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Relationship of Disease Duration, Glycemic Control and Gender with Cardiac Autonomic Neuropathy in Type 2 Diabetes Mellitus

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ABSTRACT
To investigate the impact of gender, glycaemic control over the disease in the duration oof cardiac auton-omicfuncti-on parameters in patients with type II diabetes mellitus (T2-DM).Fifty participants with type 2 diabetes mellitus (age: 52.7±7.37 years, height: 1.6±0.17 m, weight: 72.7±12.81 kg, body mass index: 27.6±4.40 kg/m^2) were recruited into this study. After assessment of clinical characteristics including gender, disease duration and glycaemic control, and cardiovascular risk factors, standard cardiovascular autonomic reflex testing was performed. Appropriate statistical tests were performed in order to determine the effect of gender, disease duration and glycaemic control on parameters of cardiac autonomic control. When the participants were segregated and analyzed on the basis of glycaemic control (good, fair, poor, and very poor), only E/I ratio was found to be significantly different between the groups ($p<0.05$). Regarding the effect of gender on cardiac autonomic function, females showed greater impairment in cardiac autonomic function parameters as compared to their male counterparts ($p<0.05$). Impairment in parameters of parasympathetic reactivity was associated with greater disease duration ($p<0.05$).Poor glycaemic control and greater disease duration are associated with impairments in cardiac autonomic function parameters in T2DM patients. Moreover, females tend to show poorer autonomic profile as compared to their male counterparts in T2DM patients.
Key words: *Diabetes; Autonomic dysfunction; Glucose control; Gender*

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INTRODUCTION

A recent report by International Diabetes Federation (IDF) suggests that currently around 415 million people are affected by diabetes mellitus (DM) globally and it is projected that approximately 642 million are going to get affected by it by the year 2040 [1]. DM is closely linked with the development of various cardiovascular complications and thus it almost doubles the mortality rate despite availability of management strategies [2]. Cardiac autonomic neuropathy (CAN) is a common cardiovascular ramification of DM which is seen to be mostly prevailing in comparison to type 1 diabetes mellitus (T1DM) in type 2 diabetes mellitus (T2DM) [3]. CAN has been linked to several unfavorable health outcomes such as silent myocardial ischemia, and subclinical left ventricular dysfunction [4]. Assessment methods for CAN in DM primarily includes CARTs which consist of dynamic heart rate (HR) and blood pressure (BP) tests, Cardiovascular [5]. Heart rate variability (HRV) has been acknowledged as a straightforward and non-invasive technique for examining cardiac autonomic dysfunction in both healthy and sick subjects.[6]. The level of hyperglycemia is a significant determinant of the prognosis of T2DM [7]. There is a close association between the low incidence of complications in T2DM and the effective glycemic control. A previous study has reported glycaemic control to be the major cause of comorbidities and complications in patients with T2DM [8]. Research has also indicated towards the role of optimal glycemic control in preventing complications and mortality in newly T2DM patients [9, 10]. These studies clearly points towards to the impact of hyperglycaemia on complications of DM.Gender differences have also been seen to play its role in altering cardiac autonomic function. Cardiovascular and autonomic responses are different for men and women regardless of the level of aerobic capacity [11]. Men present with cardiac autonomic modulation that favors the sympathetic component, whereas women favors the vagal component [12]. Some other

studies [13, 14] have shown that males have a more favorable autonomic profile as compared to female participants. However, research so far has not given any clear conclusion regarding the impact of gender on autonomic function in T2DM patients with CAN.

The impact of DM duration on CAN is still an unexplored area of research. Only a few recent studies have observed changes in HRV with respect to duration of diabetes and these changes were more commonly observed within first 5 years of diabetes [15, 16]. Significant inverse associations have been observed between heart rate variability parameters and duration of diabetes at 5–10 years indicating a disruption in parasympathetic cardiac control with increasing duration of DM [16]. However, the literature is still insufficient in T2DM patients with CAN.

