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Prevalence of cardiovascular autonomic neuropathy in type-2 diabetes mellitus and role of corrected QT interval for its diagnosis

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Abstract

The prevalence of cardiac autonomic neuropathy (CAN) in type 2 DM patients increases with the duration and poor glycemic control. Patients with CAN are at increased risk for autonomic dysfunction like resting tachycardia,abnormal systolic and diastolic function leading to syncope and dizziness, prolonged QT interval, silent ischemia/infarction, lethal arrhythmias and sudden death.Usage of 5 simple and cheap bed side tests for autonomic function and corrected QT interval from ECG are helpful in early diagnosis of CAN. Early recognition of CAN is helpful in delaying effects of CAN by strict control of blood sugar and following healthy life style. Our study was conducted on100known and newly diagnosedType 2 Diabetes Mellitus patients<60 years whopresentedto Medicine OPD and admitted in IPD wardsin Maharani LaxmiBai Medical College.Out of total 100 patients,49% had normal score(0,1); 25% had borderline score(2,3,4); rest 26% had abnormal score ≥5; the prevalence of CAN was 51%.Among 100 patients 47% patients were foundwith poor glycemic control (HbA1C ≥ 8),in these 17% had early and 21% had definite CAN. Out of 100 patients of the study, 55% patients had QTc>440ms out of which 17% had early and 23% had definite CAN. The CAN also increased with older age group. So it is important to diagnose CAN early in asymptomatic diabetics. There is significant correlation between CAN and QT prolongation. QT interval in ECG can be used to diagnose CAN with reasonable sensitivity and specificity. Usage of 5 bedside autonomic function tests are very helpful in early diagnosis of CAN.Strict control of blood sugar can delay the early development of CAN. Intensive control of blood sugar can delay the early development of CAN.

Keywords: Autonomic neuropathy, diabetes mellitus, tachycardia, ischemia, QT interval, age, HbA1C, ECG

Introduction

Diabetes mellitus is a multi-metabolic disorder that shares the common phenotype of hyperglycemia. The cardiovascular complications of DM can be classified into three groups: Atherosclerotic Coronary Artery Disease, Diabetic Cardiomyopathy and Cardiac Autonomic Neuropathy (CAN)[1]. CAN is a common form of diabetic autonomic neuropathy that causes abnormalities in heart rate control as well as central and peripheral vascular dynamics. CAN is a clinically important form of diabetic autonomic neuropathy, as it is associated with increased risk of mortality. Presence of cardiac autonomic neuropathy (CAN) is responsible for silent myocardial infarction[2]and sudden death in diabetics. Hence recognizing cardiac dysautonomia early, which is asymptomatic will help to delay or arrest its progression. The autonomic function tests[3],are now widely used for the assessment of dysautonomia. These

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tests are non-invasive and do not require sophisticated equipment. All that required is an electrocardiogram machine, Heart rate monitor and sphygmomanometer.

Objectives of my study are to evaluate the prevalence of cardiovascular autonomic neuropathy in type 2 diabetes patients in our hospital, to find the relationship between cardiovascular autonomic neuropathy with duration of diabetes and to investigate the relationship between cardiac autonomic neuropathy and QTc interval prolongation. This highlights the importance of simple non-invasive tools like ECG and sphygmomanometer in diagnosing asymptomatic cardiac autonomic neuropathy. Type 2 diabetic patients with abnormal Cardio vascular reflex tests (CVR) may have increased mortality and those combined with postural hypotension have higher mortality than those without.

In 1980, for the first time, an association of prolonged QTc interval with cardiac autonomic neuropathy was noted, thereby opening the possibility of a rapid objective method for detecting cardiac autonomic neuropathy[7].Further studies demonstrated an association of prolonged QTc interval with cardiac dysautonomia in diabetes mellitus[1].This study is performed to estimate the Prevalence of Cardiovascular Autonomic Neuropathy with relation to duration of diabetes in our hospital and to check the utility of corrected QT interval in diagnosing it.

Methodology

Type of study: Hospital-based Observational Study.

Sample size and type

After considering the inclusion and exclusion criteria, a total number of 100 eligible cases were taken up for the study.

Ethical consideration

Ethical approval to conduct the study was obtained from the Institutional Ethics Committee (H) of the institute prior to the study.

