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Original Article

Physiology Section

Cardiac Autonomic Activity among Normal and Type 2 Diabetic Patients: A Cross-sectional Study

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ABSTRACT

Introduction: Diabetic Cardiovascular Autonomic Neuropathy (DCAN) is one of the most dreaded but least recognised complications of diabetes, which manifests as a spectrum of abnormalities, ranging from resting tachycardia and decreased Heart Rate Variability (HRV) to "silent" myocardial infarction. Early identification of DCAN is essential, as timely intervention can delay or reverse autonomic dysfunction. Limited Indian data on this subject underscore the need for further research.

Aim: To assess cardiovascular autonomic function in patients with Type 2 Diabetes Mellitus (T2DM) in comparison with healthy controls and also to analyse its association with age, gender, Body Mass Index (BMI), duration of diabetes, and glycaemic control.

Materials and Methods: This cross-sectional study was conducted in the Department of General Medicine and Physiology at Government Medical College, Kozhikode, Kerala, India, from January 2020 to January 2021, involving 98 patients diagnosed with T2DM (diabetic group) and 98 healthy controls (control group). Cardiovascular autonomic function was assessed using a 16 channel Physiolab and PHYSIOPAC software system employing Ewing's five standard cardiovascular reflex tests. Glycaemic parameters such as Fasting Blood Sugar (FBS), Post-prandial Blood Sugar (PPBS) Random Blood Sugar (RBS), and HbA1c were also measured. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software version 18.0, with unpaired t-tests for quantitative parameters and Chi-square tests for qualitative variables. Fischer's-exact test was used to determine the association between various parameters.

Results: The study population comprised adults aged 33-60 years, with a mean age of 50.34±6.09 years in the diabetic group and 50.84±6.55 years in the control group (p-value=0.581). Gender distribution was comparable, with 47 males and 51 females in each group (p-value=1.00). The prevalence of Cardiac Autonomic Neuropathy (CAN) was significantly higher among diabetic subjects (74.5%) compared with controls (9.2%) (p-value <0.001). Severity of CAN showed a positive correlation with age (p-value=0.002), BMI (p-value <0.001), duration of diabetes (p-value <0.001), and HbA1c (p-value <0.001), but not with gender (p-value=0.09). Parasympathetic dysfunction preceded sympathetic involvement in diabetic patients.

Conclusion: T2DM is strongly associated with reduced cardiovascular autonomic function. Early detection through routine autonomic function testing, coupled with optimal glycaemic control and lifestyle modification, is recommended to prevent progression of DCAN.

Keywords: Autonomic reflex tests, Ewing's criteria, Glycaemic control, Heart rate variability, Parasympathetic dysfunction

INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases characterised by chronic hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. India's diabetic population is projected to rise from 89.8 million in 2024 to 156.7 million by 2050, representing an approximate 74.5% increase over this period [1]. This escalating burden is associated with increased complications including cardiovascular diseases, nephropathy, retinopathy, and neuropathy, contributing significantly to morbidity and mortality [2]. Autonomic Nervous System (ANS) dysfunction is one of the most serious yet under-recognised complications of Diabetes and usually has a poor prognosis [3,4].

The CAN Subcommittee of Toronto Consensus Panel on Diabetic Neuropathy defines CAN as an "impairment of cardiovascular autonomic control in patients with established diabetes after excluding other causes" [3,5]. Studies indicate that CAN remains significantly underdiagnosed despite its diverse clinical manifestations, such as: (i) resting tachycardia; (ii) orthostatic hypotension, seen as dizziness, light-headedness, fainting, blurred vision; (iii) abnormal blood pressure regulation characterised by predominance of sympathetic tone during night and development of nocturnal hypertension; (iv) Orthostatic tachycardia or bradycardia and chronotropic incompetence; (v) exercise intolerance; (vi) impaired HRV- the earliest clinical indicator of CAN; (vii) QT interval prolongation (QTi) prolongation- hyperglycaemia and acute hypoglycaemia can induce the prolongation of QTi in both healthy and diabetic patients; (viii) silent myocardial infarction/cardiac denervation syndrome; and (ix) intraoperative cardiovascular lability. Sudden unexpected death has also been reported in patients with CAN [5,6]. Beyond cardiac involvement, Diabetic Autonomic Neuropathy (DAN) affects multiple systems including gastrointestinal, urogenital, sudomotor, and pupillary function, contributing to substantial morbidity. Hence, it is a severely debilitating complication as well as a major cause of morbidity and mortality in patients with diabetes [6,7].

