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ASSOCIATION OF CARDIAC AUTONOMIC NEUROPATHY AND PERIPHERAL NEUROPATHY IN TYPE 2 DIABETES MELLITUS.

Diabetology

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ABSTRACT

Diabetes is a metabolic disorder with debilitating complications which affects several million people worldwide. Cardiac autonomic neuropathy (CAN) and peripheral neuropathy are the two most common chronic complications of type 2 diabetes mellitus (T2DM). Diagnosing neuropathies at subclinical stage and knowing the association between the two neuropathies can help us to prevent the morbidity and mortality because of these neuropathies. Cross sectional study was conducted in Department of Physiology, in collaboration with Rajeev Gandhi Centre for Diabetes and Endocrinology on patients of T2DM attending Diabetes clinic in Jawaharlal Nehru Medical college hospital (JNMCH), Aligarh Muslim University from 2014 to 2016 after approval from the ethical committee of JNMC. Total 90 subjects were taken , among them 60 subjects were diagnosed cases of T2DM, which were divided in two groups on the basis of duration of diabetes. Rest 30 subjects were non diabetic control group. Cardiac autonomic reflex tests and sensory nerve conduction velocity studies were done for assessing these neuropathies. Statistical analysis was performed using SPSS version 21.0. Association between two neuropathies (CAN and Peripheral neuropathy) was tested by Fisher test. Significant (p value<0.05) association was seen between cardiac autonomic neuropathy and peripheral neuropathy in T2DM patients. Chronic hyperglycemia in diabetes leads to the degeneration and damage of autonomic and peripheral nerves.

KEYWORDS

Autonomic dysfunction, peripheral neuropathy, Type 2 Diabetes mellitus

INTRODUCTION:

Diabetes Mellitus (DM) refers to a group of common metabolic disorders characterized by chronic hyperglycemia. In DM, factors causing hyperglycemia are primarily decreased insulin secretion, decreased glucose utilization, and increased glucose production [1]. These metabolic disturbances associated with DM leads to secondary patho -physiological changes in multiple organ systems which leads to high physiological stress on the patient [1]. Cardiac autonomic neuropathy (CAN) and peripheral neuropathy are the two most common chronic complications of type 2 Diabetes Mellitus (T2DM)and have significant negative impact on quality of life of patients with T2DM [2].

In case of DM, chronic hyperglycemia leads to lesion in the nerve which mainly include demyelination , axon degeneration and vessel wall degeneration. In CAN, there is alteration of parasympathetic and sympathetic function, but still these dysfunctions are concealed for longtime. Because autonomic system can respond to many different types of stresses, both from internal and external environment , hence CAN is diagnosed at later stages [3]. CAN is one of the leading cause of increasing incidence of silent myocardial ischemia and sudden death is in T2DM patients. [4], [5].

Symptoms of Peripheral neuropathy in patients of T2DM range from severely painful symptoms at one extreme to the completely painless variety. As a result of damage to the nerves the patients also develops the inability to perceive important sensations like heat, cold and pain in extremities. Hence peripheral neuropathy is the major contributory factor to foot ulceration.[6].

Since these two neuropathies are concealed and ignored at subclinical stage and ultimately leads to debilitating complication in T2DM patients. Thus, early screening, appropriate intervention and treatment, and studying association between CAN and Peripheral neuropathy in T2DM is of paramount importance.

MATERIAL AND METHOD:

This study was conducted in Department of Physiology, in collaboration with Rajeev Gandhi Centre for Diabetes and Endocrinology on patients of T2DM attending Diabetes clinic in Jawaharlal Nehru Medical college hospital (JNMCH), Aligarh Muslim University from 2014 to 2016 after approval from the ethical committee of JNMC.

Design of the study was cross sectional and total 90 subjects were taken. Out of these 90 subjects 60, who met the inclusion and exclusion criteria and gave the valid consent in writing after explaining the procedure to the subject prior to entering for further investigations, were selected as cases for further study. A detailed history and physical examination was carried out for every subject who entered the study as per a pre-designed proforma. Selected cases of T2DM patients between age 30 to 69 years were assessed for diabetic cardiac autonomic neuropathy through cardiac autonomic reflex tests (CARTs) and peripheral neuropathy through sensory nerve conduction velocity tests.

