ORIGINAL ARTICLE

Study of Cardiovascular Autonomic Neuropathy in Symptomatic and Asymptomatic Type II Diabetic Patients

KRANTHI KUMAR GARIKAPATI[1], YOGESH TRIPATHI[2], RINKU GARG[3], BINDU GARG[4]
[1]*Ph.D. Scholar, Department of Physiology, Santosh deemed to be University, Ghaziabad.*
[2]*Professor & Head, Department of Physiology, School of Medical Sciences and Research, Greater Noida*
[3]*Professor & Head, Department of Physiology, Santosh deemed to be University, Ghaziabad*
[4]*Professor & Head, Department of Physiology, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly.*
Corresponding Author: Mr. Kranthi Kumar Garikapati, E-mail:kranthigarikapati86@gmail.com

ABSTRACT

Introduction: Cardiovascular autonomic neuropathy (CAN) is the most common and serious complication of diabetes, strongly associated with cardiovascular morbidity and mortality. The patients of early stages of diabetic autonomic neuropathy could be clinically asymptomatic or present with a few symptoms. But, these symptoms become severe and irreversible with the progression of the disease. Hence, this study aimed to identify CAN in symptomatic and asymptomatic diabetic patients.

Methodology: This study was conducted on 39 asymptomatic and 35 symptomatic T2DM subjects on their visit to the diabetic clinic OPD. CAN diagnosis and severity were assessed using Ewing's battery and frequency-domain parameters of heart rate variability (HRV).

Results: Symptomatic T2DM subjects had higher values of body mass index, waist circumference, and glycemic parameters compared to asymptomatic subjects. Progression of CAN was strongly associated with duration of diabetes and poor glycemic control. CAN was present in 97.1% of symptomatic subjects and 47.2% of asymptomatic subjects with different stages of severity. All frequency-domain parameters of HRV were significantly low in symptomatic subjects except of normalized low frequency and low frequency to high frequency ratio.

Conclusion: The severity of CAN was significantly higher in symptomatic subjects. Asymptomatic T2DM subjects also had significant CAN. CAN diagnosis should be done frequently in clinical setup even when the diabetic patients are asymptomatic. So that, appropriate management can be done and delay the progression of CAN as well reverse the condition.

Keywords: type 2 diabetes mellitus, cardiovascular autonomic neuropathy, heart rate variability.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder affecting most organ systems in the body and its incidence is rapidly rising all over the world. In many patients, typical symptoms associated with DM manifest clinically only after sufficient cumulative adverse effects of the disease have taken place in the body. As a consequence, diabetic complications may be present by the time it is clinically diagnosed and are of sufficient severity (1).

Neuropathy is the most common form of microvascular disease, accounting for a major share of morbidity and hospitalization among diabetic patients. Diabetic Autonomic Neuropathy (DAN) is a chronic, diffuse form of diabetic neuropathy, associated with significant morbidity and mortality (2). DAN affects many organ systems of the body and in particular, cardiovascular autonomic neuropathy (CAN) is considered an advanced disease and a major cause of cardiovascular events like arrhythmias, myocardial ischemia, and stroke (3).

CAN is a chronic complication of type 2 diabetes mellitus (T2DM) with prevalence ranging from 25% to 75%. CAN is divided into subclinical and clinical stages. The subclinical stage of CAN manifests in the form of reduction in heart rate variability (HRV) whereas, clinical CAN, due to predominance in sympathetic activity manifests as resting tachycardia and exercise intolerance. With the further clinical progression of the severity of CAN due to complete sympathetic loss, orthostatic hypotension and syncope become evident. The severity of CAN and its monitoring can be assessed using standard cardiac autonomic reflex tests (CARTs) (4).

It becomes evident that early recognition of CAN and its associated factors at the subclinical stage and intervention of appropriate management delays the complications and associated high risk of mortality by reversing it. HRV analysis is one of the most sensitive and specific diagnostic tests and classical Ewing's battery CARTs are still the gold standard for the CAN evaluation (5). In this study, we used both standard Ewing's battery and HRV analysis to detect CAN. To the best of our knowledge, no comprehensive studies showing the comparison of HRV and severity of CAN between symptomatic and asymptomatic T2DM patients could be identified on an extensive literature search. Hence, the present study was undertaken to evaluate the HRV and its associated risk factors in type 2 diabetic subjects.

