Section: Medicine

Research

UTILITY OF CORRECTED QT INTERVAL IN DIAGNOSIS OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN TYPE 2 DIABETES MELLITUS

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Abstract

Background: Cardiovascular autonomic neuropathy (CAN) is a common and serious complication of type 2 diabetes mellitus which is associated with a surge in cardiovascular mortality. Ewing's test, which is considered as a gold standard test for CAN is time consuming and cumbersome to execute. Corrected QT interval (QTc) prolongation is a method to diagnose CAN. In this study, we compare and correlate the Ewing's test score and QTc in patients with symptomatic and asymptomatic CAN and thereby assess the utility of using QTc in diagnosing CAN. This is an observational case-control study of 90 Type 2 Diabetes patients, who are divided into two groups as cases (30) and controls (60) based on the presence and absence of symptoms of autonomic neuropathy. Ewing's test score and QTc was done in all patients. 24(80%) patients in the case group had Ewing's test score of > 4 and prolonged QTc. 51(85%) patients in the control group had negative Ewing's test score and normal QTc. 9 (15%) patients in the control group had prolonged QTc and their Ewing's test score was borderline (2-3). A positive correlation between Ewing's test score severity and prolongation of QTc was present in patients with symptomatic cardiovascular autonomic neuropathy. We also ascertained that CAN was severe in patients with higher HbA1c and prolonged duration of Diabetes. We concluded that corrected QT interval could be used as a marker of cardiovascular autonomic neuropathy. Early diagnosis using QTc and adequate management of diabetes can prevent the progression of CAN and sudden death in diabetic patients.

INTRODUCTION

Diabetes Mellitus is a complex metabolic disorder due to absolute or relative deficiency of insulin secretion and/or its action. India is one of the epicentres of the global diabetes mellitus pandemic. Rapid socioeconomic development and demographic changes, along with increased susceptibility for Indian individuals, have led to the explosive increase in the prevalence of diabetes mellitus in India over the past four decades. It is estimated that the global prevalence of diabetes mellitus by 2040 is expected to be around 700 million.[1]

Complications of Diabetes are classified into acute and chronic complications. Microvascular diseases like neuropathy, retinopathy and nephropathy are some of the chronic complications. Diabetic autonomic neuropathy (DAN) is one of the peripheral polyneuropathies that occur in Diabetes. DAN may involve multiple organ systems causing cardiovascular, gastrointestinal (colonic hypomotility, enteropathy), urogenital (erectile dysfunction or female sexual dysfunction), ocular and sudomotor dysfunction. Many patients and physicians may miss DAN due to the subtle and varied symptoms.

Cardiovascular autonomic neuropathy (CAN), a type of DAN, is an under looked and deadly

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complication of type 2 diabetes mellitus. Clinical features vary from orthostatic hypotension to fatal myocardial infarction.[2] The pathophysiology of CAN is complex and multifactorial; the major culprit being hyperglycemia which leads to increase in production of reactive oxygen species and nitrogen (ROSN). ROSN induces DNA damage, resulting in endothelial dysfunction and formation of advanced glycation end products (AGE). AGE interacts with cells surface receptors leading to activation of inflammatory cascade causing neuronal and vascular damage.[3] Other hypotheses suggested are polyol pathway hyperactivity and increased diacylglycerol-protein kinase C cascade causing alterations the nerve tissue.[4] Ewing's battery is currently the gold standard method in clinical autonomic testing. Many studies has observed a close correlation between incidence of CAN and other diabetic microvascular complications, such as retinopathy, nephropathy and other peripheral neuropathies.[5]

Prolongation of corrected QT interval (QTc) is proved to be a specific indicator of CAN in many studies. Since ECG is widely available, cheap and practicable, we wish to study the utility of QTc in diagnosing CAN in our population. QT interval represents the duration of ventricular depolarization and repolarization and it is measured from the start of the QRS complex till the termination of the T wave. QT interval can vary with heart rate. To compare the QT interval with varying heart rates, we use the Bazett's formula which gives the QTc. QTc is considered prolonged if it is > 440 ms in men and > 460 ms in women.[6]

In our study, we compare and correlate the Ewing's test score and QTc in patients with symptomatic and asymptomatic CAN and thereby assess the utility of using QTc in diagnosing CAN. We also analyse the prevalence of QTc prolongation in asymptomatic CAN. Treatment of CAN is mainly aggressive control of diabetes along with lifestyle modification, treatment of dyslipidemia and supplementation with antioxidants and vitamins.[7]