The CAN in T2DM is primarily influenced by disease duration and glycaemic control, although age, gender, ethnicity, and microvascular complications also contribute [8,9]. Many studies highlight poor glycaemic control as a key factor in both onset and progression of CAN, involving early microcirculatory dysfunction and later neuronal damage [10,11]. Reduced Heart Rate Variability (HRV), linked to diabetes duration, is found to be associated with increased mortality and coronary artery disease risk [4,12], The most marked HRV decline occurs within the first 5-10 years of T2DM [13]. Since the vagus nerve, the longest autonomic nerve mediating approximately 75% of parasympathetic activity- is affected earliest, initial CAN manifestations reflect parasympathetic denervation with compensatory sympathetic dominance. Also, parasympathetic

impairment was found to be more sensitive to the detection of autonomic dysfunction [12].

Emerging evidence suggests autonomic imbalance- vagal withdrawal and sympathetic dominance- can occur even before diabetes or insulin resistance develops [9,11]. Early recognition of DCAN is vital, as timely interventions can prevent progression or even reverse nerve damage. Screening for CAN should begin at T2DM diagnosis and after five years in T1DM, especially in patients with HbA1c >7%, cardiovascular risk factors, or chronic complications [4]. This can be achieved through non-invasive computational techniques. Following ADA (1992) guidelines, five standard cardiovascular reflex tests- originally proposed by Ewing DJ et al., are widely used to assess autonomic function [12]. These tests are reliable, reproducible, and cost-effective compared to managing advanced complications. Despite growing recognition of CAN's impact, significant barriers persist including limited awareness among clinicians, perceived complexity of testing, and inadequate integration into routine practice. Previous Indian studies have reported varied CAN prevalence rates, but comprehensive data examining the relationship between CAN severity and multiple risk factors remain limited [14,15].

The present study addresses this gap by systematically evaluating cardiovascular autonomic function in T2DM patients using standardised Ewing's battery of tests and examining associations with demographic and metabolic parameters in an Indian population.

Hence, the present study aimed to evaluate the effect of type 2 diabetes on cardiovascular autonomic function in comparison with age and gender-matched healthy subjects and also to find the association of age, gender, BMI, duration of diabetes, and glycaemic control with DCAN in diabetic patients.

MATERIALS AND METHODS

A cross-sectional study was conducted over a period of one year from January 2020 to January 2021 in the Departments of Physiology and General Medicine, Government Medical College, Kozhikode, Kerala, India. The Study was commenced after obtaining prior approval from the Institutional Research Committee and Institutional Ethics Committee (IEC approval no. GMCKKD/RP 2020/IEC/354).

Inclusion criteria: Group 1 included diagnosed cases of T2DM with a disease duration of more than one year, aged between 30 and 60 years, who were willing to participate in the study. Group 2 comprised age- and gender-matched healthy individuals who consented to participate, had no clinical evidence of DM, hypertension, or any acute or chronic illness. All control subjects had a FBS value less than 126 mg/dL and were not on any medication known to influence ANS function.

Exclusion criteria: Subjects were excluded if they were seriously ill diabetic patients admitted to the Intensive Care Unit (ICU); had uncontrolled hypertension, acute coronary syndrome, or stroke; had a history of bronchial asthma or Chronic Obstructive Pulmonary Disease (COPD); or were taking medications such as beta-blockers, antipsychotics, anticholinergics, or other drugs known to affect autonomic function. Patients with fever, liver cirrhosis, or chronic kidney disease were also excluded.