Method of collection of data

Detailed clinical history regarding diabetes mellitus (onset, duration), any history of long term illness, any previous cardiac, respiratory or neurologic symptoms, previous history of any kind of drug therapy, whether the patient was on insulin or oral hypoglycemic drugs was sought. A thorough clinical examination including vitals, general physical examination, systemic examination and investigations was carried out. Biochemical investigations were carried out using proper aseptic precautions for collecting blood.

Patients were examined for presence of diabetes mellitus according to ADA criteria for diagnosis of diabetes mellitus. All diabetic patients were then subjected to estimation of BMI, FBS, PPBS, HBA1C, ECG, chest Xray, KFT.

Our study was a hospital based prospective observational study which was conducted in M.L.B Medical College, Jhansi (U.P.) done to evaluate the prevalence of cardiac autonomic neuropathy in type-2 diabetes and to assess its correlation with duration of diabetes, to investigate the relationship between cardiac autonomic dysfunction and corrected qt interval. The study includedknown and newly diagnosed acute type 2 diabetics patients who presented to OPD and admitted IPD department of general medicine, MLB Medical College, Jhansi and a total of 100 patients were selected for the study. The patients were grouped into three according to the duration of diabetes. Autonomic neuropathy tests were done by 5 bed side tests be done in medical ward using ECG monitor, pulse oximeter and sphygmomanometer. All patients were subjected to the 5 tests:Heart rate response to valsalva manoeuvre, heart rate variation during deep breathing, immediate heart rate response to standing, blood pressure response to standing and blood pressure response to sustained hand grip.Grading of cardiac

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autonomic function results are classified into normal, borderline and abnormal (scores 0,1and 2 respectively). An overall score of 0 or 1 was considered normal, score 2,3,4 wereconsidered borderline and score >5 were considered asabnormal autonomic function. Corrected QT interval was calculated using the Bazettes formulae[8].A QT interval >440 millisec was considered prolonged.

Results

Table 1: Association of Cardiac Autonomic Neuropathy with duration of DM

Duration of DM	Cardiac Autonomic Neuropathyby overall score			Total
	Normal	Border-line	Abnormal	
< 5 years	46 (95.8%)	1 (2.1%)	1 (2.1%)	48 (48%)
5 to 10 years	3 (10.7%)	24 (85.7%)	1 (3.6%)	28 (28%)
> 10 years	0 (0%)	0 (0%)	24 (100%)	24 (24%)
Total	49 (49%)	25 (25%)	26 (26%)	100 (100%)

χ^2-value=165.5;df=4;p-value<0.001(Significant).

Out of 48 (48%) patients having duration of diabetes under 5 years, majorly 46 (95.8%) patients don't have cardiac autonomic neuropathy, 1 (2.1%) patient have borderline cardiac autonomic neuropathy and 1 (2.1%) patient have abnormal cardiac autonomic neuropathy. Out of 28 (28%) patients having duration of diabetes between 5 to 10 years, majorly 24 (85.7%) patients have borderline cardiac autonomic neuropathy, 3 (10.7%) patients don't have cardiac autonomic neuropathy and 1 (3.6%) patient have abnormal cardiac autonomic neuropathy. Remaining 24 (24%) patients have duration of diabetes above 10 years. All of these patients having duration of diabetes above 10 years have abnormal cardiac autonomic neuropathy. Significantly higher numbers of patients with duration of diabetes above 10 years have cardiac autonomic neuropathy compared to patients with duration of diabetes less than 5 years and 5 to 10 years. (p<0.05; Significant).

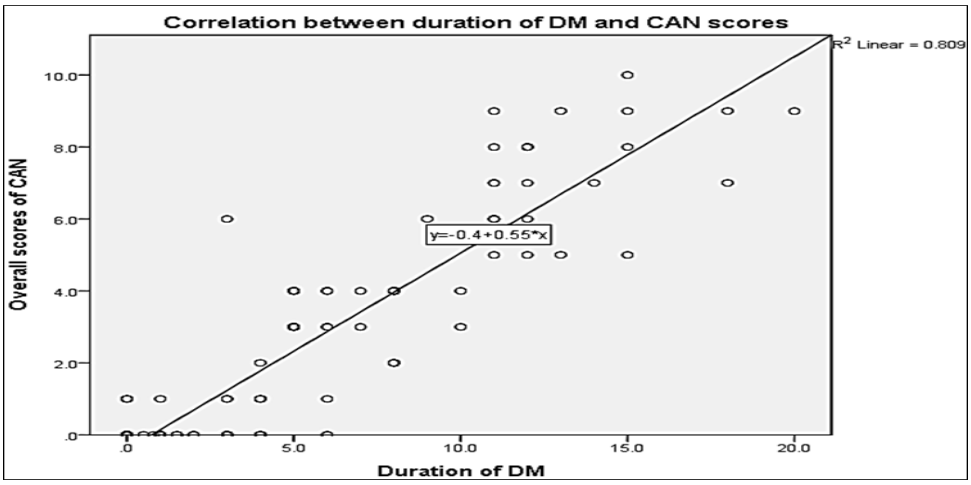

Table 2: Association between severity of Diabetes mellitus and cardiac autonomic neuropathy (CAN)