MATERIALS & METHODS

The study was conducted in the diabetic clinic of the General Medicine department in a tertiary care hospital, Uttar Pradesh, India. Approval of the Institutional ethics committee was taken prior to the conduction of the study. A well-informed written consent was obtained from all the subjects in accordance with the Helsinki Declaration of 1975 (revised in 2013). Seventy-four type II diabetes patients were enrolled in the study and subjects were divided into 2 groups based on the history of presence or absence of symptoms of autonomic neuropathy.

Inclusion criteria: Type II diabetic patients diagnosed according to World Health Organization (WHO) criteria (6), aged between 30 years and 65 years of both sexes.

Exclusion criteria: Subjects with hypertension, any history or electrocardiographic evidence of cardiac disease, history of renal dysfunction, endocrine disorders, psychiatric disorders, and any other major illness, under the treatment of any medications that known to influence the autonomic nervous activity, smokers and / alcoholics, females while menstruating, pregnancy and lactation, with any movement restriction diseases or physical inability to perform autonomic function test were excluded from the study.

Methodology: The subjects who fulfilled the inclusion and exclusion criteria were recruited in the study. Fasting blood sugar (FBS) and glycated hemoglobin (HbA1c) values of all the subjects were recorded from the patient file and for the missed parameters blood samples were collected and evaluated. In their next visit, patients were asked to abstain from tea, coffee, or heavy meal for at least two hours and refrain from strenuous physical activity at least 24 hours prior to the study procedure. The study was conducted between 8:30 AM and 12 Noon in a quiet ambient room with a temperature between 22-25^{o}C (7).

Assessment of symptomatic history: Detailed symptomatic history suggestive of diabetic autonomic neuropathy was taken from all the subjects which included cardiac symptoms like postural dizziness, exercise intolerance, fatigue, syncope, GI symptoms like abdominal discomfort, epigastric fullness, bloating, alternating nocturnal diarrhea and constipation, sweating changes like gustatory sweating, nocturnal hyperhidrosis of trunk or face, anhidrosis of feet, sexual dysfunction in males like erectile dysfunction or impotence and females vaginal dryness, dyspareunia and decreased sexual desire, symptoms of bladder dysfunction like urinary retention, incontinence, and dribbling (7).

Anthropometric parameters like height, weight, waist circumference & hip circumference were recorded using standard methods and body mass index, body surface area & waist hip ratio were calculated.

Assessment of autonomic function test: Cardiovascular autonomic neuropathy status & severity were assessed using the standard five-test battery recommended by Ewing and Clarke and frequency-domain parameters of HRV. The CARTs consisted of three heart rate response tests and two BP response tests for various physiological activities.

Deep breath test: Heart rate response during deep breathing was measured on lying position with patient breathing 6 times/minute. The mean of the difference of heart rate between inspiration and expiration over the 6 cycles was measured. Delta heart rate (beats/min): normal- ≥15; borderline- 11-14; abnormal- ≤10.

Valsalva ratio: Patients were asked to blow air into the mouthpiece connected to the sphygmomanometer and maintain the pressure of 40 mm Hg for 15 seconds in a sitting position. Valsalva ratio was calculated from the longest R-R interval after the manoeuvre to the shortest R-R interval during the manoeuvre. Valsalva ratio: normal- ≥1.21; borderline- 1.11-1.20; abnormal- ≤1.10.

Heart rate response to standing: Patients were asked to stand as quickly as possible from the supine position and remain motionless. The 30:15 ratio was calculated from longest R-R interval at 30th beat after standing to shortest R-R interval at 15th beat after standing. Postural fall in SBP: normal- ≥1.04; borderline- 1.01-1.03; abnormal- ≤1.00.

Systolic blood pressure response to standing: Baseline blood pressure was recorded in supine position and patients were asked to stand as quickly as possible. After 2 minutes of standing, blood pressure was recorded. Postural fall of SBP was taken as the difference between baseline SBP and SBP after 2 minutes of standing. Postural fall in SBP: normal- ≤10; borderline- 11-29; abnormal- ≥30. (8, 9).

