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RESEARCH ARTICLE

A study of cardiovascular autonomic function tests in alcoholic patients with Type-2 diabetes mellitus attending North Bengal Medical College and Hospital

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ABSTRACT

Background: Diabetes mellitus (DM), a growing and alarming disease of today's India, causes a great deal of micro- and macro-vascular complications. One of the most overlooked of all serious complications of diabetes is cardiovascular autonomic neuropathy (CAN). Alcohol adds more to the problem and causes alteration to the hemodynamics. Recently, it has also been shown that patients with alcoholic dependence frequently suffer from autonomic neuropathy. In the rising trend of alcoholism today in respect to stress and social status maintenance, people including diabetics are silently slipping toward this grave disease of CAN. In this context, we have tried to evaluate the cardiovascular autonomic functions and their correlations, if any, among the people of alcoholic and non-alcoholic Type-2 DM (T2DM). **Aims and Objectives:** The present study was conducted to assess the cardiovascular autonomic functions to find out the amalgamated effect of alcohol with T2DM. **Materials and Methods:** The study was conducted in the Department of Physiology in North Bengal Medical College and Hospital based on non-invasive techniques to determine the cardiovascular autonomic functions in the alcoholic and non-alcoholic type-2 diabetic mellitus individuals. Our study was focused mainly on the heart rate (HR) and blood pressure (BP) variation for diagnosing CAN although other parameters have also been taken into consideration. The simple, reliable, and quantitative autonomic function tests such as the deep breathing test, postural tachycardia index, Valsalva maneuver, COLD PRESSOR TEST, handgrip, and head tilt tests were done among a group of Type-2 diabetic alcoholic and non-alcoholic patients of more than 3 years duration, comprising 73 males and 27 females in the age group of 40–70 years. Taking permission from the Institutional Ethical Committee and after thorough examination of the patients, autonomic function tests were carried out and the collected data have been analyzed statistically. **Results:** It has been seen after tests that 98% of the subjects are suffering from cardiac autonomic neuropathy (variable HR and BP) indicating that diabetes alone can lead to autonomic nervous system (ANS) dysfunction even to a smaller degree after few years of onset of the disease. The degree of affection showed an increasing trend in the alcoholic diabetic subjects than the non-alcoholic diabetic subjects in tests such as supine to standing, Valsalva maneuver, deep breathing test, and cold pressure test as *P*-values were significantly different in those tests ($P < 0.05$). There was a non-significant difference in change of BP in tilt table test and handgrip test between the alcoholic and non-alcoholic diabetic groups where $P > 0.05$ was detected. **Conclusion:** The ANS plays a pivotal role in cardiovascular homeostasis. HR variability is considered the earliest indicator and most frequent finding in symptomatic cardiovascular autonomic dysfunction. The uniqueness of this study is that it included the combined diabetic alcoholic group for which very few studies have been conducted.

KEY WORDS: Diabetes Mellitus; Chronic Alcohol Abuses; Micro- and Macro-vascular Angiopathy; Autonomic Neuropathy; Coronary Artery Disease; Cerebrovascular Events

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INTRODUCTION

In a worldwide study in 2013[1] shown that diabetic population of India is 65.1 million which is next to China harboring 98.4 million diabetics which is presumed to be increased to 101 million in 2030 in India and will occupy the second position worldwide. The autonomic nervous system (ANS) is the integrated nervous system having sympathetic and parasympathetic division, maintains internal homeostasis by regulating cardiovascular, gastrointestinal, genitourinary, thermoregulatory, exocrine, and pupillary functions[2] which could not be easily controlled voluntarily, hence, called "autonomic." Diabetes mellitus (DM) causes a great deal of microvascular and macrovascular complications, leading to neuropathies and organ damage. Cardiovascular autonomic neuropathy (CAN) is one of the most overlooked of all serious complications of diabetes[3-5] which encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate (HR) control and vascular dynamics.[6] The increased resting HR observed in diabetic patients is most likely due to the vagal cardiac neuropathy. Alcohol adds more to the problem and causes alteration to the hemodynamics. Alcohol leads to primary axonal neuropathy that is characterized by Wallerian degeneration and a reduction in the myelination of neural fibers,[7] impairs axonal transport, disturbs cytoskeletal properties, and decreases the concentration of endogenous antioxidants.[8,9] There are evidences that vagal neuropathy occurs in chronic alcoholics. It results in significantly higher mortality in chronic alcoholics. Damage to ANS may occur in systemic diseases involving the cyclic vomiting syndrome (CVS) such as DM, hypertension, vascular disease, ischemic heart disease, cardiac arrhythmia, Parkinsonism, amyloidosis, and polyneuropathies.[10] Vagal cardiac neuropathy leads to tachycardia due to unopposed sympathetic activity that is followed by a decrease in HR and, finally, a fixed HR due to progressive cardiac sympathetic nervous system neuropathy. CAN results in systolic dysfunction that leads to decreased diastolic filling and reduced cardiac output. Impaired sympathetic and parasympathetic responses lead to reduced exercise tolerance as these responses to exercise increase cardiac output to fulfill the increased demands of exercising muscles.

