Original Article

Physiology Section

Comparison of Autonomic Neuropathic Changes in Type 1 and Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Diabetes is the most common endocrine metabolic disorder. Duration of Diabetes affects the quality and longevity. Autonomic neuropathy is postulated to be an indicator of impending demise.

Aims & Objectives: The aim of the present study was to compare the autonomic nervous system activity between Type 1 and Type 2 diabetes mellitus and with normal control subjects and to evaluate the effect of duration of disease.

Materials and 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 assessed in the physiology department. Sympathetic activity was measured by cold presser test, hand grip test, and blood pressure response to standing. Parasympathetic activity was measured by S/L ratio, 30/15 ratio, valsalva ratio and I/E ratio. The results were statistically analyzed.

Results: Changes in sympathetic activity as observed by changes in SBP, CPT & HGT were significantly ($p< 0.001$) affected by type of diabetes (Type 1 DM vs Type 2 DM) and by the duration of disease (<5 yrs vs >5yrs)as compared to normal. 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 yrs vs >5yrs, $p<0.05$) 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.

Key Words: Diabetes, Autonomic nervous system, Cold presser test, Hand grip test

INTRODUCTION

Diabetes mellitus (DM) is a disorder in which the concentration of blood glucose is persistently raised above the normal range. It occurs either because of lack of insulin or because of the presence of factors which oppose the action of insulin. Quoting for type 1 and type II diabetes There are many associated metabolic abnormalities – notably, the development of hyperketonaemia more in type1 DM, together with alterations of the fatty acids, lipids, and protein turn over [1].

According to the World Health Organization (2008), reference, needed at least 171 million people worldwide had diabetes; by 2030, this figure is likely to become more than double of the current figure. The major concern is that most of this increase will occur in the developing countries due to population growth, ageing, unhealthy habits, obesity and sedentary life styles. There is an increasing incidence of Type 2 diabetes - which accounts for about 90% of all the cases [2].

The assessment of the autonomic nervous activity (ANS) 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 involvement of the autonomic nervous system in diabetes mellitus is of special interest because this abnormality has a direct bearing on mortality [3].

Autonomic neuropathy is a well-recognized complication of diabetes mellitus. The clinical manifestations of diabetic autonomic neuropathy include postural hypotension, gastro-intestinal symptoms, hypoglycaemic unawareness and sweating disturbances. These clinical manifestations are slowly progressive and usually irreversible and are associated with considerable mortality. It is important to quantify the degree of diabetic autonomic neuropathy to obtain a physiological measure of the progression of the neuropathy as a guide for the clinical assessment of the diabetes [4].

The diagnosis of autonomic neuropathy relies on detecting its cardiovascular component, particularly abnormalities in the heart rate control and the response of blood pressure to the postural changes. Loss of heart rate variability is the hallmark of cardio vascular autonomic neuropathy and it is diagnosed by measuring the heart rate response to physiological stimuli [5].

This type of neuropathy can usually be found in approximately 25% of the patients with Type-1 diabetes mellitus (DM1) and in 34% of those with type-2 diabetes mellitus (DM2). The great majority of DM1 patients with cardiovascular autonomic neuropathy remain totally asymptomatic for years and by the time the symptoms appear, the cardiovascular autonomic neuropathy may have progressed into the advanced and irreversible stages [10].

MATERIALS AND METHODS

This study was conducted on one hundred patients of Diabetes Mellitus, who attended the Guru Nanak Dev Hospital, Amritsar and on twenty five normal subjects. The patients were divided into two major groups depending on the type of diabetes i.e. type 1 and

type 2 and two subgroups depending upon the duration of the disease.

The groups were divided as:

Group I:

- Group Ia included: type 1 < 5 years of duration.
- Group Ib included: type 1 >5 years of duration.

Group II:

- Group IIa included type 2 <5 years of duration.
- Group IIb included type 2 >5 years of duration.

Group III

- Normal patients in group III

Each group comprised of 50 patients and each subgroup of 25 patients.

The ethical committee clearance and an informed consent of the subjects were taken. A detailed clinical history of all the subjects was taken and a thorough physical examination was performed. The examination of autonomic nervous.

