neuronal regeneration and suggested that an increase in plasma superoxide generation may be able to predict decline in cardiac nerve function.[14] Increased reactive oxygen species are thought to depress autonomic ganglion synaptic transmission, contributing to increased risk of fatal cardiac arrhythmias as well as to sudden death after myocardial infarction due to posttranslational protein modifications.[16] Another postulated mechanism is the change in vagal activity due to autonomic nerve damage which might have an impact on inflammatory responses. Inflammation can lead to micro and macrovascular complications of diabetes. [16] Since, most of the autonomic changes in diabetes are because of hyperglycemia therefore improved glycemic control can slow down the development and progression of abnormal autonomic function.

Shortcoming or limitation of this study

Though the study has tried to cover the population uniformly distributed among all age groups, still some discrepancies cannot be denied because of slight preponderance towards older age group. Also the number of male subjects was slightly more than female subjects.

V. Conclusion

At the end of study, patients with improved autonomic functions had significant reductions in FBS as well as PPBS levels while reduction in Hba1c levels was not significant.

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