ORIGINAL ARTICLE

HEART RATE VARIABILITY AS AN EARLY INDEX OF AUTONOMIC NEUROPATHY IN DIABETICS

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Background: Cardiac autonomic neuropathy (CAN) is a critical intricacy of diabetes mellitus. Autonomic neuropathy is postulated to be an indicator of impending demise. It is not very easy to detect the diabetic autonomic neuropathy at an earlier stage. The objective of the study was to weigh up the affiliation between autonomic neuropathy and the heart rate variability (HRV) in diabetics. **Methods:** The present study was conducted on 100 Diabetics attending the diabetic clinic of Guru Nanak Dev hospital Amritsar and 25 healthy attendants served as controls .The patients were divided into two major groups, i.e., Type 1 and Type 2 diabetes and two subgroups (<5 years of duration, >5 years of duration) , Autonomic nervous system activity was evaluated in the Department of Physiology of the institute. HRV was measured by Standing to lying ratio (S/L ratio), 30/15 ratio, Valsalva ratio and Deep breathing test (DBT). The results were statistically analyzed. **Results:** Significant changes in parasympathetic activity (30:15 ratio, DBT, S/L ratio) were observed in diabetics as compared to normal which progressed with duration of disease (<5 years vs >5 years, $p<0.05$) but were similar in both types of diabetes. **Conclusion:** With early detection of autonomic neuropathy, use of aggressive approach in management of Diabetes Mellitus would reduce mortality and morbidity in these patients.

Keywords: Diabetes Mellitus, Autonomic nervous system, Heart Rate Variability (HRV)

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INTRODUCTION

The evaluation of the autonomic derangement is a frequent and challenging goal of clinical research. Widespread studies on ANS have been conducted in healthy persons as well as in various diseased people. The study on the complicity of autonomic nervous system in diabetes mellitus is of special interest because this abnormality has a direct bearing on mortality. Neuropathy is a well-recognized complication in diabetics. Diabetes mellitus imparted autonomic neuropathy can entail multiple systems, including cardiovascular, gastrointestinal, genitourinary, sudomotor and metabolic systems. The clinical manifestations of neuropathy include postural hypotension, gastro-intestinal symptoms, hypoglycaemic obliviousness and sweating upheavals. Autonomic neuropathies impinging cardiovascular system cause resting tachycardia and orthostatic hypotension. Reports of sudden death have also been ascribed to autonomic neuropathy.[1]

These clinical manifestations are sluggardly progressive and mostly irreversible and are associated with noteworthy mortality. It is important to quantify the degree of diabetic autonomic neuropathy to obtain a physiological measure of the course of the neuropathy as a navigator for the clinical assessment of the diabetes.[2] Autonomic neuropathy causes massive morbidity and increased mortality peculiarly if cardiovascular autonomic neuropathy is present.[3]

The pronouncement of autonomic neuropathy depends on detecting its cardiovascular component, particularly abnormalities in heart rate control and response of blood pressure to postural changes. Loss of heart rate variability is the hallmark of cardio vascular autonomic neuropathy and is recognised by measuring heart rate response to physiological stimuli.[4]

The evaluation of cardiovascular autonomic function is the cornerstone of the clinical investigation of autonomic function. The anatomic situation of the cardiovascular autonomic nervous system renders it inconvenient for simple direct physiological testing. A group of clinical tests measuring cardiovascular autonomic function and dysfunction have been evolved to combat this problem by measuring the end-organ responses to various physiological manoeuvres.[5]

Consequently, autonomic tests based on cardiovascular reflexes to various physiological agitations (e.g., heart rate response to deep breathing, postural change, and the Valsalva manoeuvre and blood pressure response to sustained hand grip and postural change) are usually employed. Since introduction of these non-invasive tests of the cardiovascular functions, the significance of detecting and tracking impaired autonomic dysfunctions in patients with diabetes has been highlighted. However, these tests do not provide an indiscriminate, quantitative assessment of autonomic function and are imperceptive to early sympathetic neuropathy.[6]

Awareness of the extent to which the autonomic nervous system is entailed in the causation of symptoms in a patient with diabetes is worthwhile as a support in management .Aim of this paper is to briefly summarize available evidence about potential usefulness of heart rate variability (HRV) analysis for the clinical evaluation of autonomic diabetic neuropathy.

This study was carried out to investigate a simple method for identifying abnormality of circulatory reflexes, based on ephemeral changes in heart rate which has also been shown to be reliable and has the advantage of being non-invasive.[7]

SUBJECTS AND METHODS

The present analysis has been done on one hundred patients of Diabetes Mellitus attending Guru Nanak Dev Hospital, Amritsar, and twenty-five normal subjects from general population with an aim to compare the autonomic neuropathic changes between the two types of DM as compared to normal population. The patients were divided into two major groups depending on the type of diabetes, i.e., Type 1 and Type 2, and two subgroups each depending upon the duration of disease.