Sample size calculation: The sample size was calculated using the formula:

$$N=\frac{(Z\alpha+Z\beta)^2\times p\times q\times 2}{d^2}$$

based on a prevalence of 53.2% for CAN in individuals with T2DM, with an α error of 5%, β error of 20%, and an effect size of 20% [16], yielding a minimum required sample size of 98 in each group.

Accordingly, 98 patients with T2DM were enrolled attending the endocrine or general medicine outpatient departments and 98 age- and gender-matched healthy controls were recruited from among the bystanders of patients and medical or paramedical staff.

Eligible T2DM patients meeting the inclusion and exclusion criteria were consecutively recruited until the target sample size was reached.

Study Procedure

After obtaining informed consent, data were collected using a structured questionnaire, including demographics, medical history, and drug intake. Height and weight were recorded for BMI calculation. A 5 mL of fasting venous blood samples (after 8-12 hours of fasting) were collected under aseptic precautions for FBS and HbA1c estimation. General examination, basal blood pressure, heart rate (after 10 minutes rest), and Electrocardiograph (ECG) were recorded. ECG limb leads were connected and continuous ECG monitoring was done using the 16 channel Physiolab and Physiopac software.

Standard cardiovascular autonomic function tests were employed based on the five non invasive reflex tests originally described by Ewing DJ et al., These included heart rate response to deep breathing, which evaluates parasympathetic activity by assessing respiratory sinus arrhythmia; the E:I ratio is derived from the longest expiratory and shortest inspiratory R-R intervals. Heart rate response to standing (30:15 ratio) assesses immediate autonomic adjustment on standing; the ratio is calculated from the longest R-R interval near beat 30 and the shortest near beat 15. The Valsalva manoeuvre tests both autonomic limbs by observing cardiovascular changes during forced expiration; the Valsalva ratio is the longest post-strain R-R interval divided by the shortest during strain. Blood pressure response to standing assesses sympathetic vasoconstrictor function, calculated as the fall in Systolic Blood Pressure (SBP) after 2-3 minutes of standing. Blood pressure response to sustained handgrip evaluates sympathetic activity by measuring the rise in diastolic pressure during the final 30 seconds of maintaining 30% Maximal Voluntary Contraction (MVC). These tests together assess cardiac autonomic function. Each test was individually scored using Ewing's criteria, where test results were classified as normal (score 0), borderline (score 1), or abnormal (score 2). The cumulative score allowed grading of CAN severity in each participant as "early involvement" (two borderline test results or one abnormal result on HR test), "definite involvement" (two or more abnormal results on HR tests), and "severe involvement" (development of orthostatic hypotension) [17]. The specific diagnostic criteria were that if at least two out of the three HR tests were scored as abnormal, it was labelled as parasympathetic neuropathy and labelled as sympathetic neuropathy if at least one out of the two BP tests for assessing sympathetic function was scored as abnormal [7].

STATISTICAL ANALYSIS

The SPSS version 18.0 for windows program was used to analyse the data. Normality assessment of the data was done with the Kolmogorov Smirnov test, for which a non significant result (p-value>0.05) indicates normality. For data that follows normality, independent t-test was used for comparing quantitative parameters and the Chi-square test was used for comparing qualitative parameters. Fischer's-exact test was used for finding the association of various parameters like age, gender, BMI, duration of diabetes, and glycaemic control with the severity of CAN.

RESULTS

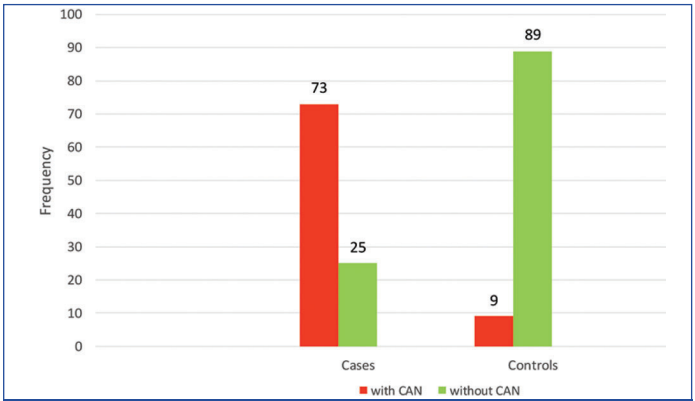
Present study compared cardiovascular autonomic function between 98 type 2 diabetics and 98 age- and gender-matched healthy controls (n=196). The tabular and graphical representations of the analysis are given below. The 30:15 ratio in the diabetic group ranged from 0.89 to 1.41, with a mean of 1.06±0.11, while in the control group, the range was 1.01-1.43, with a mean of 1.15±0.09.