All diabetic patients were divided in two groups based on duration of T2DM.

Group I (n=30) with less than 8 years
Group II (n= 30) with equal to or more than 8 years.
The findings were also compared with group of 30age, sex and BMI matched control group who were free from diabetes mellitus, hypertension, coronary artery disease or any other illness which could hamper with the test results.

Clinical data were obtained of all patients included in study and were also evaluated by medical records revision for other complications CVD and hypertension.

Inclusion criteria:

- Only T2DM patients aged 30-69 years.
- The diagnosis of diabetes was made on the basis of revised American Diabetic Association Criteria i.e. fasting plasma glucose ≥ 126 mg/dl (≥6.1 mmol/1) and 2 hours postprandial plasma glucose ≥ 200 mg/dl (≥1 1.1 mmol/1).

Exclusion criteria:

- Previous history of cardiac arrhythmia.
- Hypertension.
- Heart block.
- Clinical coronary artery disease.
- Presence of thyroid disease (hypo or hyperthyroidism).
- Previous history of any systemic condition related to peripheral neuropathy(malnutrition, alcoholic neuropathy, renal failure)
- Trauma in the course of nerve to be examined.
- Neuropathies associated with exogenous toxins, metals, or drugs .

CLINICAL DIAGNOSIS OF DIABETIC CARDIAC AUTONOMIC NEUROPATHY:

CARDIOVASCULAR AUTONOMIC REFLEX TESTS (CART's):

Pre-requisite for the test:

- Warm room
- Relaxed and cooperative subject/parents
- Proper posture
- Abstained from smoking and caffeine for 2 hours and alcohol for 36 hour prior to the experiment.
- Should have taken adequate rest, had at least 8 hours of uninterrupted sleep on the night prior to the experiment.
- All recordings were conducted between 10:30 A.M to 1:00 P.M.
- ECG machine(CARDIART 108T-DIGI KERALA INDIA 678007)
- Jelly
- Sphygmomanometer
- Ruler

After comfortable strapping and rest for 5 min on the couch, ECG was recorded using limb lead electrodes in standard lead II configuration.

Measurement and calculation of the various ratios was calculatedby just using the ECG strip and a ruler.

1). RESTING HEART RATE (HR):

The subject was asked to lie quietly on a couch and allowed to rest for 5 minutes, and then the subject was connected to ECG machine the ECG recording was done and resting heart rate was calculated.

2).HEART RATE RESPONSE TO STANDING UP:

The Subject was asked to lie quietly on a couch while the heart rate was recorded continuously on an electrocardiograph and then the subject was asked to stand up unaided as quickly as practicable and the point at starting to stand was marked on the electrocardiogram. The characteristic heart rate response can be expressed by the 30:15 ratio which is the ratio of the longest R-R intervalaround the thirtieth beat after standing up to the shortest R-R interval around the fifteenth beat.It depicts the cardiac parasympathetic activity.

3). HEART RATE RESPONSE TO DEEP BREATHING:

ECG was recorded with the subject in supine position, connected to the limb leads of a standard electrocardiogram. Before beginning the test, subjects were taught to breathe deeply and evenly at 6 breaths/min (5seconds in and 5 seconds out). The examiner raised his hand to signal the start of each inhalation and lowered it to signal the start of each exhalation; this was supported by verbal signals. Lead II electrocardiogram was then recorded continuouslyat a speed of 25 mm/s for 60 seconds while the subject breathed as instructed. The R-R intervalswere measured accurately. Mean of the expiration and inspiration ratio is calculated as E:I ratio (ratio of the shortest RR during inspiration to the longest RR during expiration).It also depicts about the cardiac parasympathetic activity.

4). BLOOD PRESSURE RESPONSE TO STANDING UP:

This test was performed by measuring the blood pressure while the subject was lying down, and again 1 minute after standing up. The difference in systolic blood pressure was taken as the measure of postural blood pressure change.It depicts about the cardiac sympathetic activity.