Existing literature [7, 11, 15] indicates some link between glycaemic control, DM duration, gender and cardiovascular profile of T2DM patients. However, there is still a prevalent knowledge gap regarding the impact of these parameters on cardiac autonomic profile of T2DM patients with diagnosed CAN. Hence, This study's objective was to investigate the outcome of gender, disease duration & glycemic management on parameters of CAN & cardiovascular risk in T2DM patients with CAN. We hypothesized that gender, disease duration and glycemic control will have a significant effect on cardiac autonomic function parameters in T2DM patients with CAN.

MATERIAL AND METHODS

2.1. Study protocol

T2DM patients were recruited as per the pre-decided eligibility criteria from the lifestyle disorders clinic of the medical centre of Jamia Millia Islamia, New Delhi, India. Initial assessment and screening of the participants was performed at the medical centre of the university by medical professionals Eligible participants identified in first stage of screening were then tested for glycemic control at the hospital's laboratory. The Jamia Millia Islamia's centre for physiotherapy and rehabilitation sciences then carried out a general demographic and clinical examination as well as a cardiac autonomic function assessment. Prior to the start of the study, institutional ethics approval was sought from Jamia Millia Islamia in New Delhi, India. Written consent was also collected from each participant before their participation. The study's procedures were carried out in accordance with the 1964 Helsinki Declaration.

Study participants

Software G. Power 3.1.9.2 was used to compute the sample size for this study. An impact size of 0.64 was discovered using data on changes in the average of R-R intervals (Mean NN) from a prior study [17] with a power of 0.94 and a p value of 0.05. A sample size of 100 individuals was discovered to be required to test the study's hypothesis based on these effect estimations. Patients diagnosed with T2DM for ≥ 1 year and positive for CAN based on CARTs were enrolled into the study and those with any cardio-pulmonary disorder, uncontrolled hypertension, acute inflammatory disease, and morbid obesity were excluded.

Cardiovascular autonomic reflex tests (CARTs)

CARTs consists of two blood pressure (BP) tests (HUT, hand grip test) and three heart rate (HR) tests, including the deep breathing test (DBT), the valsalvamanoeuvre (VM), and the head-up tilt (HUT) test (HGT). To evaluate parasympathetic (30/15 ratio, Valsalva ratio) and sympathetic cardiac activity [systolic blood pressure (SBP) and diastolic blood pressure [DBP]], the aforementioned tests were serially performed. The subjects underwent CARTs using the prescribed methods. Using the Ewing's criteria and the results of CARTs, patients were divided into two groups: no-CAN and with CAN (early, definite, or severe CAN) [5, 18].

HRV recording and analysis

After giving the subject enough time to rest in the supine posture, an HRV test was conducted in a soothing environment with a controlled ambient temperature (24 °C). The American Heart Association's recommended procedures for skin preparation and electrode implantation were followed [19]. ECG was recorded for 10 minutes using the standard lead II configuration for the resting HRV measurement, of which the final 5 minutes were used for time and frequency domain analysis by recognising R waves with the software's peak detection module (AD instruments Lab Chart version 7.3.7 with HRV module version 1.4.2.). HRV was measured using conventional time- and frequency-domain variables. Additionally, ime-domain variables such as the standard deviation of N-N intervals, the root mean square of successive differences between neighboring intervals, and the average of N-N intervals proportion of differences in consecutive N-N intervals that are longer than 50 ms (pNN50) were calculated. Low frequency (LF) power, high frequency (HF), and the ratio of low to high frequency (LF/HF ratio) are examples of variables that were discovered by frequency domain research [20].

Biochemical analysis

Venous blood samples were taken after 8-12 hours of fasting. For measuring HbA1c high-performance liquid chromatography was used [21]. Fasting blood sugar was calculated using the glucose oxidase-

peroxidase method [22], and the lipid markers were measured using the diagnostic kit method (Randox Labs Ltd., UK). Friedwald's equation was used to calculate low density lipoprotein cholesterol and extremely low density lipoprotein cholesterol.