Group Ia included type 1, <5 years of duration. Group Ib included type 1, >5 years of duration. Group IIa included type 2, <5 years of duration. Group IIb included type 2, >5 years of duration. Each group comprised of 50 patients and each subgroup had 25 patients. Normal subjects constituted group III

The ethical committee approval the study design and informed consent of the individual subjects was taken. A detailed clinical history of all the subjects was asked and a thorough physical examination was performed .The examination of autonomic nervous system was done by simple techniques.

Heart rate, respiratory rate, pulse and temperature were recorded per standard methods.

Heart rate (R-R interval) variation during deep breathing[8]: In Deep Breathing Test (DBT), the subjects sat quietly and breathed deeply at a rate of 6 breaths/min for 1 minute. ECG lead II was recorded throughout the period of deep breathing and a marker was used to convey the onset of each inspiration and expiration. The maximum heart rate during inspiration and the minimum heart rate during expiration were calculated for each breath and the mean of the differences between the maximum and the minimum heart rate for 6 breaths represented as the result of the DBT. A value of less than 10 beats per minute was certainly aberrant, 11 to 14 was borderline and 15 or more was a normal test.

The Valsalva manoeuvre[8] was employed to study both low and high pressure baroreceptor integrity. The subjects were asked to exhale forcefully through a mouth piece which was attached to a manometer and generate a pressure of 40 mmHg and this level was maintained for 15 sec. Throughout the course of this manoeuvre, and the next 45 seconds, the ECG was recorded and the Valsalva ratio was calculated, which is the ratio between the maximal R-R interval (after the release of the strain) and the minimal R-R interval (during the strain). A ratio of 1.20 or more is contemplated as normal.

The heart rate response to standing (30:15) ratio[9] is an index of the postural pressor response. The subjects were connected to the ECG while lying down and then while the subject was in the upright position. The ECG tracings were entailed to conclude the 30:15 ratio, which was calculated as the ratio of the longest R-R interval (at beat 30) to the shortest R-R interval (at beat 15). A ratio of 1.05 or higher was considered as normal.

The standing to lying ratio (S/L ratio)[10] is an index of the postural pressor response. In this test, the subjects were asked to stand quietly and then to lie down without assistance, while an incessant electrocardiogram was recorded from 20 beats and 60 beats after lying down. The S/L ratio was taken as ratio of the longest R-R interval during the 5 beats before lying down to the shortest R-R interval during the 10 beats after lying down.

ECG for autonomic function testing was done with RMS ECG machine, using standard limb lead-II. Blood pressure was measured using sphygmo-manometer. Observations were recorded and interpreted. Data were analysed using SPSS-10. The statistical difference in mean values was tested using ANOVA with post hoc turkey, and $p<0.05$ was taken as significant.

RESULTS

Table-1 shows the distribution of the subjects in various groups.

Table-1: Distribution of subjects into Groups

GROUP	Duration of disease	Patients
IDDM (Ia)	<5 Year	25
IDDM (Ib)	>5 Year	25
NIDDM (IIa)	<5 Year	25
NIDDM (IIb)	>5 Year	25
CONTROL (III)	---	25

Autonomic nervous system parameters in diabetic (type 1 and type 2) patients and control groups are depicted in Tables-2 to 6. Increase in the mean pulse rate was more in both DM groups compared to that in the normal subjects.

Systolic blood pressure (SBP) showed increase in both groups of diabetes mellitus compared to that in the controls. Increase in the mean systolic blood pressure was more in subgroup Ib.

Diastolic blood pressure (DBP) showed increase in types 1 and 2 DM compared to that in controls. Increase in the mean values of the diastolic blood pressure was more in subgroup Ib. Autonomic

symptoms were more common in type 1 than in type 2 diabetes mellitus.

Duration of disease in type 1 diabetes mellitus patients, increased the change in systolic blood pressure. There was deterioration of the parasympathetic activity in these patients.

Table-2 shows that there was increase in mean pulse rate values in two major groups compared to the normal subjects but there was not much difference when two subgroups were compared with each other. Systolic blood pressure showed an increase in mean values in both major groups of DM in contrast to normal subjects. It is clear from the table that increase in mean value of systolic blood pressure was more in subgroup Ib. Diastolic blood pressure showed increase in the two groups of DM in comparison with normal subjects. Increase in mean value of diastolic blood pressure was more in subgroup Ib.