Heart rate response to deep breathing is mediated almost exclusively by cardiac parasympathetic pathways. Lying to standing heart beat response rely to some extent on the integrity of sympathetic as well as parasympathetic pathways. While postural blood pressure control is predominantly dependent on intact peripheral sympathetic vasoconstriction, others factors such as blood volume may also contribute.

Diagnostic criteria of abnormal cardiovascular reflex test

Diagnostic criteria	Pathological values
Parasympathetic tests:	
HRV on deep breathing	E:I ratio <1.20
HRV lying-standing (L-S)	R-R beat 30/R-R beat 15 <1.00
Sympathetic tests	
Sitting to standing SBP	SBP fall>30 mmHg

* HRV: heart rate variation, SBP: systolic blood pressure

NERVE CONDUCTION VELOCITY

Apparatus:

Neuroperfect EMG/NCV/EP SYSTEM(Medicaid systems,Chandigarh,160002,India).

TECHNIQUE OF EXPERIMENT:

The principals of nerve conduction study: NCS involves the application of depolarizing square wave electrical pulses to the skin over a peripheral nerve producing:

A propagated nerve action potential (NAP) recorded at a distant point over the same nerve.

Pre-requisite for the test:

- Warm room
- Relaxed and cooperative subject
- Proper posture
- Impedance of electrodes is kept minimum
- EEG jelly or paste
- Pre-amplifier
- Spirit and cotton
- Adhesive tape

SENSORY NERVE CONDUCTION VELOCITY STUDY (SNCV)

In this study SNAP was recorded antidromically.

The SCV is calculated by dividing the distance (mm) between the stimulating and recording sites by the latency (ms).

SNCV = Distance / Latency (m/s)

Stimulation sites for recording SNAP.

Nerve	Antidromic /Orthodromic	Stimulation Site	SNAP Recorded From
Median	Antidromic	Wrist	Index finger
Ulnar	Antidromic	Wrist	Little finger
Sural	Antidromic	Distal to lower border of gastrocnemius at the junction of middle and lower 1/3rd of the leg	Ankle
SPN	Antidromic	10-15 cms proximal to the upper edge of lateral malleolus anterior to peroneus longus.	Ankle

STATISTICALANALYSIS

Analysis was performed using SPSS version 21.0 statistical package for windows (SPSS, Chicago, IL). Continuous variables were expressed as mean +/- Standard Deviation (S.D) or range, and qualitative data was expressed in percentages. Association between two neuropathies (CAN and Peripheral neuropathy) was tested by Fisher test. P-value of < 0.05 was considered significant.

OBSERVATIONS & RESULTS

In this study, a total of 60 patients with diagnosed type 2 diabetes mellitus were covered, who met the inclusion and exclusion criteria and had given valid consent in writing. These 60 patients were selected in a manner to segregate them in two groups of 30 each. One group of thirty patients had T2DM of less than 8 years duration with mean duration of 3.31 ±1.72 years, whereas the second group of thirty patients had T2DM for more than 8 years duration with mean duration of 12.80 ± 4.42 years. A group of 30 normal individuals without diabetes served as control in this study. The observations made during the study are as follow.

The baseline characteristics of Non-Diabetic control group and patients with less than 8 years T2DM and patients with more than 8 years T2DM are given in Table 1 and Table 2 respectively. There was no significant difference in both the T2DM groups when compared with non diabetic control group.

TABLE 1 Baseline characteristics of control group and T2DM< 8years

Variable	For Non-diabetic Control Group (mean ± S.D)	For T2DM < 8 years Group (mean ± S.D)
N (male/female)	30 (male 16 /female 14)	30(male 13 /female 17)
Age(yrs)	52.50±7.31	51.23±7.99
Duration of T2DM (years)	0	3.31±1.72
Weight(kg)	62.37±10.43	64.63±10.37
Height(m)	1.56±0.10	1.59±0.10
BMI(Kg/m2)	25.48±2.68	25.68±3.82
Waist/hip ratio	0.87±0.09	0.99±0.07
Systolic B.P(mmHg)	129.67±9.23	127.13±8.11
Diastolic B.P(mmHg)	81.87±5.53	81.33±3.21

All mean ± standard deviation, Comparisons between the groups using an independent 't' test. *p value< 0.05.