Diastolic blood pressure response to sustained isometric handgrip: After recording the baseline BP in sitting posture, patients were asked to maintain the handgrip pressure at 30% of the maximum for 4 minutes. BP was recorded in each minute from the contralateral arm. A rise in the DBP during the handgrip exercise from the baseline DBP obtained before the test was measured. Rise in DBP: normal- ≥16; borderline- 11-15; abnormal- ≤10 (9, 10).

Staging of CAN: After obtaining CARTs results, the staging was done based on their cut-off values. No CAN or normal: all the tests normal or only one test borderline; early CAN: one of the three heart rate tests abnormal or two tests borderline; definite CAN: any two of the heart rate tests abnormal; severe CAN: any two of the heart rate tests abnormal and concurrent one or both BP tests abnormal (11).

Recording of frequency-domain parameters of HRV: Variation in R-R intervals for heart rate response tests, and frequency domain parameters of HRV were assessed from Lead-II electrocardiogram recorded using LabChart ECG analyzer of a bio-amplifier data acquisition module, Power lab 26T-ML4856, AD Instruments (Australia). After 15 minutes of rest, Lead II ECG was recorded in the supine position for 15 min at a sampling rate of 1k Hz. Power spectral analysis was performed for the last 5 minutes of recording using Lomb-Scargle periodogram with HRV module of LabChart Pro analyzer (v 8.1.16). The power spectrum was expressed as frequency-domain components such as Total power (TP), Very Low Frequency power (VLF: <0.04Hz- denotes the sympathetic activity), Low Frequency power (LF: 0.04–0.15 Hz- shows the combination of both sympathetic control & parasympathetic modulation) & High Frequency power (HF: 0.15–0.4 Hz- reflects the status of parasympathetic activity) in absolute units, LF & HF components were also obtained in normalized units and as a ratio (LF/HF ratio- indicates the sympathovagal balance) (12, 13).

Data analysis: Statistical data analysis was done using IBM SPSS for Windows, Version 20.0. Qualitative data were expressed in the form of frequencies. Comparison of quantitative data between groups was done using Student's t-test (Independent), demographic data were expressed as mean ± standard deviation and HRV parameters were represented as mean ± standard error due to high variability in the data.

RESULTS

Based on the history of symptoms, 74 T2DM study subjects were divided into two groups: symptomatic (n=35) and asymptomatic (n=39). Table 1 shows a comparison of the demographic parameter between the two groups: no

significant difference was noted in age, BSA, and HC; whereas, in BMI (p=0.014), WC (p=0.03), and WHR (p=0.035) a statistically significant difference was noted between the two groups with higher values in symptomatic subjects. Further, a statistically significant difference was noted in the duration of diabetes (p=0.019), and FBS (p=0.001) & HBA1c (p=0.003) with higher values in the symptomatic subjects.

Table 2 shows the clinical symptoms of autonomic dysfunction with GI symptoms (80%) being the most common and exercise intolerance (28.6%) and bladder disturbances (25.7%) were the least common symptoms.

Table 3 shows the results of the CARTs, distribution & staging of CAN based on heart rate/BP response to predefined physiological activities. Maximum abnormality in heart rate response CARTs was noted in deep breath test (54.3%) followed by heart response to standing & Valsalva ratio (37.1% in each). In the BP response for CARTs, sustained handgrip test (20%) was noted to show greater abnormality followed by an SBP response to standing (5.7%). In the symptomatic diabetic group, the subjects were graded as having no CAN (2.9%), early CAN (45.7%), definite CAN (25.7%), and severe CAN (25.7%); whereas, in asymptomatic diabetic cases the observations were; no CAN (53.8%), early CAN (38.5%), and definite CAN (7.7%).

A comparison of baseline heart rate and short-term frequency-domain parameters of HRV between two study groups were shown in Table 4. Total power (p<0.000), VLF power (p<0.000), LF power (p=0.005), and HF power (p=0.002) in absolute units, HF power in normalized units (p<0.000) were significantly reduced symptomatic subjects compared to asymptomatic subjects; whereas heart rate (p<0.000), LF power in normalized units (p=0.006) and LF/HF ratio (p=0.002) were significantly higher in symptomatic subjects compared to asymptomatic subjects.

