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Autonomic Neuropathic Changes in Diabetes: Early marker of Impending Complications

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Abstract
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 this study was to weigh up the affiliation between autonomic neuropathy and the heart rate variability (HRV) in Type 2 Diabetics. HRV can indicate early subclinical manifestation of autonomic dysfunction, and this could be of value from clinical perspective to understand the risk associated with the subject and further management. In other words, having HRV insight may influence the aggressiveness of the intervention and the choice of therapy when dealing with hyperglycaemia and the complications and also for identifying potential risks, which are not obvious (e.g., CAN).* ***Methods:*** *The present study was conducted on 50 type 2 Diabetics attending the diabetic clinic and 25 healthy attendants served as controls.The patients were divided into two major groups, i.e. (<5 years of duration, >5 years of duration), Autonomic nervous system activity was evaluated. 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 analysed.* ***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).* ***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: *Cardiac autonomic neuropathy(CAN), Diabetes Mellitus, Heart Rate Variability (HRV)*

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I. Introduction

According to WHO, Chronic diseases are defined as diseases of long duration and slow progression , precipitated by factors having close association with surroundings and lifestyle of a person.[1] Diabetes is a silent killer affecting all organs either directly or indirectly through various mechanisms which are mainly due to changes in blood glucose , free fatty acids and biochemical markers levels.[2]
Stress , lifestyle, environment, genetic predisposition add on to the complications which include various microvascular and the macrovascular complications.[3,4,5] Autonomic dysfunction is the most deadly complication leading on to organ dysfunction and cardiac autonomic neuropathy which leads to alteration in the rhythm of heart involving parasympathetic system initially then sympathetic system.[6-9]

Cardiovascular autonomic neuropathy is defined as the impairment of autonomic control of the cardiovascular system [10]. Subclinically, the disease is defined by cardiovascular reflex testing, which may have prognostic implications. Clinically, the impairment in autonomic function is associated with resting tachycardia, exercise intolerance, orthostatic hypotension, syncope, intraoperative cardiovascular instability, silent myocardial infarction and ischemia, and increased mortality [11].Autonomic neuropathies impinging cardiovascular system cause resting tachycardia and orthostatic hypotension. Reports of sudden death have also been ascribed to autonomic neuropathy.[12]

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. 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.

II. Material And Methods

The study was conducted on 50 Type 2 diabetics which were further divided into two groups according to the duration of disease,less than 5 years of disease and more than 5 years of disease. Detailed history of the patients were taken and enquired about their lifestyle and the various battery of tests were done assessing their pulse rate, blood pressure and ECG with posture variations i.e. sympathetic and parasympathetic parameters were completely evaluated. ECG for autonomic function testing was done with RMS ECG machine, using standard limb lead-II. Blood pressure was recorded using sphygmomanometer. Sympathetic activity was measured by cold pressor 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.

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.

III. Results

TABLE 1

GROUP	DURATION OF DISEASE	NO.OF PATIENTS
NIDDM Ia	<5 years	25
NIDDM Ib	>5 years	25
CONTROL II		25

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

Groups	No.	Pulserate **(per min)** (range)	Pulse rate **Mean±SD**	SBP **(mm Hg)**(range)	SBP **Mean±SD**	DBP **(mm Hg)**(range)	DBP **Mean±SD**
Ia	25	66–107	86.88±11.49	120–160	136.08±9.44	70–92	84.64±4.78
Ib	25	60–130	82.52±16.48	110–154	138.40±9.52	68–100	86.40±6.21
II	25	70-80	76.84±5.46	104-134	120.16±9.39	60-88	76.96±7.83

TABLE 3 Mean values of parasympathetic function tests

Data analysis showed that:

1. Out of 50 diabetics only 8 had active life style while 42 had sedentary mode of living adding on to the disease status.
2. Increase in mean pulse rate, Systolic blood pressure and diastolic blood pressure in the two groups. Increase in pulse rate is statistically significant $p<0.05$ as compared to the control group and loss of variability of heart rate with duration of disease is seen.Pre test mean value for DBP is highly significant when compared between the two groups $p<0.01$.
3. Sympatheic impairment evident by postural fall in BP, occurred in Group Ib and is statistically significant. But the cold pressor test and Hand grip test did not show significant change.

Groups	30:15 ratio Range **Mean±SD**		Valsalva ratio Range **Mean±SD**		DBT Range **Mean±SD**		S/L ratio Range **Mean±SD**	
Ia	0.9-1.12	1.01±0.05	0.8-1.93	1.15±0.28	4-13	7.80±2.27	0.75-1.35	0.95±0.14
Ib	0.93-1.08	1.00±0.05	0.9-1.85	1.19±0.25	3-12	7.40±2.30	0.8-1.08	0.95±0.08
II	1.0-1.14	1.05±0.04	1.04-1.25	1.15±0.08	12-22	17.88±3.14	1-1.5	1.22±0.18

4. Parasympathetic parameters showed deterioration with theduration of the disease. The statistical comparison for 30:15 ratio, Valsalva ratio and Deep breathing were highly significant and progressed with the duration of the disease.

IV. 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. 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).[13]

Cardiac marker heart rate variability (HRV) is an eloquent, sensitive and early prognosticator which can be used for early diminution of complications among diabetics.[14] It was observed that there is resting tachycardia in diabetics. These findings are consistent with the study done by Shuldiner*et al*[15] in which the authors observed resting tachycardia in diabetics suffering from cardiovascular autonomic neuropathy. Similar were the observations of other authors.[16,17] The involvement of the vagal parasympathetic component of autonomic nervous system is obvious in Diabetic 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 arein line with those of Frecceroet *al*[18] 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.[19,20]

In fact significantly reduced HRV measures in DM patients compared to controls have been previously verified in large-population-based studies.[21,22] The same results had also been documented in the Framingham Heart Study and in the Atherosclerosis Risk in Communities (ARIC) cohort.[22,23]

V. Conclusion

Autonomic signs and symptoms are common in diabetes and 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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