Hence, we, the Indians, are on a serious uptrend of a fatally morbid disease like diabetes superadded with alcoholism which certainly needs an eye to it. In this context, we were tempted to do a study to assess the effect on cardiac autonomic function among patients of chronic alcoholic and non-alcoholic Type-2 DM (T2DM).

Aims and Objectives

The present study was conducted to find out the amalgamated effect of alcohol with T2DM on cardiovascular autonomic functions.

These were non-invasive, easily reproducible quantitative autonomic nervous function tests, performed in 100 T2DM subjects grouped into alcoholic and non-alcoholic category. This descriptive cross-sectional study was conducted for a period of 1 year in the Department of Physiology among 100 alcoholic and non-alcoholic subjects of both sexes of Type 2 DM for at least 3 years, attending medicine Outpatient Department (OPD) of North Bengal Medical College and Hospital aged from 40 to 70 years. The aim of the present study was to determine the prevalence of CAN among the alcoholic and non-alcoholic subjects with T2DM.

MATERIALS AND METHODS

The study was approved by the institutional ethics committee to continue, maintaining institutional rules and regulation.

T2DM

According to the World Health Organization,[11] laboratory criteria of T-2-DM will be called when fasting plasma glucose ≥126 mg/dl, 2 h plasma glucose ≥200 mg/dl, and symptoms of diabetes plus random blood glucose ≥200mg/dl.

Inclusion Criteria

Alcoholic and non-alcoholic group of diagnosed T2DM cases of both sexes aged from 40 to 70 years, under treatment for at least 3 years in medicine OPD with and without alcoholism were included in the study.

Exclusion Criteria

Patients who developed major illness during data collection, examination, already developed diseases such as proliferative diabetic retinopathy and diabetic nephropathy, respiratory illnesses such as asthma, ischemic heart disease, and major psychiatric illnesses were excluded from the study. Patient taking medicine that can alter HR and blood pressure (BP) such as diuretics, β-blockers, and calcium channel blockers, anticholinergics were also excluded.

They were classified into two main groups: Group I: Alcoholic Type-2 diabetics and Group II: Non-alcoholic Type-2 diabetics.

We selected total of 100 numbers of Type-2 diabetic patients comprising 73 males and 27 females. As shown in Table-1, out of these, 43 male and 12 female subjects were alcoholic and rest 30 male and 15 female subjects were non-alcoholic. Altogether 55 subjects with Type-2 diabetic mellitus were alcoholic and 45 subjects were non-alcoholic.

Parameters Studied

HR and BP responses in supine position at rest, standing position from supine, head-up tilted position, Valsalva

maneuver, isometric exercise (handgrip test), cold pressor test, and 12-lead electrocardiography (ECG) were recorded.

Study Material

ECG machine (BPL, CARDIART 108T DIGI), tilt table, refrigerator, ice and cold water, thermometer, polygraph machine – RMS Polyrite version: 3.0.16 were used.

Methods

HR response to deep breathing

ECG was recorded continuously while the subject was breathing deeply, steadily, and slowly for 1 min at the rate of 6 breaths/min. The HR changes with deep breathing were recorded. The deep breathing difference (DBD) was then expressed as the mean of the differences between the maximal and minimal HR in 6 respiratory cycles.[12]

HR response to Valsalva maneuver

The subject was asked to blow through the mouthpiece attached to a mercury manometer and maintain a pressure of 40 mmHg up to 15 s. Throughout the maneuver, ECG was recorded continuously. The HR changes induced by the Valsalva maneuver were expressed as the ratio of the maximal tachycardia during the maneuver to the maximal bradycardia after the maneuver.