Statistical analysis

The distribution of the data includes the mean, standard deviation, median, frequencies, and percentages. Shapiro-Wilk test was used to determine the normality of the data. Prior to further investigation, non-normal data was turned into log format.. Patients were divided into groups based on theirglycaemic control [(very poor: 5-6.9%), (poor: 7-7.9%), (good: 8-9.9%), (very good: ≥10%)], DM duration [(<5 years, 5-7.9 years, 8-9.9 years, ≥10 years) and gender (male and female). Cardiac autonomic function parameters and cardiovascular risk factors were compared between the groups based on glycaemic control, DM duration and gender using one way analysis of variance (for glycaemic control and DM duration) and independent t-test (for gender). For glycaemic control and DM duration, bonferroniA post-hoc test was used to identify the noteworthy changes. The threshold for statistical significance in this investigation was fixed at p 0.05.

RESULTS

All participants completed the study procedures. T2DM patients in this study showed increased BMI and impaired lipid profile (Table 1). It was found that ΔDBP and 30/15 ratio showed significant impairment with an increase in disease duration (Table 2). No other cardiac autonomic function parameter showed any significant difference with increasing disease duration. Results of post-hoc analysis showed that significant difference was observed for 30/15 ratio between DM duration groups 7-7.9 years versus 8-9.9 years (Table 3). When the participants were segregated and analyzed on the basis of gylcaemic control (good, fair, poor, and very poor), E/I ratio was found to be significantly impaired between good versus fair and good versus poor glycaemic control groups (Tables 4 and 5). Regarding the effect of gender on glycaemic control, females showed greater impairment in cardiac autonomic function parameters as compared to their male counterparts with a significant difference in parameters such as ΔHR, VR, 30/15 ratio, Mean NN, SDNN, pNN50, LFnu, HFnu and LF/HF ratio (Table 6).

Table 1. Demographic characteristics, cardio-metabolic risk factors and cardiac autonomic function parameters in T2DM patients

Variables	**Mean±SD (n=100)**
Age (years)	52.7±7.37
Weight (kg)	72.7±12.81
Height (cm)	1.6±0.17
BMI (kg/m^2)	27.6±4.40
DM duration (years)	8.4±5.21
SBP (mmHg)	127.1±14.97
DBP (mmHg)	76.3±8.94
HR (beats/min)	81.4±11.28
FBG (mg/dl)	154.0±52.17
PPBG (mg/dl)	220.0±75.01
HbA1c (%)	8.0±1.43
TC (mg/dl)	173.4±34.19
TG(mg/dl)	157.2±65.83
HDL(mg/dl)	44.7±9.14
LDL(mg/dl)	98.9±32.99
VLDL(mg/dl)	27.8±9.48
E/I ratio	1.14±0.14
ΔHR	1.49±6.72
VR	1.21±0.38
30/15 ratio	1.13±0.20
ΔDBP	18.3±4.86
ΔSBP	4 (-34, 30)
Mean NN (ms)	747.3±107.91
SDNN (ms)	28.6±13.08
RMSSD (ms)	24.5±13.61
pNN50 (%)	3.47±3.08
TP (ms^2)	1046.0±626.90
LF power (ms^2)	393.9±147.95
LFnu	53.3±14.50
HF power (ms^2)	364.2±191.70

HFnu	46.6±14.50
LF/HF ratio	1.42±1.02

SD: standard deviation; T2DM: type 2 diabetes mellitus; BMI: body mass index; DM: diabetes mellitus; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; FBG: fasting blood glucose; PPBG: post-prandial blood glucose; HbA1c: glycosylated haemoglobin; TC: total cholesterol; TG: triglycerides; HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein; E:I ratio: ratio of the average of longest R-R interval during expiration and the shortest R-R interval during inspiration of the deep breathing test; ΔHR: change in R-R intervals during six consecutive cycles of deep inspiration and expiration;30:15 ratio: ratio of the longest R-R interval during 30s and the shortest R-R interval during 15th s of the head-up tilt test; VR: valsalva ratio; ΔSBP: change in systolic blood pressure during head-up tilt test; ΔDBP: change in diastolic blood pressure during hand grip test; Mean NN: average of N-N intervals; SDNN: standard deviation of N-N intervals; RMSSD: root mean square of successive differences between adjacent N-N intervals; pNN50: Proportion of differences in consecutive N-N intervals that are longer than 50 ms; TP: total power; LF: low frequency; HF: high frequency; LF/HF ratio: ratio of low and high frequency power