Table 1: Demographic profile of T2DM patients with and without symptoms

Parameters	T2DM subjects with symptoms (N=35)	T2DM subjects without symptoms (N=39)	p-value
Age (yrs)	53.20 ± 5.33	50.87 ± 4.90	0.054
BMI (Kg/m^2	27.14 ± 1.76	25.93 ± 2.32	0.014*
BSA (m²)	1.82 ± 0.14	1.80 ± 0.11	0.533
WC (cm)	102 ± 10.55	96.72 ± 9.94	0.03*
HC (cm)	95 ± 4.95	94.15 ± 4.33	0.435
WHR	1.07 ± 0.10	1.03 ± 0.09	0.035*
Duration of T2DM (yrs)	7.90 ± 4.27	5.72 ± 3.53	0.019*
FBS (mg/dl)	141.37 ± 23.32	122.46 ± 23.22	0.001*
HBA1c (%)	8.47 ± 0.90	7.76 ± 1.05	0.003*

*Significant. Data presented as mean ± SD. BMI: Body mass index; BSA: Body surface area; WC: Waist circumference; HC: Hip circumference; WHR: Waist hip ratio; FBS: Fasting blood sugar; HBA1c: Glycosylated haemoglobin.

Table 2: Frequency of symptoms in symptomatic T2DM subjects (N=35)

Symptoms	No. of subjects with symptoms	Percentage (%)
Dizziness on standing	14	40
GI symptoms	28	80
Bladder disturbances	9	25.7
Sleeping disturbances	18	51.4
Sexual dysfunction	12	34.3
Exercise intolerance	4	28.6
Sweating disturbances	11	31.4

Table 3: Frequency of cardiovascular autonomic reflex tests (CARTs)

Name of CART	Test result	T2DM subjects with symptoms (N=35)		T2DM subjects without symptoms (N=39)	
		No. of cases	Percentage (%)	No. of cases	Percentage (%)
Deep breath test	Normal	0	0	20	51.3
	Borderline	16	45.7	14	35.9
	Abnormal	19	54.3	5	12.8
Valsalva ratio	Normal	10	28.6	25	64.1
	Borderline	12	34.3	12	30.8
	Abnormal	13	37.1	2	5.1
Heart rate response to standing (30:15 ratio)	Normal	7	20	23	59
	Borderline	15	42.9	12	30.8
	Abnormal	13	37.1	4	10.3
BP response to standing (fall in SBP)	Normal	15	42.9	37	94.9
	Borderline	18	51.4	1	2.6
	Abnormal	2	5.7	1	2.6
Sustained handgrip test (HGT) (change in DBP)	Normal	13	37.1	37	94.9
	Borderline	15	42.9	2	5.1
	Abnormal	7	20	0	0
Distribution & stages of CAN					
Normal/ No CAN		1	2.9	21	53.8
Early CAN		16	45.7	15	38.5
Definite CAN		9	25.7	3	7.7
Severe CAN		9	25.7	0	0

Table 4: Comparison of heart rate and frequency-domain parameters of HRV between study groups

Parameters	T2DM subjects with symptoms (N=35)	T2DM subjects without symptoms (N=39)	p-value
Heart rate (b/min)	97.14 ± 1.86	87.01 ± 1.53	0.000*
Total Power (ms^2)	244.34 ± 38.39	602.97 ± 78.36	0.000*
VLF (ms^2)	120.66 ± 19.42	289.66 ± 33.10	0.000*
LF (ms^2)	90.30 ± 17.58	188.17 ± 27.75	0.005*
HF (ms^2)	32.60 ± 7.92	124.05 ± 25.96	0.002*
LF (nu)	74.05 ± 1.66	66.77 ± 1.89	0.006*
HF (nu)	24.91 ± 1.40	33.86 ± 1.83	0.000*
LF/HF ratio	3.41 ± 0.25	2.38 ± 0.20	0.002*

*Significant. Values expressed as mean ± SE. VLF: Very low frequency power; LF: Low frequency power; HF: High frequency power.

DISCUSSION

The present study was undertaken with an aim to assess one of the underdiagnosed complications of diabetes i.e. CAN, and identify the cardiovascular autonomic status in T2DM subjects. The study also aimed to get an insight into the associated risk factors of CAN in the 2 study groups.