The difference between groups was statistically significant for the patient group and the control group (p-value <0.001). The diabetic group showed significantly reduced HRV during deep breathing (p-value <0.001), lower Valsalva ratio (p-value=0.033), greater fall in SBP on standing (p-value <0.001), and a smaller rise in diastolic BP during handgrip compared to controls (p-value <0.001). These findings indicate impaired parasympathetic and sympathetic cardiovascular reflexes in patients with T2DM [Table/Fig-1].

Parameters	Diabetes group (Mean±SD)	Control group (Mean±SD)	p-value
30:15 Ratio	1.06±0.11	1.15±0.09	<0.001
HRV during deep breathing	13.71±4.23	17.41±2.93	<0.001
Valsalva ratio	1.24±0.16	1.29±0.13	0.033
SBP difference on standing	10.32±8.02	5.85±3.60	<0.001
Diastolic BP rise (Sustained Handgrip)	16.83±4.35	24.25±7.48	<0.001

[Table/Fig-1]: Distribution and comparison of various cardiac autonomic function tests among diabetes group and control group.
CAN: Cardiovascular autonomic neuropathy; HRV: Heart rate variability; SBP: Systolic blood pressure; BP: Blood pressure; SD: Standard deviation

Among the 98 controls, 9 subjects demonstrated abnormal autonomic reflex test results suggestive of subclinical CAN and of the 98 type 2 diabetic patients, 73 (74.5%) had some degree of CAN [Table/Fig-2].



[Table/Fig-2]: Bar graph showing distribution and comparison of cardiovascular autonomic neuropathy in cases and controls.

The criterion for labelling as parasympathetic neuropathy is that at least two out of the three heart rate tests should be abnormal and for considering as sympathetic neuropathy, at least one out of the two tests for assessing sympathetic function should be abnormal. In the present study, among the 98 diabetic patients, 64 were found to have parasympathetic neuropathy and 27 of them had sympathetic neuropathy also. Among the 98 healthy subjects, six had parasympathetic neuropathy and one of them had sympathetic neuropathy too. Even though four of the healthy subjects showed sympathetic neuropathy, three of them had sympathetic involvement alone without any parasympathetic involvement.

A statistically significant association was found between CAN severity and increasing age (p-value=0.002), BMI (p-value <0.001), duration of diabetes (p-value <0.001), and HbA1c levels (p-value <0.001). However, no significant association was observed with gender (p-value=0.092) [Table/Fig-3].

Factor	Subgroup	n (%)	E (%)	D (%)	S (%)	Total (N)	p-value
Age group (years)	30-42	3 (25.0)	8 (66.7)	1 (8.3)	0	12	0.002[a]
	43-51	15 (36.6)	23 (56.1)	0	3 (7.3)	41	
	52-60	7 (15.6)	18 (40.0)	8 (17.8)	12 (26.7)	45	
Gender	Male	13 (25.5)	21 (41.2)	5 (9.8)	12 (23.5)	51	0.092[b]
	Female	12 (25.5)	28 (59.6)	4 (8.5)	3 (6.4)	47	
BMI	Normal weight	6 (66.7)	0	0	3 (33.3)	9	<0.001[c]
	Overweight/ pre-obese	19 (35.2)	32 (59.3)	0	3 (5.6)	54	
	Obese	0	17 (48.6)	9 (25.7)	9 (25.7)	35	
Duration of diabetes	≤ 7 years	25 (30.1)	49 (59.0)	9 (10.8)	0	83	<0.001[d]
	> 7 years	0	0	0	15 (100.0)	15	
HbA1c	Good control	22 (38.6)	33 (57.9)	1 (1.8)	1 (1.8)	57	<0.001[e]
	Poor control	3 (7.3)	16 (39.0)	8 (19.5)	14 (34.1)	41	