Table 2. Effect of disease duration on cardiac autonomic function parameters in T2DM patients

Variables	<5 years	5-7.9 years	8-9.9 years	≥10 years	*p*-value
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
DM duration (years)	2.4±1.05	5.9±0.86	9.1±0.92	15.5±2.47	<0.001*
E/I ratio	1.18±0.12	1.18±0.15	1.13±0.11	1.10±0.15	0.12
ΔHR (beats/min)	16.7±6.47	16.0±4.86	13.8±6.26	13.2±8.17	0.16
VR	1.26±0.47	1.34±0.45	1.16±0.29	1.0±0.18	0.14
ΔDBP	20.6±3.92	19.1±2.65	17.4±4.86	16.4±6.0	0.02*
30/15 ratio	1.10±0.21	1.26±0.28	1.07±0.10	1.10±0.14	0.01*
#ΔSBP (mmHg)	4 (-12, 22)	6 (-34, 20)	2 (-20, 18)	7 (-8, 30)	0.66
Mean NN (ms)	724.8±70.92	768.3±132.27	778.7±134.96	724.3±81.58	0.14
SDNN (ms)	30.7±12.50	30.4±14.28	29.2±12.15	24.7±13.36	0.21
RMSSD (ms)	24.4±10.69	26.7±14.16	26.0±16.06	21.5±13.56	0.44
pNN50 (%)	3.37±2.11	4.16±5.18	3.8±2.44	2.6±2.09	0.06
TP (ms^2)	1162.0±799.85	1050.8±695.05	1013.8±289.85	956.0±619.79	0.48
LF power (ms^2)	430.1±175.64	417.6±157.85	399.2±123.45	334.2±117.17	0.08
LFnu	55.3±15.73	56.7±12.47	50.5±12.52	51.2±16.23	0.37
HF power (ms^2)	351.0±170.83	334.3±190.66	419.0±210.97	350.0±194.17	0.36
HFnu	44.6±15.73	43.2±12.47	49.4±12.52	48.7±16.23	0.37
LF/HF ratio	1.59±1.22	1.51±0.77	1.19±0.75	1.38±1.18	0.44

SD: standard deviation; T2DM: type 2 diabetes mellitus; BMI: body mass index; DM: diabetes mellitus; E:I ratio: ratio of the average of longest R-R interval during expiration and the shortest R-R interval during inspiration of the deep breathing test; ΔHR: change in R-R intervals during six consecutive cycles of deep inspiration and expiration; 30:15 ratio: ratio of the longest R-R interval during 30s and the shortest R-R interval during 15th s of the head-up tilt test; VR: valsalva ratio; ΔSBP: change in systolic blood pressure during head-up tilt test; ΔDBP: change in diastolic blood pressure during hand grip test; Mean NN: average of N-N intervals; SDNN: standard deviation of N-N intervals; RMSSD: root mean square of successive differences between adjacent N-N intervals; pNN50: Proportion of differences in consecutive N-N intervals that are longer than 50 ms; TP: total power; LF: low frequency; HF: high frequency; LF/HF ratio: ratio of low and high frequency power; nu: normalized units; #ΔSBP is reported as median (interquartile range); *significant difference

Table 3. Findings of post-hoc analysis for disease duration

Pairwise comparisons	ΔDBP	30/15 ratio
<5 vs 5-7.9 years	1.00	0.06
<5 vs >10 years	0.058*	1.00
<5 vs 8-9.9 years	0.10	1.00
<5 vs >10 years	0.058*	1.00
8-9.9 vs >10 years	1.00	0.46
5-7.9 vs >10 years	0.51	0.89
5-7.9 vs 8-9.9 years	0.74	0.01*