In the present study, BMI, WC, WHR, FBS & HBA1c were significantly higher in symptomatic subjects compared to asymptomatic subjects. Despite the higher age of the symptomatic subjects as compared to the other group, the difference noted was not statistically significant. A similar observation was also noted in BSA and HC between the study groups.

The study results are consistent with the cohort study by Andersen ST et al., in which the T2DM population was followed up for progression of CAN at 6 years and 13 years. The study reported a strong association of prolonged duration of diabetes, higher values of BMI, and HBA1c with CAN progression. Demova R et al., in their study, noted age & central obesity (WC) as predictors of CAN.

The commonest autonomic dysfunction symptoms noted in symptomatic subjects were GI symptoms, sleep disturbances, and postural dizziness. Varied symptomatology was noted by other researchers in their studies. Prabhakar RR et al., reported that postural dizziness, GI symptoms, and impotence were the common symptoms found in diabetic patients; whereas, Mottera KS et al., in their study observed sexual dysfunction, postural giddiness, and sweating disturbances as the common symptoms. The difference in the reported profile of symptoms could be due to age, gender, ethnicity, literacy level, disease duration, and glycemic control of the study subjects.

Further, symptomatic subjects showed greater abnormalities of all CARTs as compared to asymptomatic subjects. The maximum abnormality was noted in the deep breath test and the least was noted in the SBP response to standing. Similar observations were reported by Pathak A et al. In their study they stated heart rate response to deep breathing was the most sensitive and postural hypotension was the least sensitive in detecting CAN in diabetic patients.

Various stages of CAN were noted in both the study groups with the higher occurrence in the symptomatic diabetic subjects (97.1%) as compared to asymptomatic diabetic subjects (47.2%) in the present study. Usharani M et al., also reported similar results of CAN distribution in their study. Further, they noted that the occurrence of CAN increased with age, duration of diabetes, and poor glycemic control (18).

The present study also noted, increase in resting heart rate, normalized LF & LF/HF ratio, and reduction in remaining frequency domain parameters including TP, VLF, HF, LF in absolute units, and normalized HF in symptomatic diabetic subjects. Similar observations were noted in a study conducted by Lee MY et al., who noted the reduction of HRV prior to the occurrence of diabetes (19). A decrease in HF power and an increased resting heart rate & LF/HF ratio are the sign of parasympathetic dysfunction and sympathetic overdominance in autonomic dysfunction associated with diabetes (5). Duration of diabetes and poor glycemic control are the major risk factors independently associated with CAN development and progression (20).

The vagus nerve being the longest is the first autonomic nerve affected in DAN. As it controls nearly two-thirds of the body's parasympathetic activity, its damage shows widespread parasympathetic derangement including a reduction in HRV and CARTs (21). Development of autonomic neuropathy in diabetes is a result of hyperglycemia-induced multifactorial metabolic derangements including hyperactivation of the polyol pathway, accumulation of advanced glycation end products (AGEs), increase in oxidative stress, abnormal activation of diacylglycerol-protein kinase C signal transduction pathway, and inflammation. All these pathogenic processes in combination, result in reduced neuronal blood flow, neuronal damage, and eventually the development of DAN. This damage rapidly progresses with an increase in the duration of diabetes and poor glycemic control. Hence, identification at an initial stage and good glycemic control can delay the onset & progression of autonomic neuropathy (22).

CONCLUSION

Symptomatic diabetic subjects had more abnormalities in CARTs with higher severity whereas, asymptomatic diabetic subjects despite having abnormalities in CARTs did not have severity as seen in symptomatic subjects. Reduction of HRV which is an indicator of parasympathetic dysfunction correlated highly with symptomatic T2DM subjects, who had a prolonged duration of diabetes and poor glycemic control. At the early stage of DAN, autonomic dysfunction could be asymptomatic or mildly symptomatic. Further, the clinical symptoms associated with DAN were more remarkable with disease progression. As the patients become symptomatic, the severity of autonomic neuropathy increases, and the prognosis worsens. It becomes imperative to detect CAN at early stages so that, quality of life can be improved by better management and further morbidity due to complications may be reduced. Hence, the study suggests that autonomic

function tests should be routinely carried out in clinical workup of diabetic subjects.

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