

Prognosis of Cardiac Autonomic Neuropathy in Patients with Diabetes Mellitus

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Abstract Back ground: Autonomic neuropathy is a serious complication of diabetes mellitus. Cardiac autonomic neuropathy (CAN) is chronic diabetic complication with variable prevalence and clinical manifestations. Aim: To analyse CAN in patients with DM & normal persons. Materials and methods: A total of 100 subjects diabetic patients & healthy controls were selected for the study following strict inclusion and exclusion criteria. All the subjects underwent a battery of cardiovascular reflex tests designed by Ewing. Results: We observed that there was significant difference was between parasympathetic and sympathetic function tests in between these patients & normal persons. Evaluation of autonomic nervous system revealed that CAN progressively increases & autonomic function tests diversify to abnormality as duration of disease increase. Conclusion: Evaluation of autonomic nervous system revealed that CAN is more prevalent in diabetic patients than normal persons & progressively increases with the duration of disease.

Keywords Autonomic Dysfunction, Autonomic Function Test, Cardiovascular Autonomic Neuropathy, Diabetes Mellitus

1. Introduction

Diabetic Autonomic Neuropathy (DAN) is among the least recognized and least understood complication despite its significant impact on survival and quality of life in people with diabetes. The early recognition and appropriate management of diabetic neuropathy is important.[1,2]

Cardiovascular autonomic neuropathy leads to hampered life of patients due to dizziness because of postural hypotension, unawareness of hypoglycaemic symptoms which make him more liable to various injuries, exercise intolerance, chronic fatigue, enhanced intra operative cardiovascular liability, increased incidence of asymptomatic ischemia, myocardial infarction, and decreased likelihood of survival after myocardial infarction.[3]

Purpose of this study was to evaluate the autonomic nervous system in diabetic patients and healthy subjects using battery of cardiovascular reflex tests designed by Ewing and compare the results between two groups. We have also analysed the effect of duration of disease on autonomic functions in diabetic patients.

2. Material & Methods

With the permission of IRB committee, 100 study subjects were chosen from medicine outpatient department of Sir Takhtasinhji Hospital, Medical College Bhavnagar were divided into two groups, 50 with diagnosed diabetes mellitus, and 50 age and sex matched healthy control. Each group contains 25 males & 25 females. The diabetic group was subdivided in three groups according to duration of disease. Group I (0- 5 year), Group II (5- 10 year), Group III (10-15) year this 100 subjects were examined and autonomic nervous system's evaluation was done by instrument cardiac autonomic nervous system analyzer -304 by Diabetic Foot Care India Pvt. Ltd

2.1. Inclusion Criteria for Cases

Male or female patient age being between 30 to 70 years & known case of diabetes.

2.2. Inclusion Criteria for Controls

Subject must be non-diabetic, matched for age, sex as that of test group are included as controls.

2.3. Exclusion Criteria for Case & Controls

Subjects who did not give consent, hypertensive, suffering from renal failure, suffering from disease that can cause autonomic neuropathy (leprosy, alcoholic neuropathy, multi system atrophy thyroid disorders) suffering from any other disease (amyloidosis, beriberi, HIV, TB, leprosy, chronic uraemia or hepatic disease (usually subclinical dysautonomia)), taking any drug that can cause neuropathy or affect AFT (nicotine, amiodarone, cis-Platinum, B12 deficiency or drug

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that can affect ANS like L-dopa, ganglion blockers, alpha-blockers, bromocryptine). Subjects who has addiction like nicotine, alcohol.[4]

Table 1. Distribution according to Duration of diabetes mellitus

Duration of exposure	Percentage
<5years	36
6-10 years	30
>10 years	34

Table 2. Autonomic Function Test in controls and cases (values are in mean and standard deviation)

Tests	Controls	Cases
RHR	85.8±12.90	88.02±11.10
P value		0.35
T value		0.92
E/I RATIO	3.51±1.15	3.51±1.15
P value		<0.05
T value		1.823
30:15 RATIO	1.26±0.50	0.89±0.27
P value		<0.05
T value		4.52
RSBP(mmHg)	117.48±10.94	127.8±11.74
P value		<0.05
T value		4.54
RDBP(mmHg)	73.84±7.48	81.26±10.95
P value		<0.05
T value		3.95
Fall in SBP on standing (mmHg)	5.14±4.79	9.68±9.28
P value		<0.05
T value		3.07
Fall in DBP on standing (mmHg)	2.84±3.43	4.42±4.30
P value		<0.05
T value		2.03
Rise in DBP on handgrip test (mmHg)	13.3±6.42	6.32±7.55
P value		<0.05
T value		4.976