Severity of DM	Cardiac Autonomic Neuropathyby overall score			Total
	Normal	Borderline	Abnormal	
Controlled DM (HbA1C≤8%)	40 (75.5%)	8 (15.1%)	5 (9.4%)	53 (53%)
Uncontrolled DM (HbA1C>8%)	9 (19.1%)	17 (36.2%)	21 (44.7%)	47 (47%)
Total	49 (49%)	25 (25%)	26 (26%)	100 (100%)

χ^2-value = 32.455; df = 2; p-value < 0.001 (Significant).

Majority (75.5%) of patients with controlled diabetes mellitus (HbA1C≤8%) are not having cardiac autonomic neuropathy. But, majority (44.7%) of patients with uncontrolled diabetes mellitus (HbA1C>8%) have abnormal cardiac autonomic neuropathy. This difference is

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significant statistically. (p<0.05; Significant).

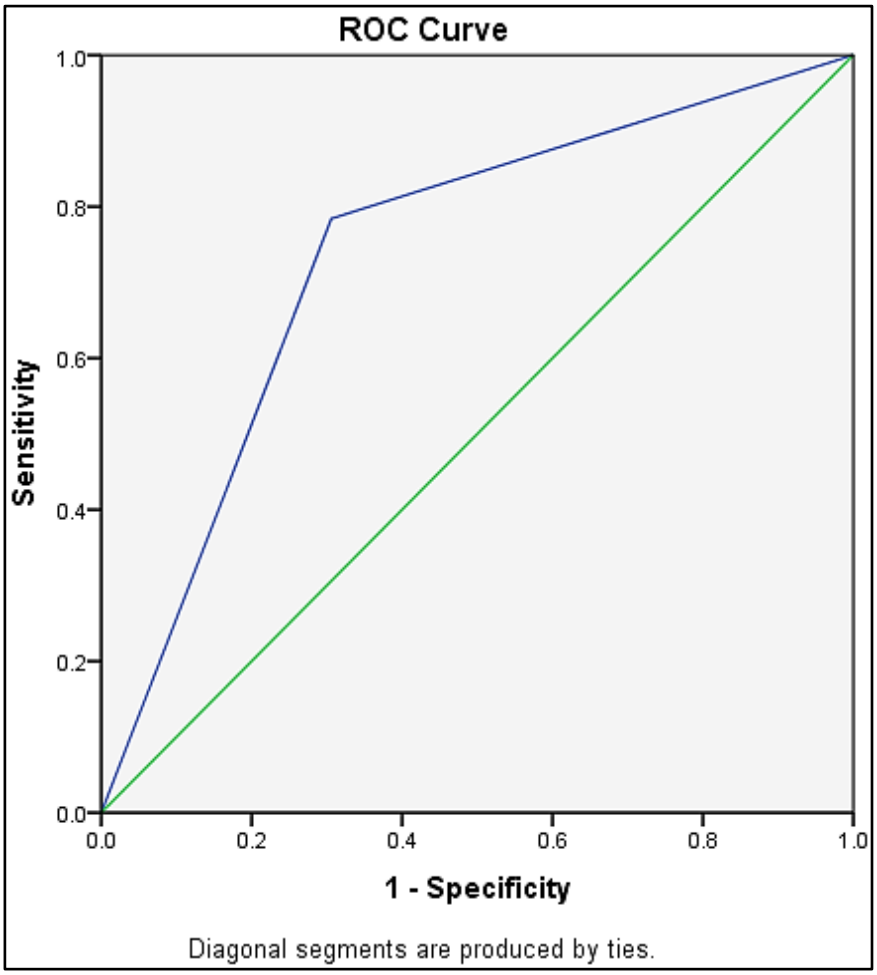
Table 3: Association of cardiac autonomic neuropathy with QTc interval

Corrected QT (QTc) interval	Cardiac Autonomic Neuropathyby overall score			Total
	Normal	Border-line	Abnormal	
QTc interval >440 milli seconds	15 (27.3%)	17 (30.9%)	23 (41.8%)	55 (55%)
QTc interval ≤440 milli seconds	34 (75.6%)	8 (17.8%)	3 (6.6%)	45 (45%)
Total	49 (49%)	25 (25%)	26 (26%)	100 (100%)

Majority of the patients with QTc interval more than 440 milli seconds have abnormal cardiac autonomic neuropathy (41.8%). But, in patients with QTc interval ≤440 milli seconds, majority of the patients don't have cardiac autonomic neuropathy (75.6%). This difference is significant statistically.(p<0.05; Significant).