$$\text{Valsalva Ratio} = \frac{\text{Longest R} - \text{R interval following release of pressure}}{\text{Shortest R} - \text{R interval during the act of blowing}}$$

$$\text{Tachycardia Ratio} = \frac{\text{Shortest R} - \text{R interval during the act of blowing}}{\text{Longest R} - \text{R interval before the act of blowing}}$$

As shown in Table 3, a value of 1.10 or less – an abnormal response, 1.11–1.20 – borderline, and 1.21 or more – normal response.[13,14]

HR response to standing (postural tachycardia index [PTI]=PTI)

The subject was asked to lie in supine position and rest for 2 min and then stand unaided and remain standing for 1 min while ECG is recorded continuously.

Table 1: Sex-wise distribution of subjects with alcohol habit

Gender	Alcoholic	Non-alcoholic
Male	43	30
Female	12	15
Total	55	45

PTI = Longest RR at 30 beats/shortest RR at 15 beats. As shown in Table 3, a ratio of 1.00 or less was defined as an abnormal response, 1.01–1.03 as borderline, and 1.04 as normal response.[15,16]

Response to head-up tilt (change in systolic BP [SBP])

The subject was placed supine over the tilt table for 10 min and after that with the ECG leads and BP cuff connected, the head end of the table was inclined upward to an angle of 70° with horizontal plane.[17] The immediate response of HR and BP was recorded.

Sustained handgrip test

The subject was instructed to perform handgrip in a dynamometer to apply maximum pressure for 3–4 s. Then, the patient was instructed for a sustained handgrip exercise, maintaining a pressure of 30% of maximal activity for 5 min with that dynamometer.[18] The change in diastolic BP from the basal value was recorded. It evaluates mainly the sympathetic function.

Cold pressor test

The subject was asked to submerge one of the upper limbs in very cold water (at or <4°C) for 60 s. The BP and HR were recorded at 30 s, 60 s, 90 s, and 120 s of submersion of the limb. Plunging the limb in cold water raises the BP by reflex sympathetic stimulation.

RESULTS

Results obtained by these tests were tabulated and statistical analysis was performed using EPI INFO Software (Version 3.5.1).

Student's independent *t*-test was performed to assess differences between continuous variables (expressed as mean ± standard deviation [SD]) and tests were used for categorical variables (expressed as number and percentage). We considered the results statistically significant when P =0.05 or less.

Among the patients aged between 40 and 70 years, mean alcoholic diabetics were 55.14 years with SD of 8.76 and non-alcoholic diabetics were little bit elderly with mean age of 56.90 years with SD of 7.64, P = 0.019 and <0.05 depicting significant age difference between two groups as shown in Table 2.

It is shown from Table 2 that the mean and SD of body mass index (BMI) in alcoholic and non-alcoholic diabetic groups did not very much in the study as they were 24.97 ± 2.63 and 24.26 ± 2.24. Hence, in the sample size, P value came out to be 0.15 which was not statistically significant. The mean of basal HR between the study and the control group

were 80.56 and 78.48, respectively, with a SD of 10.82 and 11.63 which were not a widely varied data to be meant for statistical significance as $P = 0.35$. The mean BP value was not statistically significant as the mean of BP was 94.04 and 95.20, respectively, with an SD of 8.84 and 9.84 between the alcoholic and the non-alcoholic diabetic groups. The result showing a *P* value of 0.53 indicates a non-significant differences of mean BP value between the alcoholic and non-alcoholic diabetic group of people.

It has been seen from the autonomic function tests that 98% of the subjects are suffering from CAN indicating that diabetes alone can lead to ANS dysfunction even to a smaller degree after few years of onset of the disease. The degree of affection showed an increasing trend in the alcoholic diabetic subjects than the non-alcoholic diabetic subjects in tests such as supine to standing, Valsalva maneuver, deep breathing test, and cold pressure test as *P* values were significantly different in those tests.

As depicted in Table 4, mean and SD of PTI in our study group was 1.05 ± 0.07 and 1.08 ± 0.06, respectively. There was a statistically significant difference between the alcoholic and non-alcoholic diabetic groups as $P = 0.02$ ($P < 0.05$). Thus, it is conspicuous that the HR response to standing, which is a measure of parasympathetic function, was significantly reduced in the study group.

P value in tilt table test between the two groups was not statistically significant ($P = 0.92$).