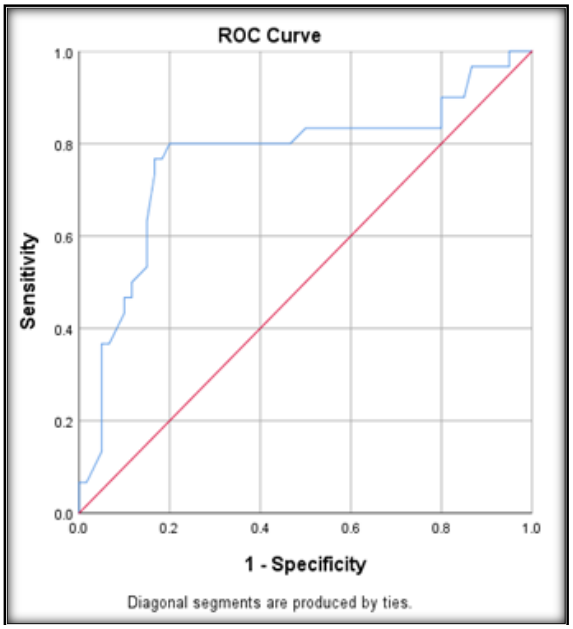
MATERIALS AND METHODS

An Observational case-control study was conducted at SRM Medical college hospital and Research Centre from September 2020 to March 2022 for 18 months. After obtaining consent from the patients, they were subjected to a detailed history including drug and family history, clinical examination, and investigations. A total of 90 type 2 diabetes mellitus patients admitted in medical wards satisfying the inclusion and exclusion criteria were included in the study. Patients with the presence of cardiovascular autonomic neuropathy symptoms (Palpitation, orthostatic hypotension, exercise intolerance) were taken as Cases and patients with the absence of these symptoms were taken as Control. Type 2 diabetes patients >18 years of age fulfilling 2019 American Diabetes Association (ADA) guidelines were included in the study. Diabetes patients with a history of alcohol consumption, consumption of drugs that prolong QT interval, sympatholytic drugs, patients with renal failure, Electrolyte abnormalities, obstructive airway disease and coronary artery disease, and family history of QT prolongation were excluded.

All the patients underwent the following investigations: Blood Sugar-Fasting & Postprandial, Blood Urea, Serum creatinine, Haemoglobin A1c, Blood Haemoglobin, Serum electrolytes including serum magnesium and calcium, urine routine and Electrocardiogram. The parameters in Ewing's battery and the procedure of performing each test and its normal value range are mentioned in detail in [Table 1].

RESULTS

From [Table 2], among total study population males were more than females, but higher prevalence of cardiovascular autonomic neuropathy was found in female subjects. More than half (66%) of the patients had diabetes mellitus for more than ten years, which was statistically significant. Among cases, 25 out of 30 (83%) patients had HbA1c>10, which is statistically significant [p value 0.0003]. There was higher prevalence of cardiovascular autonomic neuropathy in patients with HbA1c>10. Only 36% of controls had a higher HbA1c value>10.



As shown in [Table 3], there is a statistically significant difference in the cases and control groups in the Ewing's battery of Heart rate response to standing, valsalva and deep breathing, Blood pressure response to hand grip and standing, with a p-value of <0.05.

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[Table 4] shows that all the patients (30) in the case group have Ewing's test score of > 4 and 24 of them (80%) have prolonged QTc as well. In the control group 23 patients had negative CAN with normal QTc. 37 patients in the control group had a CAN score of 2-4 out of which 9 patients had prolonged QTc and 28 patients had normal QTc.

[Figure 1] indicates that the cut-off value of QTc interval in cardiovascular autonomic neuropathy in type 2 diabetes mellitus is 443.5ms with 80% sensitivity and 80% specificity. The AUC is 0.768 with significant p value of 0.0001.

Table 1: EWING'S BATTERY

TEST	TECHNIQUE	NORMAL RESPONSE
Heart rate response during deep breathing	With the patient at rest and supine, heart rate is monitored by ECG while the patient breathes in and out at 6 breaths/min.	A difference in increase in heart rate of > 15 bpm is normal and < 10 bpm is abnormal. The value for the expiration-inspiration ratio of the R-R interval is calculated.>1.21 is normal, 1.1-1.2 is borderline and, <1.1 is abnormal.
Heart rate response to standing	During continuous ECG monitoring, the R-R interval is measured at beats 15 and 30 after standing	Typically, a tachycardia is followed by reflex bradycardia. The 30:15 ratio should be > 1.03. <1 is abnormal and between 1-1.03 is borderline
Heart rate response to Valsalva maneuver	The subject forcibly exhales into the mouthpiece of a manometer to 40 mm Hg for 15 s during ECG monitoring	Healthy subjects develop tachycardia and peripheral vasoconstriction during strain and an overshoot bradycardia and rise in blood pressure with release. The normal ratio of longest to shortest R-R is > 1.2 and <1.1 is abnormal and between 1.1 and 1.2 is borderline
Systolic blood pressure response to standing	Systolic blood pressure is measured in the supine subject. The patient stands and the systolic blood pressure is measured after 2 min.	Normal response is a fall of < 10 mm Hg; borderline is a fall of 10–29 mm Hg; abnormal is a fall of > 30 mm Hg with symptoms.
Diastolic blood pressure response to isometric exercise	The subject squeezes the handgrip dynamometer at 30% pressure for a maximum period of 5 min.	A normal response for diastolic blood pressure is a rise of > 16 mm Hg in the opposite arm.11-15mmg hg is borderline and <10 is abnormal

