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Cardiac autonomic neuropathy in type 2 diabetes mellitus using Bellavere's score system

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ABSTRACT

Objective: Determine the frequency of cardiac autonomic neuropathy (CAN) in type 2 diabetics using Bellavere's score system.

Subjects and Methods: The present cross-sectional study was conducted at the Department of Medicine, Isra University Hospital Hyderabad from March to November 2011. Sixty voluntary participants of type 2 diabetes mellitus (DM) were selected through non-probability purposive sampling. Cardiac autonomic nerve function was assessed using Bellavere's score system. The data were analyzed on the Statistix version 10.0 (USA) using Student's *t*-test, Chi-square test, one-way ANOVA, and Tukey-Cramer test ($P \leq 0.05$).

Results: Of 60 diabetics, CAN was observed in 29 (41.4%). Abnormal heart rate variability (HRV), valsalva ratio, 30-15th ratio, blood pressure (BP) response to standing, and handgrip was noted in 43 (61.4%), 27 (38.5%), 17 (24.2%), 5 (7.14%), and 18 (25.7%), respectively. The hemoglobin A1c was negative correlated with HRV, valsalva ratio, 30-15th ratio, and BP response to sustained handgrip; and positively correlated with BP response to standing, systolic BP, and diastolic BP. Duration of DM was not correlated with cardiac autonomic nerve function tests.

Conclusion: The CAN was observed in 29 (41.4%) using Bellavere's score system. The CAN score may be used as feasible and reproducible bedside clinical test in diabetic patients.

Keywords: Bellavere's score, Cardiac autonomic neuropathy, diabetes mellitus, Sindh

Introduction

The Pakistan ranks sixth position in the world regarding the burden of diabetes mellitus (DM).[1] The chronic hyperglycemia of DM, in the long-term, causes damage of the target organs; eyes, nerves, kidney, heart, and blood vessels.[2,3] The damage to nerve fibers both somatic and autonomic including cardiac autonomic nerve fibers is a feature of DM.[4] Cardiac autonomic neuropathy (CAN) is a debilitating and life-threatening complications of DM.[4-6] The CAN is an established indicator of cardiovascular mortality because of cardiac arrhythmias.[7,8] There are three stages of the CAN; Early stage: Abnormality of heart rate with a deep breath alone. Intermediate stage: An abnormality of valsalva response. Severe stage: The presence of postural hypotension.[4,9] Extensive clinical studies have been reported on CAN during the past two decades due to the availability of simple non-invasive tests of cardiac autonomic nerve function.[10] The CAN can be tested as bedside technique using a battery of cardiovascular reflex tests; the heart rate variability (HRV) with deep breathing, valsalva ratio, 30-15th ratio, blood pressure (BP) response to active standing, and sustained handgrip. The original Ewing's criteria are used in previous studies, however, present study uses Bellavere's scoring for evaluation of cardiac autonomic nerve function.[4,8] As Pakistan is passing through an epidemic of DM and many new cases are being diagnosed, there is dire need to study the cardiovascular autonomic nerve function. The present study intends to determine the frequency of CAN in type 2 DM in our tertiary care hospital using simple non-invasive tests of cardiovascular autonomic nerve function.

Subjects and Methods

The study was conducted at the Isra University Hospital Hyderabad from March to November 2012. Sixty voluntary participants of type 2 DM were selected through non-probability purposive sampling. A verbal consent was taken from the participants. Medical history of duration of DM, and symptoms of diabetic complications, ischemic heart disease, and brain stroke were recorded on a structured pro forma. Type 2 DM participants of ≥5 years were included and those complicated with ischemic heart disease, renal failure,

limb amputation, and brain stroke were excluded from the study. DM was defined as Random blood glucose level of ≥200 mg/dl or fasting blood glucose level of ≥126 mg/dl.[11] The body mass index (BMI) was calculated from the weight and height by formula; BMI = Weight (kg)/Height (m^2). Stadiometer was used to measure height and a calibrated beam balance for weight. Systemic BP was recorded with a mercury sphygmomanometer after the patient had taken 5 min rest. For each participant, the average of two readings was recorded in supine and standing position. Systemic hypertension was defined as; the "systolic BP ≥140 mmHg" or "diastolic BP ≥90 mmHg."[12] The blood samples were collected after asepsis was secured; using standard methods of blood sampling by trained paramedics.

The hemoglobin A1c (HbA1c) was used as an indicator of glycemic control, measured on automated clinical chemistry analyzer (Hitachi 902, Roche Diagnostics, the USA).

The cardiac autonomic nerve function was assessed using a battery of five cardiovascular autonomic reflex tests of Bellavere's score system as shown in Table 1.[8-10]

The diagnosis of CAN is established; if two or more of the tests results are abnormal.[13,14]

The sum of the score obtained from each test determines the final classification of the patient's degree of CAN. The total score ranges from 0 to 10. Classification of patients is done according to the total score. It is shown in Tables 1 and 2.