[Table/Fig-3]: Association of various factors like age, gender, BMI, duration of diabetes and glycaemic control with severity of CAN.
CAN: Cardiac autonomic neuropathy; N: No CAN; E: Early CAN; D: Definitive CAN; S: Severe CAN
[a]Chi-square test, exact p=0.002, [b]Chi-square test, exact p=0.092, [c]Chi-square test, exact p<0.001 (BMI), [d]Chi-square test, exact p<0.001 (Duration of diabetes), [e]Chi-square test, exact p<0.001 (HbA1c category)
A p-value <0.05 was considered statistically significant.

DISCUSSION

The present study assessed the effect of T2DM on cardiovascular autonomic function by comparing outcome variables- CAN derived from HRV during deep breathing, Valsalva ratio, 30:15 ratio, postural hypotension, and blood pressure response to sustained handgrip, with age- and gender-matched healthy subjects.

Upon standing, there is reflex tachycardia, peaking around the 15th beat, followed by relative bradycardia at about the 30th beat. These responses are mediated by both vagus and baroreflex pathways. A comparison of heart rate responses between diabetic and age-/gender-matched control groups showed that reflex tachycardia was reduced in diabetic patients. These findings are consistent with those of Chorepsima S et al., [18]. In diabetics, reflex pathway damage likely causes abnormal responses. Pharmacological studies by Ewing DJ et al., demonstrated vagal mediation, as the typical response was abolished by intravenous atropine and by combined atropine and propranolol, but not by propranolol alone [19].

Heart rate response to deep breathing is measured as the average difference between maximum and minimum heart rate during each respiratory cycle, reflecting inspiration-induced acceleration and expiration-induced deceleration. In the present study, T2DM patients showed significantly reduced HRV compared to controls, consistent with findings by Rivera AL et al., and Sridhar B et al., [20,21]. This variation, known as sinus arrhythmia, is primarily mediated by vagal innervation. Respiratory center output modulates afferent and efferent activity at the nucleus tractus solitarius, with input from pulmonary stretch receptors, cardiac mechanoreceptors, and possibly baroreceptors. In diabetics, parasympathetic dysfunction leads to reduced HRV. The deep breathing test is a simple, sensitive, specific, and reproducible method for assessing vagal cardiac control. Decreased HRV in diabetics suggests DAN. Studies like that of Fareedabanu AB et al., have shown this test to be the most sensitive for detecting autonomic neuropathy [22].

Heart rate responses to the Valsalva manoeuvre are primarily mediated by baroreceptor reflexes involving the parasympathetic and, to a lesser extent, sympathetic nervous systems. During the manoeuvre, increased intrathoracic and intra-abdominal pressures reduce venous return, leading to a fall in arterial pressure and a compensatory baroreflex-mediated tachycardia. After straining ceases, arterial pressure overshoots, triggering a baroreflex-mediated bradycardia that lasts until blood pressure and heart rate normalise. Cardiopulmonary and chemoreceptor reflexes also

contribute, though less significantly. The mechanism of tachycardia during the manoeuvre remains debated-attributed variously to increased sympathetic activity, parasympathetic withdrawal, or combined effects. Due to the rapid parasympathetic response, the bradycardia in phases III-IV is largely parasympathetic, with minimal sympathetic inhibition. In diabetics with autonomic dysfunction, these reflex pathways are impaired, resulting in a blunted heart rate response and delayed recovery. Similar findings were reported by Sharpey-Schafer EP and Taylor PJ who observed impaired circulatory responses in diabetic neuritis , and by Kruter RH et al., who found low Valsalva ratios correlated with diabetes complications [23,24].