2.4. Precaution

We had taken care that Autonomic nervous system evaluation was done in every subject in morning between 9am to 1pm only, subject had adequate sleep the night before the day of examination, that subject had neither eat, nor smoked or taken alcohol prior 3 hour of testing. We had ensure that subject had stopped any drug taking that affect ANS functioning (like B blocker) before adequate duration. Because ANS system is widely affected by time of day, sleep, posture, fasting, smoking, caffeine.[5,6]

Battery of following tests was performed by each subject.1)Resting heart rate - observed over a period of one minute in all the subjects after a rest period of 15 minutes. (>90 beats minute will be considered to have resting tachycardia). 2) The Expiratory/Inspiratory ratio- (Normal value of E/I ratio is various according to age groups. 31-35yr>1.16, 36-40yr>1.14, 41-45yr>1.12, 46-50yr>1.11,

51-55yr>1.09, 56-60yr>1.08, 61-65yr>1.07, 66-70yr > 1.06, values less than these according to different age group is considered abnormal). 3) Immediate heart rate response to standing, 30/15 ratio (a ratio less than 1.04 is considered abnormal). 4) Resting systolic and diastolic BP (greater than or equal to 130 mmHg systolic BP and 85 mmHg of diastolic BP is considered abnormal or pre hypertensive). 5) Systolic and diastolic BP fall in response to standing (fall in SBP >20 mmHg and fall in DBP > 10 mmHg it is said orthostatic hypotension). 6) Rise in diastolic blood pressure in response to isometric exercise handgrip test (A value of more than 15mmHg rise in diastolic BP is taken as normal. Less than 10 mmHg rise in diastolic BP is taken as sympathetic insufficiency. 10 -15 mmHg is borderline. And increase in heart rate up to 30% of basal value is normal.)[7].

3. Result

Result was compared between the controls and patients of diabetes mellitus. Statistical tools: Data were entered and analysed with the Graph Pad.com. Statistical tests used for comparison is Student's t-test. Results are presented as mean (SD) and number (%) of cases as appropriate. The level of significance was set at $P < 0.05$, and 95% confidence intervals were calculated for the main outcome measures.

Table 3. Autonomic Function Test in controls and cases (groups according to duration of disease, group I-0 to 5 year) (values are in mean and standard deviation)

Tests	Controls	Group I
RHR	85.8±12.90	83.83±9.80
P value		0.55
T value		0.59
E/I RATIO	3.51±1.15	2.94±1.36
P value		0.55
T value		2.490
30:15 RATIO	1.26±0.50	0.93±0.30
P value		0.01
T value		2.62
RSBP(mmHg)	117.48±10.94	124.88±10.62
P value		0.01
T value		2.506
RDBP(mmHg)	73.84±7.48	79.94±10.32
P value		0.08
T value		2.70
Fall in SBP on standing (mmHg)	5.14±4.79	13.82±10.84
P value		0.001
T value		1.87
Fall in DBP on standing (mmHg)	2.84±3.43	4.16±3.86
P value		0.0054
T value		1.37
Hand grip test (mmHg)	13.3±6.42	6.5±7.5
P value		0.04
T value		3.72

Table 4. Autonomic Function Test in controls and cases (groups according to duration of disease, groupii-6 to 10 year) (values are in mean and standard deviation)

Tests	Controls	Group II
RHR	85.8±12.90	88.06±12.91
P value		0.56
T value		0.59
E/I RATIO	3.51±1.15	3.52±1.69
P value		0.99
T value		2.48
30:15 RATIO	1.26±0.50	0.98±0.20
P value		0.04
T value		2.06
Resting SBP	117.48±10.94	128.93±10.29
P value		0.05
T value		3.462
RDBP	73.84±7.48	82.66±10.76
P value		0.006
T value		3.637
Fall in SBP standing (mmhg)	5.14±4.79	6.72±6.44
		0.28
		1.08
Fall in DBP standing	2.84±3.43	4.2±5.1
P value		0.008
T value		1.20
Hand grip test (mmhg)	13.3±6.42	10.26±9.36
P value		0.15
T value		4.31