TABLE 2 Baseline characteristics of control group and T2DM> 8years

Variable	For Non-diabetic Control Group (mean ± S.D)	For T2DM > 8 years Group (mean ± S.D)
N (male/female)	30 (male 16 /female 14)	30(male 15 /female 15)
Age(yrs)	52.50±7.31	58.33±6.45
Duration of T2DM (years)	0	12.8±4.42
Weight(kg)	62.37±10.43	63.87±9.43
Height(m)	1.56±0.10	1.58±0.09
BMI(Kg/m2)	25.48±2.68	25.43±3.10
Waist/hip ratio	0.87±0.09	0.97±0.09
Systolic B.P(mmHg)	129.67±9.23	126.76±6.27
Diastolic B.P(mmHg)	81.87±5.53	81.87±3.52

All mean ± standard deviation, Comparisons between the groups using an independent 't' test. *p value< 0.05.

To assess Cardiac Autonomic Neuropathy, three cardiac autonomic reflex tests (CARTs) were done. Tests of Cardiac parasympathetic activity included heart rate change on timed deep breathing (E:I ratio) and heart rate change from lying to standing as 30:15 ratio. Tests of Sympathetic activity included Systolic Blood Pressure response from lying to standing (ΔSBP Lto S). The results were compiled and analysed as follows:

Variation in means of Cardiac autonomic reflex tests between non diabetic and patients with T2DM of less than 8years, in Resting Heart Rate and change in SBP from lying to standing (test of sympathetic activity) is insignificant, whereas in E:I ratio test and 30:15 ratio test(tests of parasympathetic activity) variation in means is significant as shown in Table 3.

Table 3 Cardiac Autonomic Reflex Tests in Non-Diabetes and T2 DM (Less than 8 years)

	Non Diabetes (n = 30)	T2 DM (<8 years) (n = 30)	p – value
Resting HR	74.36 ± 5.41	77.53 ± 5.79	0.067
E:I Ratio	1.30 ± 0.09	1.00 ± 0.13	0.001*
30:15 Ratio	1.34 ± 0.06	1.02 ± 0.08	0.001*
Δ SBP from L to S	-5.3 ± 2.0	-8.06± 4.88	0.107

(*p value <0.05 is significant)

Variation in means of Cardiac autonomic reflex tests between non diabetics and patients of T2DM more than 8years is significant in all Cardiac autonomic reflex testsas shown in Table 4.

Table 4 Cardiac Autonomic Reflex Tests in Non-Diabetes and T2 DM (More than 8 years)

	Non Diabetes (n = 30)	T2 DM (> 8 years) (n = 30)	p– value
Resting HR	74.36 ± 5.41	85.46 ± 5.06	0.001*
E:I Ratio	1.30 ± 0.09	0.92 ± 0.14	0.001*
30:15 Ratio	1.34 ± 0.06	0.93 ± 0.11	0.001*
Δ SBP from L to S	-5.3 ± 2.0	-19.00 ± 7.3	0.001*

(*p value <0.05 is significant)

To assess peripheral neuropathy Sensory Nerve Conduction Velocity (SNCV) test was done in Sural, SPN, Median and Ulnar nerves on both sides. The results obtained were compiled and analysed as follows.

Variation in means between non diabetic and less than 8 years diabetic in B/L median nerve SNCV is not significant, whereas SNCV in Ulnar, SPN, Sural nerves, the said variation in mean is found to be significant (Table 5).

Table 5 SNCV in Non Diabetes and T2DM (Less than 8 years)

	Non Diabetes (n = 30)	T2DM (< 8 years) (n = 30)	p – value
Rt: Median	52.12 ± 4.76	51.63 ± 4.59	0.460
Rt: Ulnar	56.29 ± 4.94	50.88 ± 4.34	0.001*
Rt: SPN	51.21 ± 3.01	45.17 ± 3.51	0.001*
Rt: Sural	51.47 ± 3.38	35.00 ± 10.00	0.001*
Lt: Median	51.86 ± 3.38	50.78 ± 4.74	0.080
Lt: Ulnar	55.53 ± 3.51	51.37 ± 4.45	0.001*
Lt: SPN	51.18 ± 2.57	45.32 ± 3.60	0.001*
Lt: Sural	51.11 ± 2.81	35.68 ± 10.38	0.001*

(*p value <0.05 is significant)

Variation in means between non diabetic and more than 8 years diabetic is significant in all the four nerves as shown in Table 6.