Table 2: Distribution of subjects used in the study

Variable		Controls		Cases		P value
		No	%	no	%	
Gender	Male	42	70	12	40	0.006
	Female	18	30	18	60	
Duration of Diabetes mellitus	<5 years	23	38.5	3	10	0.019
	5-10 years	10	16.5	7	23.3	
	>10 years	27	45	20	66.7	
HbA1c	6-7.9	20	33.3	1	3.3	0.0003
	8-9.9	18	30	4	13.3	
	10-11.9	13	21.6	16	53.3	
	>12	9	15	9	30	

Table 3: Parameters of subjects used in the study

Parameters		Controls		Cases		P value
		no	%	no	%	
HR response to Valsalva	>1.21	26	43.33	1	3.3	<0.0001
	1.1-1.20	33	55	11	36.66	
	<1.1	1	1.6	18	60	
HR Variability to deep breathing.	> 15	28	46.7	1	3.3	<0.0001
	11-14	32	53.3	14	46.7	
	<10	1	1.7	15	50	
HR response to standing	>1.04	58	96.6	1	3.3	0.0003
	1.01-1.03	1	1.7	8	6.7	
	<1	1	1.6	21	70	
BP response to hand Grip	>16	55	91.6	1	3.3	<0.0001
	11-15	4	6.7	25	83.3	
	<10	1	1.67	4	13.33	
BP response to standing	<10	29	48.3	3	10	<0.0001
	11-29	30	50	20	66.7	
	>30	1	1.67	7	23.33	

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Table 4: CAN score

VARIABLES		No of patients	
		Cases	Controls
CAN score	0-1	0	23
	2-4	0	37
	> 4	30	0
QTc in CAN score < 4	Normal QTc	0	51
	Prolonged QTc	0	9
QTc in CAN score > 4	Normal QTc	6	0
	Prolonged QTc	24	0

DISCUSSION

Cardiovascular autonomic neuropathy is common in diabetes and one of the most under diagnosed conditions associated with higher morbidity and mortality. QTc interval acts as a diagnostic tool to assess cardiovascular autonomic neuropathy.

In our study, overall sex distribution showed a predominance of male patients. However, CAN prevalence was more in female patients (60%) compared to the study done by Ashok k et al which showed no significant differences in prevalence of CAN between two sexes.[8]

On analyzing the duration of diabetes, we see that 66% of our study population had diabetes for >10 years. This is comparable to the study by J M Pappachan et al which showed increased prevalence of CAN if there is longer duration of diabetes (Odds ratio-2).[9] The study by Jae-Seyung Yun et al also shows mean duration of diabetes in CAN patients is 10.1 years same as our study.[10] Yun-ru-lai et al say that HbA1c>10% is strongly associated with increased prevalence and severity of CAN as compared to our study in which CAN prevalence is more if HbA1c>10%.[11] In a study by Arif et al, diabetic patients had a mean HbA1c of -11.36 ± 3.612 whereas in our study 83 % of cases group had HbA1c > 10 with mean of 10.8.[12]

According to case control study by Ashtoush pathak et al involving 100 diabetic patients to determine autonomic neuropathy, positive HR response to deep breathing (68% patients) was the most sensitive test followed by abnormal HR response to standing (52% of patients).[13] This was similar to our study in which heart rate response to standing (70%) followed by heart rate response to valsalva (60%) were the sensitive parameters for CAN.

In a study by Ukpabi et al., fifty-one out of the 176 diabetic subjects (29%) had CAN. The prevalence of QTc prolongation in diabetic patients with CAN was 12%. In our study prevalence of QTc prolongation was 33% which included both cases and controls. In his study he also concluded that although QTc correlated strongly with cardiac autonomic neuropathy, there was no definite relationship between QTc prolongation and CAN severity.[14] According to Kumar S et al, in his cross sectional study involving 100 diabetic patients, QTc prolongation was linked to early onset of CAN similar to our study in which 15% of the controls had prolonged QTc and CAN score <4.15 In studies by Arif et al, Kumar s et al, QTc prolongation in asymptomatic patient was not significant in comparison to our study in where 15% of controls had prolonged QTc with borderline CAN scores.[12,15]

CONCLUSION

We concluded that corrected QT interval positively correlates with cardiovascular autonomic neuropathy. Thus, QTc prolongation can be used as a marker of cardiovascular autonomic neuropathy. Diagnosis using QTc interval and adequate management of diabetes can prevent the progression of CAN and sudden death in diabetic patients. We also would like to emphasise that even in asymptomatic patients QTc to be evaluated for early diagnosis of CAN and monitoring the progression of CAN. Further studies to ascertain the development of CAN in asymptomatic patients with QTc prolongation and to evaluate the role of strict diabetic management in delaying the progression of CAN should be done.

Limitation

Recent advances - Power spectral analysis and radio nucleotide study for correlation in symptomatic CAN couldn't be done due to cost and non-availability.

Single centre study where the sample size is small.

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