Table 5. Autonomic Function Test in controls and cases (groups according to duration of disease, group III- more than 10 year) (values are in mean and standard deviation)

Tests	Controls	Group III
RHR	85.8±12.90	92.41±9.44
P value		0.05
T value		1.939
E/I RATIO	3.51±1.15	2.38±1.67
P value		0.01
T value		2.497
30:15 RATIO	1.26±0.50	0.77±0.25
P value		0.03
T value		3.84
Resting SBP	117.48±10.94	129.88±13.98
P value		0.01
T value		2.506
RDBP(mmHg)	73.84±7.48	81.44±12.20
P value		0.00031
T value		3.06
Fall in SBP standing	5.14±4.79	8.53±9.28
		0.06
		4.51
Fall in DBP standing	2.84±3.43	4.88±4.29
P value		0.002
T value		2.006
Hand grip test (mmHg)	13.3±6.42	2.64±3.06
P value		3.06
T value		6.56

Table 6. Autonomic Function Test in controls and cases (groups according to duration of disease, groupsi-0 to 5 year, groupsii-6 to 10 year, groups III- more than 10 year) (showing percentage of subjects with autonomic dysfunction)

Tests	Controls	G-I	G-II	G-III
RHR (>90beats/minute)	27%	36%	40%	52%
E/I RATIO	0%	6%	11%	24%
30:15 RATIO(<1.04)	10%	46%	55%	94%
RSBP (≥130 mmhg)	28%	44%	53%	76%
DBP (≥85mmhg)	16%	38%	46%	52%
Fall in SBP on standing (≥21mmhg)	0%	6%	12%	29%
Fall in DBP on standing (≥11mmhg)	2%	5%	6%	20%
Abnormal hand grip test	46%	77%	60%	100%

4. Discussion

Diabetes mellitus is a strong risk factor for cardiovascular disease. DAN is a risk factor that independently increases cardiovascular risk in people with diabetes mellitus. Cardiovascular autonomic function tests are widely used to detect, verify and quantify the cardiovascular autonomic dysfunction. They have been tested for their validity and reliability. Against this background, the present study was undertaken to evaluate the CAN by using Ewing's cardiovascular reflex tests in diabetes and match the data so obtained with healthy non diabetic individuals as controls.

Results shows that the mean resting heart rate in diabetic patients, with duration of disease less than 5 year(group 1) - 83.83/ beats minute duration of disease in between 6 -10 year (group 2) – 88.06/ beats minute ,duration of disease more than 10 year(group 3) is 92.41/ beats minute and Table 6 shows that 36% control,27% in group 1, 40% in group 2, and 52% diabetic patients in group 3 showing resting tachycardia(resting heart rate> 90 beats/minute). This is showing increased resting heart rate in diabetic patient with long duration of disease. The E/I RATIO of test group and control group were 2.93and 3.51 respectively. Present study shows that E/I RATIO was normal in 100% control & mean E/I ratio in diabetic patients is 2.38 which is significantly lower than control group. The heart rate response to deep breathing, a measure of cardiac parasympathetic function is reduced in test group. The mean 30:15 in test group and control group were 0.89and 1.26 respectively. Results shows that the mean 30:15 ratio in diabetic patients is gradually decreasing with duration. Group 3 showing mean 30:15 ratio 0.77 which is significantly lower than control group. 30:15 ratio is highest in control group (1.26). This mean values decreases and percentage of subjects who get abnormal results(<1.04) increases as duration of disease increases.(group 1- mean value 0.93(46% gave abnormal value), group 3- mean value 0.77 (94% gave abnormal value)). Table 6 shows that there is progressive worsening in parasympathetic function tests like RHR , E/I RATIO , 30:15 RATIO as the disease progresses. This may be because of

decreased vagal tone possibly due to vagal nerve damage by long duration of diabetes.[2,11,12]

The mean resting systolic blood pressure in test group and control group were 127.8 mmhg and 117.48 mmhg respectively. Present study shows that the resting systolic blood pressure was higher >130 mmhg in 28% control, 44% group 1, 53% group 2, and 76% group 3 diabetic patients. This means resting systolic blood pressure remains higher in diabetic than normal one and the resting systolic blood pressure increases as duration of diabetes increases. The mean value of resting systolic blood pressure is also increasing with duration of diabetes (group 1- mean value -124.88 mmhg, group 2- mean value -128.93 mmhg, group 3- mean value -129.88). One important cause is that dysfunction of the vascular endothelium causes cardiovascular disease. Increased resting systolic blood pressure may indicate here increased sympathetic tone. These may be due to imbalance between sympathetic and parasympathetic system. These imbalance may be due to damaged vagal nerve due to diabetes.[9]