Recording Techniques

- Heart rate, respiratory rate, pulse and temperature recorded.
- Heart rate (R-R interval) variation during deep breathing [3,6].
- **Deep breathing (DBT)** at 6 breaths a minute is the most convenient and reproducible technique. In this test, the subject sits quietly and breathes deeply at a rate of 6 breaths/minute for 1 minute. An electrocardiogram (lead II) is recorded throughout the period of deep breathing and a marker is used to indicate 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 difference between the maximum and the minimum heart rate for 6 breaths represented as the result of the test. A value of less than 10 beats per minute is definitely abnormal, 11 to 14 is borderline and 15 or more is a normal test.

- **The Valsalva manoeuver [6, 7]**
  This test is employed to study both the low and high pressure baroreceptor integrity. The subject is asked to exhale forcefully through a mouth piece which is attached to a manometer to generate a pressure of 40 mmHg and this level is maintained for 15 sec. During this manoeuver, and 45 seconds subsequent to this, the ECG is recorded and the Valsalva ratio is 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 considered as normal.

- **The heart rate response to standing (30:15) ratio [6]**
  This is an index of the postural pressor response. The subject is connected to the ECG while lying down and then while the subject is in the upright position. The ECG tracings are used to determine the 30:15 ratio, which is 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 is considered as normal.

- **The standing to lying ratio (S/L ratio) [8]**
  This is an index of the postural pressor response. In this test, the subject is asked to stand quietly and to then lie down without help, while a continuous electrocardiogram is recorded from 20 beats and 60 beats after lying down. The S/L ratio is taken as the 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.

- **The blood pressure response to standing and lying [9]**
  The test is performed by measuring the blood pressure of the subject with the sphygmomanometer while the patient is in the supine position and then one minute after the subject is made to stand. The postural fall in blood pressure is taken as the difference between the systolic blood pressure while lying and the systolic blood pressure on standing. A fall in the systolic blood pressure of less than 10 mmHg is normal. A fall in the systolic blood pressure of 20 mm Hg or more is abnormal.

- **The cold pressor test [6,7]**

  In this test, the subject is asked to immerse the hand in a container of ice water for one minute. The blood pressure is recorded before the test, during the test and after the test every 30 seconds till the blood pressure returns to the pretest levels. An increase in the systolic blood pressure of greater than or equal to 15 mmHg is considered as normal.

- **The blood pressure response to static exercises (Hand grip test) [6, 7]**
  Sustained isometric muscle contraction causes a reflex rise in the blood pressure and the heart rate. In this test, the subject is asked to apply pressure on a standardized handgrip at a maximum voluntary contraction for one minute. The blood pressure is measured before and at 1 minute intervals during the handgrip. The result is expressed as the difference between the highest diastolic pressure during the handgrip and the diastolic pressure before the handgrip. A rise of more than 10 mmHg during the handgrip is normally expected.

RESULT

Mean value ± standard deviation of the ANS parameters in the diabetic patients (type 1 and type 2) and the control groups are depicted in the [Tables/Fig-1 to 6]. The data was revealed as follows:

1. Increase in the mean pulse rate is more in
   - Both the DM groups as compared to that in the normal subjects
2. Systolic Blood Pressure shows
   - Increase in both the groups of DM as compared to that in the normals
   - Increase in the mean systolic blood pressure was more in subgroup Ib.
3. Diastolic blood pressure shows
   - Increase in types1 and 2 DM as compared to that in the normals
   - Increase in the mean values of the diastolic blood pressure is more in subgroup Ib_
4. Autonomic symptoms were more common in type1 than in type2 DM
5. Duration of disease in type1 DM patients, increasing effect on change in systolic blood pressure
6. There was deterioration of the parasympathetic and the sympathetic activity in these patients
7. Greater impairment of the sympathetic functions were observed in the type 1 DM patients as compared to those in the type 2 patients (the sympathetic impairment occurred in