Data analysis

The data were analyzed by Statistix version 10.0 (USA). The continuous variables were analyzed using Student's *t*-test, one-way ANOVA, and *post-hoc* Tukey-Cramer testing. The Pearson's correlation was used to analyze association of continuous variables. The Chi-square test analyzed the categorical variables. A $P \leq 0.05$ was considered statistically significant.

Results

Seventy type 2 DM, selected according to inclusion and exclusion criteria at our tertiary care hospital. The type 2 DM participants were divided into groups designated as having HbA1c <7% or ≥7% as shown in Table 3. The mean age was noted as 46 ± 5.47 and 45 ± 8.8 years, respectively. Of 70 participants, 40 (57.1%) were male and 30 (42.8%) female. The male to female ratio is 1.3:1. A significant difference was noted for the gender, HbA1c, systolic, and diastolic BP between groups with HbA1c <7% or ≥7%. The demographic characteristics of study population are shown in Table 3. The HRV, valsalva ratio, 30-15th ratio, BP response to standing, and BP response to sustained handgrip are shown in Table 4. The CAN test abnormalities are described 0-5 as shown in Table 5.

Table 1: Bellavere's scoring system

Test	Score		
	0	1	2
	Normal	Borderline	Abnormal
Heart rate variability	>15	10-15	<10
Valsalva ratio	≥1.21	1.11-1.20	≤1.10
30-15th ratio	≥1.04	1.01-1.03	≤1.0
BP response to standing (mmHg)	≥10	11-29	≥30
BP response to handgrip (mmHg)	≥16	11-15	≤10

BP: Blood pressure

Table 2: CAN scoring system

Score	Categories
0-1	No autonomic neuropathy
2-4	Early autonomic neuropathy
5-10	Severe autonomic neuropath

CAN: Cardiac autonomic neuropathy

Table 3: Demographic characteristics of study population (*n*=70)

Demographic characteristics	Groups	Mean (±SD)	*P* value
Age (years)	HbA1c≤7%	46.39 (5.47)	0.46
	HbA1c>7%	45.02 (8.85)	
Male	HbA1c≤7%	*14	0.0001
	HbA1c>7%	*26	
Female	HbA1c≤7%	*11	
	HbA1c>7%	*19	
HbA1c%	HbA1c≤7%	9.16 (3.41)	0.03
	HbA1c>7%	10.67 (1.62)	
Random blood sugar (mg/dl)	HbA1c≤7%	215 (81)	0.01
	HbA1c>7%	253 (98)	
Fasting blood sugar (mg/dl)	HbA1c≤7%	135 (56)	0.02
	HbA1c>7%	148 (79)	
Body mass index (kg/m^2)	HbA1c≤7%	26.5 (3.21)	0.28
	HbA1c>7%	25.8 (2.18)	
Systolic blood pressure (mmHg)	HbA1c≤7%	140.1 (21.70)	0.003
	HbA1c>7%	124.8 (17.01)	
Diastolic blood pressure (mmHg)	HbA1c≤7%	79.2 (12.37)	0.002
	HbA1c>7%	70.1 (9.59)	
Duration of DM	HbA1c≤7%	9.6 (3.67)	0.17
	HbA1c>7%	10.8 (3.88)	

HbA1c: Hemoglobin A1c, DM: Diabetes mellitus, SD: Standard deviation

Of seventy diabetics, CAN was observed in 29 (41.4%) (Table 6). The frequency of cardiac autonomic nerve reflex tests is shown in Table 7. The association of HbA1c with

Table 4: Bellavere's scoring system between patients (*n*=70)

Variables	Mean (±SD)	*P* value
Heart rate variability (beats/min)		
Normal >15 beats/min	16.91 (1.36)	0.0001
Borderline 10-15 beats/min	11.18 (2.22)	
Abnormal <10 beats/min	8.39 (0.94)	
Total	13.21 (4.18)	
Valsalva ratio		
Normal ≥1.12	1.23 (0.008)	0.0001
Borderline 1.11-1.20	1.15 (0.03)	
Abnormal ≤1.10	1.05 (0.02)	
Total	1.16 (0.08)	
30-15th ratio		
Normal ≥1.04	1.07 (0.01)	0.0001
Borderline 1.01-1.03	1.01 (0.008)	
Abnormal ≤1.00	0.11 (0.19)	
Total	0.74 (0.46)	
BP response to standing (mmHg)		0.0001
Normal ≤10	8.02 (0.97)	
Borderline 11-29	19.36 (7.06)	
Abnormal ≥30	33.13 (1.86)	
Total	18.05 (11.71)	
BP response to sustained hand grip		
Normal ≤16	17.44 (1.106)	0.0001
Borderline 11-15	12.09 (0.83)	
Abnormal ≤10	7.91 (1.08)	
Total	13.47 (4.346)	