Increase in the pulse rate was statistically significant in group II (Type 2 DM) ($p<0.05$) as compared to group III (control subjects); but insignificant when compared between group I (Type 1) and group II (Type 2), and between various subgroups of DM. Pre-test mean value for systolic blood pressure was statistically significant in comparison between group Ia v/s group III ($p<0.05$) and highly significant when compared between group Ib v/s group III ($p<0.001$). Duration of disease in IDDM patients had increasing effect on change in systolic blood pressure. The changes in SBP were highly significant when compared between group IIa v/s group III and group IIb v/s group III ($p<0.001$) but statistically insignificant ($p>0.05$) when compared between subgroups of group I (Type 1) and group II (Type II).

Pre-test mean value for diastolic blood pressure was statistically highly significant on comparison between group Ia v/s group III ($p<0.001$) and between group Ib v/s group III ($p<0.001$). It was highly significant when compared amongst group IIa v/s group III and group IIb v/s group III ($p<0.001$). It was significant when compared between Type 1 and Type 2 ($p<0.05$).

It was observed that 30:15 ratio in normal population was 1.05±0.04 which decreased in diseased (DM) states. The decrease in 30:15 ratio increased with duration of disease. Valsalva ratio was not affected by type of diabetes mellitus or by duration of disease. Deep Breathing Test showed that difference in R-R interval of normal subjects between inspiration and expiration values was highest. The difference between R-R interval in DBT decreased in both types of diabetes while duration of disease did not have much effect on it. S/L ratio decreased in both types of DM as compared to the normal.

The statistical comparison for the mean value for 30:15 ratio showed significant variation when compared between the group Ia v/s III and group IIb v/s III ($p<0.05$). It is highly significant when compared between group Ia+Ib v/s III and group Ib v/s III ($p<0.001$). No significant change was observed when compared between group Ia v/s IIa, group Ib v/s IIb, group Ia+Ib v/s IIa+IIb and group IIa v/s III ($p>0.05$).

The mean values for valsalva ratio were statistically insignificant when compared between different groups of DM or diseased groups with control subjects (Table-4).

The statistical comparison of the mean value for the deep breathing test showed highly significant variation when compared between group Ia v/s III, group Ib v/s IIb, group Ia+Ib v/s IIa+IIb, group Ia+Ib v/s III, group IIa+IIb v/s III, group IIa v/s III, group IIb v/s III ($p<0.001$). It is statistically significant at 5% significance level in group Ib v/s III. No statistical significance is seen when compared between group Ia v/s IIa ($p>0.05$).

The mean values for S/L ratio were highly significant when compared between the groups Ia v/s III, Ib v/s III, Ia+Ib v/s III, IIa+IIb v/s III, IIa v/s III, and IIb v/s III ($p<0.001$). It was observed that S/L ratio value was significant at 1% significance level when compared between Ia+Ib v/s IIa+IIb ($p<0.01$). No statistical significance was seen on comparison between group Ia v/s IIa ($p>0.05$). Hence type of DM in these patients did not significantly alter the values of S/L ratio or DBT during initial stages of disease.

Table-2: Pre-test mean values of pulse rate and blood pressure in all the groups

Groups	Pulse Rate (per min)		SBP (mm Hg)		DBP (mm Hg)	
	Range	Mean±SD	Range	Mean±SD	Range	Mean±SD
Ia	60–110	81.04±13.86	100–146	130.72±11.83	70–96	86.08±5.67
Ib	60–104	80.16±15.47	130–156	144.64±8.24	82–100	91.60±5.50
IIa	66–107	86.88±11.49	120–160	136.08±9.44	70–92	84.64±4.78
IIb	60–130	82.52±16.48	110–154	138.40±9.52	68–100	86.40±6.21
III	70–88	76.84±5.46	104–134	120.16±9.39	60–88	76.96±7.83

Table-3: Comparison of Pulse rate, SBP and DBP between various subgroups

Parameter	*P*								
	Ia v/s IIa	Ia v/s II	Ib v/s IIb	Ib v/s III	Ia+Ib v/s IIa+IIb	Ia+Ib v/s III	IIa + IIb v/s III	IIa v/s III	IIb v/s III
Pulse Rate/min	0.999	0.791	0.969	0.899	0.266	0.474	0.04	0.06	0.54
SBP (mmHg)	0.301	0.002	0.165	<0.001	0.377	<0.001	<0.001	<0.001	<0.001
DBP (mmHg)	0.919	<0.001	0.025	<0.001	0.02	<0.001	<0.001	<0.001	<0.001

Table-4: Mean values of parasympathetic function tests in three groups and subgroups