Groups	Number	Pulse Rate(per min)		SBP(mm Hg)		DBP(mm Hg)	
		Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD
Ia	25	60-110	81.04± 13.86	100-146	130.72± 11.83	70-96	86.08± 5.67
Ib	25	60-104	80.16± 15.47	130-156	144.64± 8.24	82-100	91.60± 5.50
IIa	25	66-107	86.88± 11.49	120-160	136.08± 9.44	70-92	84.64± 4.78
IIb	25	60-130	82.52± 16.48	110-154	138.40± 9.52	68-100	86.40± 6.21
III	25	70-88	76.84± 5.46	104-134	120.16± 9.39	60-88	76.96± 7.83

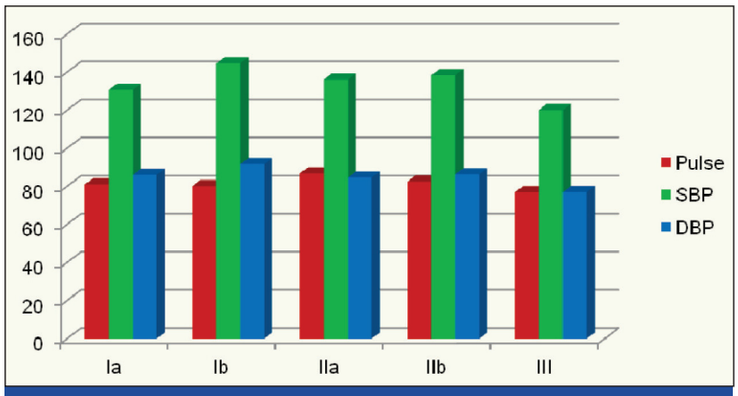
[Table/Fig-1]: Pre-Test Mean Values of Pulse Rate and Blood Pressure in allthe Groups (N=125)
SD: Standard deviation ; DBP: Diastolic blood pressure ;SBP:Systolic blood pressure

Groups	Number	FALL IN SBP (mmHg)		CPT Rise in SBP (mmHg)		HGT Rise in DBP (mmHg)	
		Range	Mean±SD	Range	Mean±SD	Range	Mean±SD
Ia	25	8-16	12.16±2.15	6-14	11.20±2.44	8-14	11.92±2.19
Ib	25	12-20	15.20±2.38	6-12	9.20± 1.73	6-12	9.04±1.92
IIa	25	6-20	8.80± 2.76	12-18	14.32±1.49	12-20	14.16±1.81
IIb	25	8-14	10.56± 1.96	10-14	12.00±1.52	8-16	12.56±2.04
III	25	4-8	6.32± 1.10	12-16	15.36±2.13	12-16	16.72±2.50

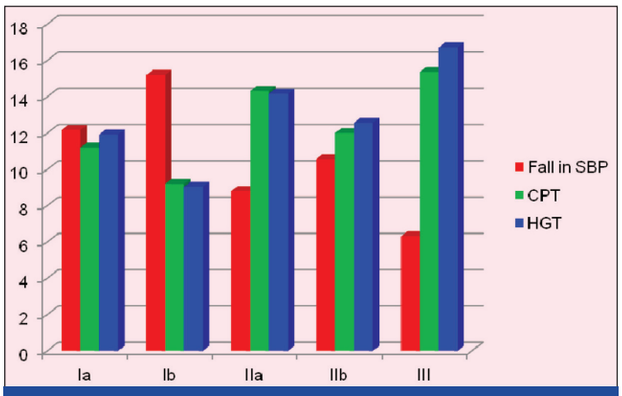
[Table/Fig-2]: Comparative Study of Sympathetic Functions in Three Groups & Sub Groups
SBP: Systolic blood pressure; CPT: Cold pressor test; HGT: Hand grip test; DBP:Diastolic blood pressure

Groups	Number	30:15 RATIO		VALSALVA RATIO		DBT RATIO		S/L RATIO	
		Range	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range	Mean±SD
Ia	25	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	25	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	25	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	25	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	25	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