At the QTc cut-off value of 440ms: Sensitivity was 78.4%,Specificity was 69.4%, Positive Predictive Value was 72.7%,Negative Predictive Value was 75.6%,Positive Likelihood ratio (+LR) = 2.56,Negative Likelihood ratio (-LR) = 0.31 and the accuracy was 74%.

Receiver operator characteristic (ROC) curve of QTc in predicting cardiac autonomic neuropathy



Area under ROC curve = 0.739 (95% C.I 0.639 to 0.839). P-value < 0.001; Significant.

Table 4: Association of Cardiac Autonomic Neuropathy with Gender

Cardiac Autonomic Neuropathy by overall score	Gender		Total
	Male	Female	
Normal (Score 0 &1)	33 (50%)	16 (47.1%)	49 (49%)

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Borderline(Score 2 to 4)	15 (22.7%)	10 (29.4%)	25 (25%)
Abnormal (Score ≥5)	18 (27.3%)	8 (23.5%)	26 (26%)
Total	66 (66%)	34 (34%)	100 (100%)

χ^2-value = 0.562; df = 2; p-value =0.755 (Not Significant).

Out of 100 patients studied, 66 (66%) patients are males, among which 33 (50%) patients doesn't have cardiac autonomic neuropathy, 15 (22.7%) patients have borderline cardiac autonomic neuropathy and remaining 18 (27.3%) patients have abnormal cardiac autonomic neuropathy.

Among 34 (34%) female patients, 16 (47.1%) patients don't have cardiac autonomic neuropathy, 10 (29.4%) patients have borderline cardiac autonomic neuropathy and remaining 8 (23.5%) patients have abnormal cardiac autonomic neuropathy.

There is no significant difference between proportion of males and females in having cardiac autonomic neuropathy. (p>0.05; Not significant).

Cardiac autonomic neuropathy in relation with habits

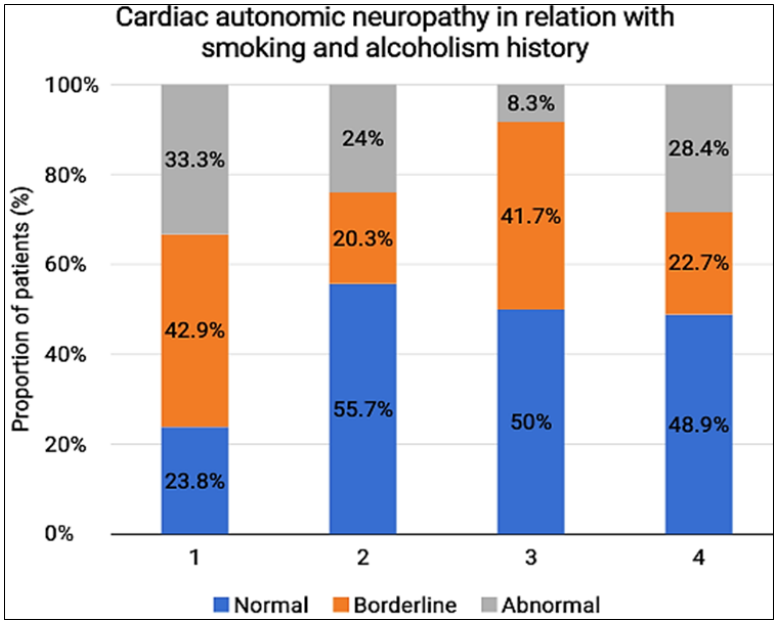

Table 5: Distribution of cardiac autonomic neuropathy with blood parameters

Blood parameters (Mean±SD)	Cardiac Autonomic Neuropathyby overall score			p-value
	Normal	Borderline	Abnormal	
Fasting blood sugar (FBS) (mg%)	118.8±19.9	129.7±28.7	147.2±30.0	<0.001; S
Post prandial blood sugar (PPBS) (mg%)	256.7±37.4	285.7±50.4	297.0±63.3	0.002; S
Blood Urea (mg%)	38.5±16.8	41.1±22.1	43.0±14.2	0.559; NS
Serum creatinine (mg%)	1.14±0.54	1.55±1.49	1.26±0.43	0.161; NS
HbA1C (%)	7.55±0.67	9.01±2.20	9.24±1.87	<0.001; S
Haemoglobin (gm%)	11.73±2.52	10.64±2.54	11.29±2.33	0.203; NS

S = Significant; NS = Not significant.