ΔDBP: change in diastolic blood pressure during hand grip test; 30:15 ratio: ratio of the longest R-R interval during 30s and the shortest R-R interval during 15th s of the head-up tilt test; vs: versus; *significant difference

Table 4. Effect of glycaemic control on cardiac autonomic function parameters in T2DM patients

Variables	Good	Fair	Poor	Very poor	*p*-value

	(5-6.9%)	(7-7.9%)	(8-9.9%)	(≥10%)	
	Mean±SD	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**
HbA1c (%)	6.6±0.31	7.3±0.25	8.4±0.46	11.0±1.09	<0.001
E/I ratio	1.27±0.14	1.08±0.09	1.11±0.13	1.15±0.10	<0.001*
ΔHR (beats/min)	17.0±8.40	14.0±4.95	14.4±7.14	14.4±5.45	0.84
VR	1.15±0.19	1.14±0.25	1.31±0.51	1.18±0.33	0.93
ΔDBP	18.9±5.04	18.6±4.85	18.17±3.40	17.2±7.85	0.12
30/15 ratio	1.12±0.18	1.1±0.22	1.13±0.19	1.14±0.22	0.97
#ΔSBP (mmHg)	4 (-12, 22)	6 (-34, 20)	2 (-20, 18)	7 (-8, 30)	0.51
Mean NN (ms)	766.6±126.36	716.1±99.70	775.7±100.46	705.5±86.95	0.056
SDNN (ms)	32.4±13.88	25.5±13.11	30.6±12.72	23.6±10.17	0.06
RMSSD (ms)	25.3±10.96	23.8±14.22	25.6±15.87	21.3±9.93	0.80
pNN50 (%)	4.65±4.70	3.0±2.58	3.2±2.24	3.0±2.0	0.38
TP (ms^2)	1218.2±854.82	1023.1±584.28	1024.8±577.97	834.9±172.16	0.31
LF power (ms^2)	449.9±177.24	367.6±121.22	388.4±150.30	368.0±127.79	0.19
LFnu	56.5±13.73	49.6±11.37	53.4±17.40	55.8±13.15	0.32
HF power (ms^2)	350.0±162.71	388.1±166.61	376.7±242.77	295.6±121.84	0.47
HFnu	43.4±13.73	50.3±11.37	46.5±17.40	44.1±13.15	0.32
LF/HF ratio	1.56±0.91	1.07±0.43	1.61±1.41	1.46±0.73	0.31

SD: standard deviation; T2DM: type 2 diabetes mellitus; E:I ratio: ratio of the average of longest R-R interval during expiration and the shortest R-R interval during inspiration of the deep breathing test; ΔHR: change in R-R intervals during six consecutive cycles of deep inspiration and expiration;30:15 ratio: ratio of the longest R-R interval during 30s and the shortest R-R interval during 15^{th} s of the head-up tilt test; VR: valsalva ratio; ΔSBP: change in systolic blood pressure during head-up tilt test; ΔDBP: change in diastolic blood pressure during hand grip test; Mean NN: average of N-N intervals; SDNN: standard deviation of N-N intervals; RMSSD: root mean square of successive differences between adjacent N-N intervals; pNN50: Proportion of differences in consecutive N-N intervals that are longer than 50 ms; TP: total power; LF: low frequency; HF: high frequency; LF/HF ratio: ratio of low and high frequency power; nu: normalized units; #ΔSBP is reported as median (interquartile range); *significant difference

Table 5. Findings of post-hoc analysis for glycaemic control

Pairwise comparisons	*p*-value (E/I ratio)
5-6.9 vs 7-7.9%	<0.001
5-6.9 vs 8-9.9%	<0.001
5-6.9 vs ≥ 10%	0.07
7-7.9 vs 8-9.9%	1.00
7-7.9 vs ≥ 10%	0.56
8-9.9 vs ≥10%	1.00

E:I ratio: ratio of the average of longest R-R interval during expiration and the shortest R-R interval during inspiration of the deep breathing test; vs: versus; *significant difference

Table 6. Effect of gender on cardio-metabolic risk and cardiac autonomic function parameters in T2DM patients