Valsalva ratio (VR) is a good indicator of HRV and the value was statistically significant. The mean and SD of VR in the alcoholic and non-alcoholic diabetic group found to be 1.11 ± 0.16 and 1.24 ± 0.18, respectively. $P = 0.00$ ($P < 0.05$) was highly significant in this study indicated that the presence of ANS dysfunction was higher in the alcoholic study group. Tachycardia ratio in alcoholic and non-alcoholic diabetic groups had a mean and SD values of 0.89 ± 0.10 and 0.83 ± 0.11, respectively, and the calculated $P = 0.00$ was highly significant in the study group compared to the control non-alcoholic group as it was <0.05.

Result of DBD in the study and control group was significant. Mean, SD, and *P* value are 16.91 ± 8.41, 25.90 ± 12.33, and 0.00 ($P < 0.05$), respectively, and it indicates that parasympathetic function has been reduced in the study group.

The mean and SD of rise of SBP of the alcoholic and non-alcoholic groups in cold pressure test were 8.77 ± 7.71 and 12.20 ± 9.40, respectively, as it is shown in Table 4. $P = 0.04$ is a statistically significant data. The alcoholic diabetic group had lesser tendency to change in SBP in the test which is a sympathetic dysfunction.

The diastolic BP changes in the handgrip test between the alcoholic and non-alcoholic diabetic groups were not statistically significant as it was evident from the higher $P = 0.94$. Mean and SD values of 9.35 ± 8.06 and 9.46 ± 8.30 were seen in this test.

DISCUSSION

CAN is one of the serious complications of DM.[3-5] CAN causes damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in HR control and vascular dynamics.[6] The clinical manifestations due to CAN result in life-threatening outcomes. The presence

Table 2: Age, BMI, basal HR, and mean BP of alcoholic and non-alcoholic group

Variables	Mean age			BMI			Basal HR			Mean BP		
	Mean	SD	*P* value	Mean	SD	*P* value	Mean	SD	*P* value	Mean	SD	*P* value
Alcoholic	55.14	8.76	0.019	24.97	2.63	0.15	80.56	10.82	0.35	94.04	8.84	0.53
Non-alcoholic	56.90	7.64		24.26	2.24		78.48	11.63		95.20	9.84	

BMI: Body mass index, SD: Standard deviation, HR: Heart rate, BP: Blood pressure

Table 3: Cardiovascular autonomic score

Tests	Normal (score 0)	Borderline (score 1)	Abnormal (score 2)
HR response tests			
HR response to Valsalva maneuver VR	1.21 or more	1.11–1.20	1.10 or less
HR response to standing PTI	1.04 or more	1.01–1.03	1.00 or less
HR response during deep breathing DBD	15 beats per min or more	11–14 beats/min	10 beats/min or less
BP response tests			
BP response to head-up tilt (fall in SBP)	10 mmHg or less	11–29 mmHg	30 mmHg or more
BP response to sustained handgrip (rise in diastolic BP)	16 mmHg or more	11–15 mmHg	10 mmHg or less
BP response to cold pressor (rise in SBP)	20 mmHg or more	19–11 mmHg	10 mmHg or less

VR: Valsalva ratio, HR: Heart rate, BP: Blood pressure, PTI: Postural tachycardia index, SBP: Systolic BP, DBD: Deep breathing difference

Table 4: Different variable of cardiac autonomic nerve function test of diabetic alcoholic and non-alcoholic

Subjects	PTI (HR response)		Tilt table test (BP response) Tachycardia ratio		Sustained handgrip test (BP response)		SBP change in cold pressor test		HR response during deep breathing		Valsalva maneuver			
											VR		Tachycardia ratio	
	Mean±SD	*P* value	Mean±SD	*P* value	Mean±SD	*P* value	Mean±SD	*P* value	Mean±SD	*P* value	Mean±SD	*P* value	Mean±SD	*P* value
Alcoholic	1.05±0.07	0.02	9.74±9.53	0.92	9.35±8.06	0.94	8.77±7.71	0.04	16.91±8.41	0.00	1.11±0.16	0.00	0.89±0.10	0.00
Non-alcoholic	1.08±0.06		9.58±7.62		9.46±8.30		12.20±9.40		25.90±12.33		1.24±0.18		0.83±0.11	