Fasting blood sugar values were significantly higher in patients with abnormal CAN compared with normal or borderline CAN patients (p<0.05; significant).Similarly postprandial blood sugar values and HbA1c was significantly higher in patients with abnormal CAN compared to others with normal or borderline CAN patients (p<0.05:significant).Very few patients with (HbA1c<8%) had CAN.But patients with HbA1C >8% had abnormal autonomic CAN in maximum numbers. This difference was found significant statistically (p<0.05;significant). Addiction to Smoking has significant correlation with development of CAN as shown in graph below.

Majority of the patients with QT interval more than 440 millisec had abnormal CAN.But in

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patients QT interval <440 milli sec, majority of patients did not have CA. This difference was found significant statistically (p<0.05; signify-cant). Majority of patients with DM, had QT interval >440 miilisec. This difference was found significant statistically. (p<0.05; significant).

Discussion

The results of our study illustrated the fact that CAN was common in diabetic patients with longer duration of DM, poor glycemic control and older age group. The sample size in our study 100 patients. We sub grouped patients according to the duration of DM, of <5 years, 5-10 years and >10 years as A, B and C respectively, to evaluate the impact of duration of diabetes onprevalence of CAN.Mohan *et al.*, studied the prevalence of CAN in 336 patients with NIDDM in south India. Prevalence of CAN increased with increased duration of diabetes.

According to many studies, prevalence of CAN ranged between 20%-73% in patients with T2DM. This huge variation in CAN prevalence was due to the inconsistency in the criteria used to diagnose CAN and significant differences in the study populations, particularly in relation to CAN risk factors (such as age, gender and DM duration amongst others)[10].According to cardiac autonomic function tests by Ewing's methodology, our study showed the prevalence of 51% (25% early and 26% definite CAN); It was comparable with prevalence 60% of PappachanJM *et al*. Study[1]. Patients with early CAN had abnormal heart rate variability, which emphasized the importance of HRV testing as screening modality similar to a study conducted by Vinik*et al*.[11] for early autonomic dysfunction in diabetes. In our study, 19 patients had autonomic dysfunction symptoms, 16 of them had definite CAN and 3 had early CAN; among 81 asymptomatic patients, 22 had borderline and 10 had definite CAN. This explained why CAN to be evaluated in asymptomatic patients too. According to Chen H S *et al*. study[12]asymptomatic patients can have silent ischemia or infarction and sudden arrhythmias. Abnormal cardiovascular reflex tests might be the important predictors of mortality in Type 2 diabetes and however subclinical autonomic dysfunction can be manifested within year in type 2 diabetes. Early observation by researchers was that near normal glycemic control seemed to be the most effective way to delay the onset of CAN and arrest its progression.Hence it was necessary to emphasize tight glycemic control[13]for individuals with CAN. Early identification of CAN helps in timely initiation of therapy with Vitamin E and antioxidant alpha lipoic acid.In ECG,in patients who had definite CAN out of 28 corrected QT interval, QTwas prolonged in 22 (78%) witha sensitivity of 78% and specificity of 82%respectively. In this study comparison of CAN with QT prolongation was found statistically significant[12].

Conclusion

In our study 24 patients with diabetes duration >10years, 28 patients in age group 51-60 years and 38 patients with poor glycemic control had CAN score≥2. The prevalence of cardiac autonomic neuropathy is high in type 2 DM in the study from our hospital, which increase with increase in the duration of diabetes, older age and poor glycemic control. It is important to diagnose CAN early in asymptomatic diabetics. Usage of 5 bedside autonomic function tests are very helpful in early diagnosis of CAN. There is significant correlation between CAN and QT prolongation. QT interval in ECG can be used to diagnose CAN with reasonable sensitivity and specificity. Strict control of blood sugar can delay the early development of CAN. Intensive control of blood sugar can delay the early development of CAN.

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