Variables	Male	Female	*p*-value

	(n=53)	(n=47)	
	Mean±SD	**Mean±SD**	
E/I ratio	1.15±0.14	1.14±0.13	0.67
ΔHR (beats/min)	16.4±4.75	13.1±8.10	0.001*
VR	1.38±0.42	1.03±0.20	<0.001*
ΔDBP	17.6±5.38	19.2±4.09	0.13
30/15 ratio	1.18±0.25	1.06±0.06	0.002*
ΔSBP (mmHg)	4 (-34, 30)	6 (-20, 22)	0.55
Mean NN (ms)	781.9±112.82	708.2±87.91	0.01*
SDNN (ms)	32.3±14.84	29.4±17.52	<0.001*
RMSSD (ms)	27.4±15.95	23.8±14.75	0.11
pNN50 (%)	3.82±3.70	3.0±2.16	0.03*
TP (ms^2)	1117.9±727.42	964.8±484.74	0.27
LF power (ms^2)	380.4±157.41	409.0±136.59	0.33
LFnu	49.8±14.26	57.20±13.91	0.01*
HF power (ms^2)	400.07±193.08	323.9±183.86	0.09
HFnu	50.15±14.26	42.7±13.91	0.01*
LF/HF ratio	1.21±0.91	1.65±1.09	0.01*

SD: standard deviation; T2DM: type 2 diabetes mellitus; E:I ratio: ratio of the average of longest R-R interval during expiration and the shortest R-R interval during inspiration of the deep breathing test; ΔHR: change in R-R intervals during six consecutive cycles of deep inspiration and expiration;30:15 ratio: ratio of the longest R-R interval during 30s and the shortest R-R interval during 15^{th} s of the head-up tilt test; VR: valsalva ratio; ΔSBP: change in systolic blood pressure during head-up tilt test; ΔDBP: change in diastolic blood pressure during hand grip test; Mean NN: average of N-N intervals; SDNN: standard deviation of N-N intervals; RMSSD: root mean square of successive differences between adjacent N-N intervals; pNN50: Proportion of differences in consecutive N-N intervals that are longer than 50 ms; TP: total power; LF: low frequency; HF: high frequency; LF/HF ratio: ratio of low and high frequency power; nu: normalized units; *significant difference

DISCUSSION

Main findings of the present study suggest that disease duration and severity of glycaemic control has an impact on certain parameters of cardiac autonomic control. Regarding the effect of gender, females were found have significantly impaired cardiac autonomic function parameters as compared to male T2DM patients. Glycaemic control plays an important role in the pathogenesis of DM and is associated with the development of various DM complications as well [7]. Findings of the present study showed a trend towards greater deterioration in autonomic function parameters with increasing hyperglycaemia, however, significant differences were observed only for E/I ratio (marker of parasympathetic reactivitiy). In conformity with the findings of the present study, former research has also indicated that glycaemic control significantly affects the parameters of cardiac autonomic control in T2DM patients. Findings of Meher and Panda [23] indicated a strong association between glycaemic control and cardiac autonomic neuropathy in T2DM patients [23]. Moreover, not only static glycaemic control but short-term glycaemic variability was also found to be linked with the pathophysiology of CAN in a previous study [24]. Furthermore, parameters of diabetic autonomic neuropathy were found to be linked with poor glycaemic control in a sample of DM where the variant of DM was undescribed [25]. Another study on Indian T2DM patients have indicated a strong link between glycaemic control and HRV parameters [26]. However, in contrary, a few studies [24, 27, 28, 29] have found no difference in HbA1c in CAN versus no CAN diabetic groups. The present investigation also showed no significant differences for majority of the autonomic function parameters. No differences observed in the present investigation in the cardiac autonomic function among different glycaemic control groups could be justified by the fact that we utilized HbA1c as a measure to categorize group while studies have indicated that continuous glucose monitoring methods are more robust indicators of glycaemic control. Moreover, we had unequal groups based on glycaemic control which could be one of the factor for insignificant results. Regarding the mechanisms that may contribute to glycaemic control related pathogenesis of CAN, hyperglycaemia could be linked with the pathophysiology of CAN via oxidative stress and endothelial dysfunction related pathways [26].