BP: Blood pressure, SD: Standard deviation

Table 5: CAN test abnormalities (*n*=70)

Test abnormalities	No. of cases (%)
0 test	21 (30)
1 test	20 (28.5)
2 test	9 (12.8)
3 test	11 (15.7)
4 test	6 (8.5)
5 test	3 (4.2)

CAN: Cardiac autonomic neuropathy

HRV, valsalva ratio, 30-15th ratio, BP response to standing, BP response to sustained handgrip, systolic BP, and diastolic BP was analyzed using Pearson's correlation as shown in Table 8.

Discussion

One of the most overlooked complications of DM is the CAN.[15] The prevalence of CAN is highly variable as reported in several studies. It varies from as low as 7.7% to as high as 90%.[16] The present study included seventy type 2 DM participants to evaluate the CAN using Bellavere's score. The present study reports a frequency of CAN of 41.4%, which is comparable

Table 6: CAN in diabetes mellitus among patients (*n*=70)

CAN	No. of cases (%)
Yes	29 (41.4)
No	41 (58.5)

CAN: Cardiac autonomic neuropathy

Table 7: Patient distribution according to cardiac autonomic neuropathy (*n*=70)

Test	*n* (%)	
	Normal	Abnormal
Heart rate variability	27 (38.5)	43 (61.4)
Valsalva ratio	45 (66.3)	27 (38.5)
30-15th ratio	51 (72.8)	17 (24.2)
Blood pressure response to standing	63 (90)	5 (7.14)
Blood pressure response to handgrip	50 (71.4)	18 (25.7)

Table 8: Pearson's correlation of HbA1c among patients (*n*=70)

Test	HbA1c (%)	
	r value	*P* value
Heart rate variability	−0.54	0.001
Valsalva ratio	−0.58	0.001
30-15th ratio	−0.56	0.001
Blood pressure response to standing	0.61	0.01
Blood pressure response to handgrip	−0.38	0.02
Systolic blood pressure	0.32	0.01
Diastolic blood pressure	0.29	0.02

HbA1c: Hemoglobin A1c

to previous study.[1,17,18] The high frequency of CAN of present study is most probably due to the bad glycemic control of our study participants because of lack of health facilities. The Nayak *et al.*[10] studied fifty type 2 DM participants and reported a frequency of CAN of 40% (20% early CAN and 20% severe CAN). Another recent study from India reported frequency of CAN in 42% of long standing type 2 DM participants by cardiac autonomic nerve function testing.[19] Yet another study has reported a frequency of CAN in 22% of diabetic participants.[20] The frequency of CAN of aforementioned studies are comparable to present study. The Canani *et al.*[7] reported CAN in 79.7% of type 2 DM participants suffering from peripheral arterial disease. The CAN of 79.7% is very high compared to our present and previous studies.[10,19,20] A frequency of 70% has been reported from a recent study from Egypt.[21]

The Keen *et al.*[17] and Noronha *et al.*[18] have reported a frequency of CAN in 32% AND 38.5% of the type 2 DM patients. In present study, we found a mean CAN score of 2.14, with males having CAN score of 2.28 and females 2.018. Similar observations have been reported by Nayak *et al.*[10] mean of CAN score of 2.04 and Noronha *et al.*[18] reported mean CAN score of 2.23. The present study reports a negative correlation of HRV, valsalva ratio, 30-15th ratio, BP response to sustained

handgrip, systolic, and diastolic BP with statistically significant difference. The BP response to standing is found positively correlated with glycemic control. However, duration of DM was not correlated with cardiac autonomic reflex tests. The findings are comparable to Nayak *et al.*[10] and Noronha *et al.*[18] but contrary to reported by Toyry *et al.*[20] The Mansour *et al*.[4] reports a frequency of 42.6% of CAN in type 2 DM, the findings are comparable to present study. In present study, the early and severe CAN had a valsalva ratio of 1.15 ± 0.03 and 1.05 ± 0.02, respectively. As the severity of CAN increases, the HRV in response to valsalva maneuver decreases. The findings are similar to as reported previously.[8,10] A study by Khandelwal *et al.*[22] reported a poor correlation of the HbA1c with the CAN score, but this might have been because of bias introduced by researcher. Further studies are recommended as Pakistan is having diabetic epidemic and study will help cope with the long-term complications of DM related to cardiovascular system.

Conclusion

The CAN was observed in 29 (41.4%) using Bellavere's score system which is simple non-invasive CAN score, may be useful in the early diagnosis and treatment of DM to prevent mortality. The CAN score may be used as feasible and reproducible bedside clinical test in diabetic patients.

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