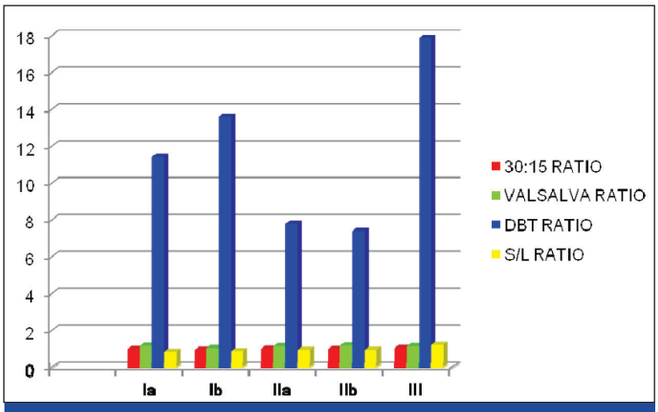
[Table/Fig-3]: Mean Values of Parasympathetic Function Tests in Three Groups & Subgroups



[Table/Fig-4]: Represents graphical representation of pretest mean values of Pulse rate, SBP, DBP



[Table/Fig-5]: Comparative Study of Sympathetic Functions in Three Groups & Sub Groups.
SBP: Systolic blood pressure; CPT: Cold pressor test; HGT: Hand grip test; DBP:Diastolic blood pressure



[Table/Fig-6]: Mean Values of Parasympathetic Function Tests
In Three Groups & Subgroups

the type1 DM patients and the changes progressed with the duration of the disease)

8. A parasympathetic impairment occurred in both the types of DM and the progression was similar in the types 1 and 2 DM with the duration of the disease.
9. The type of DM did not alter the standing to lying ratio or the deep breathing test during the initial stages.

DISCUSSION

Pulse Rate

The statistical analysis of the mean values of the pulse rate showed an increase in the mean pulse rate values in both the diseased groups as compared to the normal subjects.

PULSE RATE

Parameter	p-value								
	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 (per min)	0.999^{NS}	0.791^{NS}	0.969^{NS}	0.899^{NS}	0.266^{NS}	0.474^{NS}	0.04*	0.06^{NS}	0.54^{NS}
SBP (mmHg)	0.301^{NS}	0.002**	0.165^{NS}	<.001***	0.377^{NS}	<.001***	<.001***	<.001***	<.001***
DBP (mmHg)	0.919^{NS}	<.001***	0.025*	<.001***	0.02*	<.001***	<.001***	<.001***	<.001***

Comparison of Pulse rate, SBP& DBP between various subgroups
P> 0.05 ; Not Significant; * p<0.05; Significant at 5% significance level** p< 0.01; Significant at 1% significance level ; *** p< 0.001; Highly significant

Parameter	p-value								
	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
Fall in SBP	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001**	<0.001
CPT Rise in SBP (mmHg)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.483^{NS}	0.307^{NS}	<0.001
HGT Rise in DBP (mmHg)	<0.001	0.003**	<0.001	<0.001	<0.001	<0.001	0.740^{NS}	<0.001	0.063^{NS}

Comparative Study of Sympathetic Functions in Three Groups & Sub Groups(N=125)
P> 0.05 ; Not Significant; * p<0.05; Significant at 5% significance level** p< 0.01; Significant at 1% significance lelvel ; *** p< 0.001; Highly significant

Para meter	p-value								
	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^{NS}	0.03*	0.079^{NS}	<0.001	0.097^{NS}	<0.001	0.008**	0.108^{NS}	0.031*
Valsalva	0.983^{NS}	0.992^{NS}	0.069^{NS}	0.296^{NS}	0.313^{NS}	0.668^{NS}	0.940^{NS}	1.00^{NS}	0.958^{NS}
DBT	0.084^{NS}	<0.001	<0.001	0.02*	<0.001	<0.001	<0.001	<0.001	<0.001
S/L Ratio	0.10^{NS}	<0.001	0.589^{NS}	<0.001	0.01**	<0.001	<0.001	<0.001	<0.001

P> 0.05 ; Not Significant; * p<0.05; Significant at 5% significance level** p< 0.01; Significant at 1% significance level ; *** p< 0.001; Highly significant

Systolic blood pressure: The 'Systolic Blood Pressure' showed an increase in the mean values in both the major groups of DM as compared to the normal subjects. The duration of the disease in the type 1 DM patients had an increasing effect on the change in the systolic blood pressure. A comparison of the mean values of the 'fall in SBP on response to standing' and the 'rise in SBP in response to the cold pressor test' was done. From the data, it was observed that there was a greater and highly significant 'fall in SBP' in type 1 DM as compared to that in type 2 DM, thus showing a greater impairment of the sympathetic functions in the type 1 DM patients as compared to the type 2 DM patients.