Table 6 SNCV in Non Diabetes and T2DM(More than 8 years)

	Non Diabetes (n = 30)	T2DM(> 8 years) (n = 30)	p – value
Rt: Median	52.12 ± 4.76	44.29 ± 5.36	0.001*
Rt: Ulnar	56.29 ± 4.94	48.63 ± 4.99	0.001*
Rt: SPN	51.21 ± 3.01	35.86 ± 6.14	0.001*
Rt: Sural	51.47 ± 3.55	24.72 ± 7.59	0.001*
Lt: Median	51.86 ± 3.38	45.37 ± 5.33	0.001*
Lt: Ulnar	55.53 ± 3.51	49.18 ± 4.91	0.001*
Lt: SPN	51.18 ± 2.57	35.88 ± 6.24	0.001*
Lt: Sural	51.11 ± 2.81	23.94 ± 7.26	0.001*

(*p value <0.05 is significant)Association between CAN and

Peripheral neuropathy by assessing the involvement of number of sensory nerves and number of abnormal cardiac autonomic reflex tests is shown in Table 7. There was a significant association between CAN and Peripheral neuropathy.

TABLE 7 Association between Peripheral neuropathy and CAN

Involvement of Cardiac Autonomic Nerves	Involvement of Sensory Nerves			
	No Nerve involved	Two nerves involved (Sural and SPN)	Four nerves involved (median, ulnar, sural and SPN)	p-value
Normal Cardiac autonomic reflex tests	4 /9	0 / 28	0 / 23	0.001*
Para-sympathetic	5 / 9	25 / 28	23 / 23	
Sympathetic	0 / 9	0 / 28	6 / 23	

(*p value <0.05 is significant)

DISCUSSION:

Data of this study shows that there is significant cardiac autonomic impairement in T2DM patients. In T2DM of less duration (<8 year) there is significant decrease in Cardaic autonomic reflex tests reflecting parasympathetic activity (Table 3), depicting early impairment of cardiac parasympathetic nerves, whereas in T2DM of longer duration (> 8 years) there is significant decrease in both cardiac sympathetic and parasympathetic components when compared with controls.

It was also seen that in T2DM of long duration SNCV of both upper limb and lower limb was significantly reduced when compared to control group (Table 5 and Table 6).

Consistently high blood glucose levels can lead to macrovascular and microvascular complication that will eventually affect patients' quality of life. [7]. This increase impairement of cardiac autonomic nerves and peripheral sensory nerves can be explained by the fact that hyperglycemia leads to the activation of various biochemical pathways related to the metabolic state of the cell, which along with impaired nerve perfusion, contributes to the development and progression of diabetic neuropathies. Cardiovascular disease (CVD) complications is considered fastest growing health concerns for many diabetic patients. [8]

The association between Cardiac Autonomic Neuropathy and peripheral neuropathy, it can be derived from our study that in T2DM, there was significant association between involvement of sensory peripheral nerves and cardiac autonomic nerves (Table 7). It was also observed that CAN manifests earlier than Peripheral Neuropathy and there is concurrent development of CAN and Peripheral Neuropathy. The mechanism leading to damage of peripheral and autonomic nerves may be similar, but there can be different susceptibility to hyperglycaemia of autonomic nerves which are mostly unmyelinated and small, from the peripheral somatic nerves which are myelinated and large. The current results are in broad agreement with earlier studies showing the association of other microangiopathic complications along with increased prevalence and early onset of CAN [9],[10], [11]. These simple, non=invasive tests for CAN and Peripheral Neuropathy can be included in the routine screening procedure for Type 2 Diabetes Mellitus which can help early in the diagnosis of CAN

So, early diagnosis of CAN and Peripheral neuropathy can lead to the prevention of debilitating complications.

CONFLICTS OF INTERESTS: Nil

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