VR: Valsalva ratio, HR: Heart rate, BP: Blood pressure, PTI: Postural tachycardia index, SBP: Systolic BP

of CAN in DM increases the risk of cardiovascular morbidity and mortality. Clinical symptoms of autonomic neuropathy generally take long time to appear in patients with DM. In Type-2 diabetic patients, subclinical autonomic dysfunction can occur within a year of diagnosis while in Type 1 diabetic patient, it takes about 2 years.[19]

Few non-invasive, easily reproducible quantitative autonomic nervous function tests were performed in 100 T2DM subjects grouped into alcoholic and non-alcoholic category. In our study, there was no significant difference in the BMI, HR, and mean BP of the two study groups. Alcoholism and diabetes together affect the coronary system to produce less HR variability as found in deep breathing test. The vagal control of the heart is found to be deranged in this group. On sudden standing from supine position, there was significant decrease in the HRV as evident from the PTI in the alcoholic diabetic subjects.

The VR and tachycardia ratio which are supposed to be the better indicators of HRV showed a diminished response in the study group, thereby confirming the association of CAN with the alcoholic diabetics. The present study showed a decreased response in SBP in tilt table test which is not statistically significant as found in other studies. Further studies are needed to enquire about this observation in such group of individuals.

The increment of SBP in cold pressure test was less which signifies a sympathetic imbalance between the subjects of the study groups.

In a study on Type-2 diabetics, by Institute of Post Graduate Medical Education and Research Hospital, Kolkata, West Bengal, in 2011, CAN was found in 54% of the study cases. In the same study, parasympathetic neuropathy was found in 52% of cases and sympathetic neuropathy in 20% of cases. Majority of patients (28%) had two abnormal cardiovascular reflexes.[20]

Another study found that CAN was strong predictor of silent myocardial ischemia and subsequent cardiovascular events and a slow HR recovery after exercise.[21]

Evidence of vagal neuropathy in chronic alcoholics is associated with a significantly higher mortality than in the general population and that deaths due to cardiovascular disease are a major cause.[22] In one recent survey,[23] among 20 chronic alcoholics selected on the basis of having peripheral neuropathy, studied, and shown to have a high prevalence of autonomic neuropathy. A fixed HR that is unresponsive to moderate exercise, stress or sleep indicates almost complete cardiac denervation.[24] Autonomic dysfunction impairs exercise tolerance,[25] reduces response in HR and BP,[26] and blunts increases in cardiac output in response to exercise.[27,28] In patients with diabetes, orthostatic hypotension is usually

attributable to damage to the efferent sympathetic vasomotor fibers, particularly in the splanchnic vasculature.[29] Reduced appreciation for ischemic pain can impair early recognition of myocardial ischemia or infarction, thereby delaying appropriate therapy termed as silent myocardial ischemia.

Strength and Limitations of this Study

The present unique study was conducted in 100 T2DM subjects grouped into alcoholic and non-alcoholic category. Overall association of CAN with the alcoholic diabetic subjects was not found significantly different as compared to non-alcoholic diabetic subjects in tilt table test and handgrip test. The DBP in handgrip test showed no significant change which might be due to the physiologic adaptation of the CVS to the procedure. As the performance of BP response to sustained handgrip test was poor, it also needs more research. The reason behind this may be that the study was done with smaller population. It may also be implicated that duration of diabetes was found less ranging from 3 to 5 years in almost 40% of patients. Moreover, females were moderate drinker and the average duration of drinking was also less for them. Henceforth, a larger population study with long-term diabetes with chronic heavy alcoholics is required as it still lacks a pioneer study worldwide till date.

CONCLUSION

The present study was conducted to assess the cardiovascular autonomic functions to find out the amalgamated effect of alcohol with T2DM on ANS in 100 subjects including 73 male and 27 female subjects. The ANS functions were found to be deranged and deteriorated in the study group more than the control group in four of the six tests such as HR response to standing, Valsalva maneuver, deep breathing test, and BP response to cold pressor. The association of CAN with the alcoholic diabetic subjects was not found significantly different as compared to non-alcoholic diabetic subjects in tilt table test and handgrip test. It may be implicated that duration of diabetes was less; ranging from 3 to 5 years in almost 40% of patients and the population was smaller. Moreover, females were moderate drinker and the average duration of drinking was also less for them. Henceforth, a larger population study with long-term diabetes with chronic heavy alcoholics is required as it still lacks a pioneer study worldwide till date.

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