The mean resting diastolic pressure of test group and control group were 81.26 and 73.84 respectively. Present study shows that the resting diastolic blood pressure was higher >85 mmhg in 16% control, 38% group 1, 46% group 2, and 52% group 3 diabetic patients. This means resting systolic blood pressure remains higher in diabetic than normal one. The mean value of resting diastolic blood pressure also increases as duration of diseases increases (Group 1- mean value -79.94 mmhg, group 2- mean value -82.66 mmhg, group 3- 81.44 mean value). As diastolic blood pressure is purely sympathetic function (diameter of blood vessel is maintained by sympathetic system mainly) [10], increased resting diastolic blood pressure may indicate here increased sympathetic tone. These may be due to imbalance between sympathetic and parasympathetic system. This imbalance may be due to damaged vagal nerve due to diabetes. [9] In postural hypotension test, the mean of fall in Systolic Blood Pressure test group and control group were 9.68 mmhg and 5.14 mmhg respectively. The mean and standard deviation of fall in diastolic blood pressure test group and control group were 4.42 mmhg and 2.84 mmhg respectively.

Present study shows that the fall in systolic blood pressure on standing was higher >20 mmhg in 0% control, 2% group 1, 12% group 2, and 29% group 3 diabetic patients. The mean value of fall in systolic blood pressure also increases as duration of diseases increases (table 3,4 and 5 shows that group 1- mean value -13.82 mmhg, group 2- mean value -6.72 mmhg, group 3- mean value 8.53 mmhg). And, fall in diastolic blood pressure on standing was higher >10 mmhg in 2% control, 5% group 1, 6% group 2, and 20% group 3 diabetic patients. The mean value of fall in diastolic blood pressure also increases as duration of diseases increases (results shows that group 1- mean value -4.16 mmhg, group 2- mean value -4.2 mmhg, group 3- mean value 4.88 mmhg). Present study shows that postural hypotension (fall in systolic blood pressure on standing >20 mmhg, fall in in

diastolic blood pressure on standing >10 mmhg) is noticed in 12% diabetic patients and only 2% control. These results indicate sympathetic dysfunctions because process of decrease in venous return is exaggerated vessels are dilated due to decreased sympathetic tone. This may be due to damage to sympathetic nerves by diabetes.[2,11,12]

The present study indicates abnormal sympathetic function (postural hypotension) in diabetics. As we analyze data of group 1, 2, and 3, mean value in fall in systolic blood pressure and diastolic blood pressure on standing and percentage of patient who gave abnormal test both are increasing. This indicates that sympathetic dysfunction is increasing as duration of disease passes.

The mean of rise in diastolic blood pressure by isometric exercise (hand grip test) of diastolic blood pressure in test group and control group were 6.32 and 13.3 respectively. Present study shows that the rise in diastolic blood pressure on handgrip test was abnormal (persons who failed to show rise in DBP $\geq$ 15 mmhg) in 46% control, 77% group 1, 60% group 2, and 100% group 3 diabetic patients. It is noticed that all the diabetic patients with duration of diabetes > 10 year failed to show rise in diastolic blood pressure more than 15 mmhg. The mean value of rise in diastolic blood pressure on hand grip test also decreases as duration of diseases increases. Table 3, 4 & 5 shows that group 1- mean value -6.5 mmhg, group 2- mean value -10.26 mmhg, group 3- mean value 2.64 mmhg). This results indicate impaired sympathetic functions in diabetics, as diastolic blood pressure is purely sympathetic function. As we have discussed the resistance vessel which are responsible for maintaining diastolic blood pressure have only sympathetic nerve supply. [10] In a study it was found that in patients with type II diabetes showed a decline in exercise induced pressure response in subjects with CAN.[11]

5. Conclusions

Present study shows that there is significant difference in autonomic function test in diabetic & normal persons indicating that there is CAN in diabetics which is progressively increasing as duration of disease increases. [2,11,12]

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