The 'rise in SBP in response to the cold pressor test (CPT)' was highest in the group III patients and lowest in the group Ib patients.

Diastolic Blood Pressure: Also, a rise in the mean values of the diastolic blood pressure in response to the hand grip test were observed.

A rise in the mean values of the diastolic blood pressure in response to the hand grip test (HGT) was highest in group III patients and lowest in group Ib patients.

Autonomic Nervous System (Various Factors): The variations in the 30:15 ratio, the S/L ratio, the Valsalva ratio and the deep breathing test in the various groups and subgroups.

a) **The S/L Ratio:** A simple test which can be done to assess the cardiac para-sympathetic activity is the S/L ratio i.e. the heart rate response to lying down. It was observed that the S/L ratio value was significant at a (1%)significance level when it was compared between type 1 and type II Diabetes mellitus (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) ie. duration of the disease is less than 5 yrs. Hence, the type of DM in these patients did not significantly alter the values of the S/L ratio during the initial stages of the disease, but as the disease progressed, significant differences were observed.

b) **The deep breathing test:** The statistical comparison of the mean value for the deep breathing test showed a highly significant variation when it was compared between groups Ia v/s III, groups Ib v/s IIb, groups Ia+Ib v/s IIa+IIb, groups Ia+Ib v/s III, groups IIa + IIb v/s III, groups IIa v/s III and groups IIb v/s III (p<0.001). It was statistically significant at a 5% significance level in groups Ib v/s III. So, the measurement of the variation in the heart rate during deep breathing is a sensitive index of the autonomic dysfunction. There was a highly significant difference between both type 1 and type2 DM and the normal groups, but there was a significant difference of 5% between groups 1b and III

On correlating the findings of the 30:15 ratio, the S/L ratio, the deep breathing test and the Valsalva ratio, a para-sympathetic dysfunction was observed in both the types of diabetes. The type of DM in these patients did not significantly alter the values of the S/L ratio or the DBT during the initial stages of the disease. However, the differences became significant with the increased duration of the disease.

The data from the present study was consistent with that of earlier studies, which showed that various autonomic changes occurred in both the type 1 DM and the type 2 DM patients as compared to the normal subjects.

SUMMARY AND CONCLUSION

The present study was conducted to compare the autonomic neuropathic changes in type 1 and type 2 Diabetes Mellitus. An in depth analysis of the autonomic nervous system activity

was measured with the help of various tests with respect to the sympathetic and para-sympathetic activities in both the types of diabetes mellitus. (A questionnaire regarding the various autonomic symptoms was given to the subjects prior to the conduction of the tests for the autonomic functions.

The response to the 'Sympathetic function tests' suggested that sympathetic impairment was occurring in the type 1DM patients earlier than in the type 2 DM patients and that the changes progressed with the duration of the disease in both. Our findings indicated that autonomic signs and symptoms were common in diabetes. Most of the earlier studies had not recorded the autonomic symptom profile separately. Our study emphasizes the need to separately evaluate the autonomic symptoms by using CASS (Composite Autonomic Severity Score) as the autonomic symptoms can be recorded by any physician and as these are helpful in evaluating diabetic autonomic neuropathy.

On the other hand, the para-sympathetic activity also showed a gradual deterioration, starting earlier in the disease, but progressing similarly along with the sympathetic neuropathy. The types of diabetes in these patients did not significantly alter the values of the S/L ratio or the DBT during the initial stages of the disease.

In a nut shell, we can conclude that autonomic neuropathic changes occur in both the groups with the initial involvement of the sympathetic and the subsequent involvement of the parasympathetic system.

LIMITATIONS OF THE STUDY

The limitation of the present study was the small sample size of the patients. Secondly, in our study, the type 1 diabetes patients were of a younger age group, while the type 2 diabetes patients were of an older age group.

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