The rise in Diastolic BP during the hand grip test was significantly lower in the diabetic group compared with the control group. Normally, while performing the isometric hand grip exercise at intensities that result in muscle fatigue i.e., ~20% of MVC, there is an initial pressor response, the magnitude of which increases progressively throughout the contraction period. It has been postulated that these levels of contraction result in compression of the blood vessels perfusing the contracting muscles, which limits the hyperaemia needed to meet the increased metabolic demand, and ischaemia ensues which in turn leads to an increase in the concentration of lactic acid, adenosine, potassium etc., [25]. These are detected by the metabolite-sensitive nerve endings within the skeletal muscle interstitium, leading to an increase in discharge of the group IV (metaboreceptor) afferent fibres, thus initiating a potent reflex that increases the sympathetic nerve activity, resulting in vasoconstriction and a subsequent rise in the BP. Hence, in control subjects, during sustained hand grip, there is a sharp rise in diastolic blood pressure of more than 15 mmHg. In diabetics, due to autonomic damage, the rise in blood pressure is abnormally small. The results in the present study correlated with the studies conducted by Makwana K et al., and Endukuru CK and Mallikarjuna RN [26,27].

The present study demonstrated that the fall in SBP on standing is more in diabetics as compared to the controls, which is consistent with the findings of Pan Q et al., [28]. This is mainly due to CAN in which there is damage to the efferent limb of the baroreflex arc with damaged sympathetic vasoconstrictor fibers in the splanchnic bed, muscle, and skin. The hypotension may be augmented by a diminished plasma-renin response to standing, due to impaired sympathetic innervation of the juxtaglomerular apparatus. In addition, in some studies with analogous results, like those done by Paffili K et al., it is also suggested that specific clinical findings like orthostatic hypotension should sensitise physicians to the presence of CAN [8].

The findings of the present study suggest a significantly higher prevalence of CAN in individuals with type 2 diabetes compared to age- and gender-matched controls. It was also found that parasympathetic dysfunction precedes sympathetic involvement in DAN, aligning with Kaur D et al., demonstrating early impairment of cardiac vagal function in diabetic autonomic neuropathy [28]. This may relate to the structural differences between parasympathetic and sympathetic fibers, with the former comprising larger, myelinated preganglionic fibers. Wu J-S et al., also noted early involvement of large myelinated fibers in T2DM, supporting early parasympathetic and sensory neuropathy in glucose intolerance [29].

The study revealed that CAN was significantly more prevalent in older type 2 diabetics, aligning with findings by Booya F et al., [30]. Ageing accelerates autonomic decline, which is worsened by diabetes [31]. No significant gender differences were found, consistent with [32], though literature remains conflicting [33]. A positive correlation between BMI and CAN severity was observed, supported by studies linking increased visceral fat to impaired autonomic function and greater cardiovascular risk. The ANS also affects energy balance via leptin and sympathetic activity. Longer diabetes duration correlated with worse CAN, likely due to prolonged undiagnosed hyperglycaemia. Higher HbA1c levels, indicating poor glycaemic control, were also associated with increased CAN severity, consistent with findings by Andersen ST et al., [34]. Thus, glycaemic control is vital for preventing CAN progression.

Limitation(s)

The present study has several limitations. First, age-related cut-off values for heart rate variability ratios were not available. Second, long-term follow-up was not performed. Furthermore, the tertiary care setting of the study may have contributed to the relatively high prevalence of CAN observed in this cohort.

CONCLUSION(S)

The present study demonstrated a significantly higher prevalence of CAN among individuals with T2DM compared to age- and gender-matched healthy controls, as assessed by Ewing's cardiovascular reflex tests. The findings revealed predominant parasympathetic dysfunction with concomitant sympathetic involvement, indicating widespread autonomic impairment in diabetes. The severity of CAN correlated positively with age, BMI, duration of diabetes, and poor glycaemic control, underscoring the metabolic influence on autonomic health. Persistent hyperglycaemia appears to play a central role in the pathogenesis of this dysfunction. Early recognition of subclinical autonomic changes can help prevent serious cardiovascular complications through timely intervention and lifestyle modification. Further longitudinal and interventional studies are recommended to establish causal relationships, evaluate reversibility with strict glycaemic control, and explore novel biomarkers or technologies for early detection of autonomic dysfunction in diabetes.

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