DM duration was found to be directly linked with autonomic function parameters such as ΔDBP and 30/15 ratio in the present investigation. With increasing DM duration, deterioration was observed in both sympathetic and parasympathetic markers of autonomic function in the present sample. In accordance

with the findings of the present study, Tarvainen et al. [16] also observed deterioration in HRV with increasing duration of T2DM with most significant decrease during 5-10 years of diabetes diagnosis. Similarly a few other studies on T2DM patients [23, 25, 30] illustrated significant associations between DM duration and autonomic neuropathy outcomes which points towards the important role of disease duration in the occurrence of autonomic dysfunction in diabetes. However, some previous research also indicates no impact of disease duration on parameters of autonomic function [26]. Nevertheless, majority of the studies have shown a clear association between disease duration and severity of autonomic dysfunction in T2DM patients [16, 23, 25, 30]. It could be speculated that with an increase in disease duration, a concomitant chronic exposure to hyperglycaemia and insulin resistance may contribute to the occurrence and severity of cardiac autonomic dysfunction [26]. Literature has not only suggested a link between DM duration and severity of autonomic neuropathy but has also identified the pattern of autonomic dysfunction with parasympathetic dysfunction initially followed by loss in sympathetic modulation with commencing duration of DM.

The present study illustrated a significantly impaired autonomic profile in female T2DM patients as compared to their male counterparts. In contrary to our findings, Dutra et al. [12] observed greater HF values and lower LF values in female patients as compared to male patients which indicates a favorable autonomic profile of females in their study [12]. The contrary findings of Dutra et al. [12] as compared to the present study could be explained by the fact that the mean age of female patients in their study was 18-40 years in contrast to the mean age in the present study which was 52.7±7.37 years. It is to be noticed that majority of the females in their study could be pre-menopausal considering the age group as compared to the present study which included large number of post-menopausal females. Presence of estrogen during the reproductive phase in females has been strongly linked with an advantageous autonomic profile. In a previous study [31], it was found that estrogen levels in the patients with CAN were significantly lower than patients without diabetic CAN.These results unambiguously show that menopause results in a decrease in the body's endogenous estrogen's protective role and an increase in the incidence of CAN. The identical study[31], it was observed that CAN was negatively correlated with the estrogen level, indicating the protective role of estrogen against CAN in females. It has been seen that Dyslipidemia, central obesity, a fast rise in metabolic syndrome risk, and a lack of oestrogen all contribute to the development and occurrence of CAN.[31]. Studies have found estrogen receptors in areas related to the network of central autonomic system. Moreover, estrogen play a anti-apoptotic role on vascular endothelium and cardiac myocytes that may act as a possible mechanism behind the cardio-protective effect of estrogen [32]. The aforementioned mechanisms supports the hypothesis behind estrogen's protective effect on cardiac autonomic nervous system and partially explains the altered autonomic profile observed in the present post-menopausal sample. Moreover, in accordance with the findings of the present study, a few studies have observed favorable autonomic function profile in males as compared to females. Huikuri et al. [13] observed attenuated baroreflex responsiveness in middle-aged females compared to males. Similarly, a study on German population [14] found that parameters of parasympathetic cardiac control were higher in males as compared to females indicating a better modulation in male participants. In summary, it could be concluded that when the estrogen's cardio-protective effect is eliminated in diabetic females, they show worse cardiac autonomic function than diabetic males. However, these findings should be verified by the future studies with a more comprehensive approach in methodology.

CONCLUSION

Findings of the present study suggest that glycaemic control, disease duration and gender significantly impacts cardiac autonomic function in T2DM patients with CAN. Severity of glycaemic control and increasing DM duration were associated with parameters of parasympathetic cardiac control in these patients. Diabetic females showed significantly greater impairment parameters of sympathetic and parasympathetic cardiac control as compared to males. These findings has important implications for the prevention and management of diabetic CAN.

CONFLICT OF INTEREST

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