Groups	30:15 ratio		Valsalva ratio		DBT ratio		Standing/Lying ratio	
	Range	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range	Mean±SD
Ia	0.9–1.1	1.00±0.05	1–1.42	1.17±0.12	5–29	11.44±6.93	0.60–1.06	0.85±0.12
Ib	0.83–1.08	0.95±0.09	0.93–1.20	1.05±0.06	6–29	13.60±7.60	0.79–1.04	0.89±0.09
IIa	0.9–1.12	1.01±0.05	0.80–1.93	1.15±0.28	4–13	7.80±2.27	0.75–1.35	0.95±0.14
IIb	0.93–1.08	1.00±0.05	0.90–1.85	1.19±0.25	3–12	7.40±2.30	0.80–1.08	0.95±0.08
III	1.0–1.14	1.05±0.04	1.04–1.25	1.15±0.08	12–22	17.88±3.14	1.00–1.50	1.22±0.18

Table-5: Comparison of parasympathetic functions in Groups and Subgroups

Para meter	*P*								
	Ia v/s IIa	Ia v/s III	Ib v/s IIb	Ib v/s III	Ia+Ib v/s IIa+IIb	Ia+Ib v/s III	IIa + IIb v/s III	IIa v/s III	IIb v/s III
30:15 Ratio	0.993	0.03	0.079	<0.001	0.097	<0.001	0.008	0.108	0.031
Valsalva	0.983	0.992	0.069	0.296	0.313	0.668	0.940	1.00	0.958
DBT	0.084	<0.001	<0.001	0.02	<0.001	<0.001	<0.001	<0.001	<0.001
S/L Ratio	0.10	<0.001	0.589	<0.001	0.01	<0.001	<0.001	<0.001	<0.001

DISCUSSION

Autonomic neuropathy is a frequently observed intricacy of diabetes that has a noteworthy distressing influence on the survival and quality of life of the patients. Generally, diabetic autonomic neuropathy may be clinically evident long after the onset of diabetes. Sub-clinical autonomic dysfunctions can occur within a year of Type 2 diabetes diagnosis, and within 2 years of Type 1 diabetes. Early awareness of autonomic dysfunctions can encourage patients and physicians to improve metabolic control and use the treatments that may be effective in patients with autonomic dysfunctions, particularly cardiac autonomic dysfunction (CAN).[11]

Cardiac marker heart rate variability (HRV) is an eloquent, sensitive and early prognosticator which can be used for early diminution of complications among diabetics.[12] In our study the statistical analysis of the mean values of the pulse rate showed increase in mean pulse rate values in both the diseased groups as compared to the normal subjects. The increase in the pulse rate was statistically significant in Type 2 DM (p<0.05) compared to control subjects, but insignificant when compared between the two groups of DM, i.e., group I (Type 1) versus group II (Type 2) and between various subgroups of DM. It was observed that there is resting tachycardia in diabetics. These findings are consistent with the study done by Shuldiner *et al*[13] in which the authors observed resting tachycardia in diabetics suffering from cardiovascular autonomic neuropathy. Similar were the observations of other authors.[14,15]

Substantial autonomic dysfunction has been found to be present in early DM patients even before overt clinical symptoms of CVD became apparent. It is noteworthy that involvement of the vagal parasympathetic component of autonomic nervous system is obvious in DM patients. This is evidenced by increased resting heart rate and decreased Valsalva ratio; E/I index and standing ratio in diabetics relative to controls. These findings are in line with those of Freccero *et al*[16] who reported a high frequency of parasympathetic and sympathetic neuropathy in both type 1 and type 2 diabetic patients. They suggested that severe damage to large myelinated nerve fibres in addition to the widespread neurological degeneration which usually affects the small nerve fibres of the autonomic nervous system was culpable for profound parasympathetic neuropathy in patients with T2DM. Other researchers also found appreciable degree of autonomic neuropathy in patients with T2DM.[17,18]

In fact significantly reduced HRV measures in DM patients compared to controls have been previously verified in large-population-based studies.[19,20] The same results had also been documented in the Framingham Heart Study and in the Atherosclerosis Risk in Communities (ARIC) cohort.[20,21]

The significance of our findings is that HRV reduction in diabetics was present since the early stages of diabetes even before clinical cardiovascular disease became evident. Thus, it is imperative to screen for autonomic neuropathy as early as possible in diabetics to prevent or retard its serious consequences.

The findings from the present study were consistent with earlier studies showing that various autonomic changes occurred in both IDDM and NIDDM patients compared to normal subjects. Parasympathetic impairment occurred in both types of DM and similar progression occurred in both types of diabetes as the disease progressed.[22]

CONCLUSION

It is imperative to screen for autonomic neuropathy as early as possible in diabetics to prevent or retard its serious consequences. With early detection of autonomic neuropathy, use of aggressive approach in management of Diabetes Mellitus would reduce mortality and morbidity in these patients.

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