



## QTC Prolongation As An Indicator Of Cardiac Autonomic Neuropathy In Type 2 Diabetes Mellitus

**Saurabh Sultania**

Dr. Saurabh Sultania, Resident, Department of Medicine, Rohilkhand Medical College and Hospital, Bareilly.

**Rajeev Kumar Gupta**

Dr. Rajeev Kumar Gupta, Lecturer, Department of Medicine, GSVM medical college, Kanpur.

**Malini Kulshrestha**

Dr. Malini Kulshrestha, Professor, Department of Medicine, Rohilkhand Medical College And Hospital, Bareilly.

### ABSTRACT

Diabetes mellitus refers to a group of common metabolic disorder with micro and macro vascular complications. Cardiac autonomic neuropathy (CAN) is a common but frequently overlooked complication of diabetes mellitus. CAN is an important cause of morbidity and mortality in diabetic patients as it is associated with high risk of cardiac arrhythmias and sudden death related to silent myocardial ischaemia. Numerous non invasive tests have been described for the diagnosis of CAN. These tests although sensitive and reproducible, are time consuming and not suitable for screening a large population. Prolongation of the corrected QT interval (QT<sub>c</sub>) in the electrocardiogram (ECG) has been found to be a specific, rapid and objective method for detecting cardiac autonomic neuropathy in many studies.

The present study aims to evaluate the correlation between QT<sub>c</sub> interval and diabetic cardiac autonomic neuropathy. 50 patients of Type 2 Diabetes Mellitus who fulfilled the inclusion and exclusion criteria were included in the study. 5 cardiovascular autonomic function tests as described by Ewing et al were performed on the patients and the patients were categorized as per Ewing's criteria. QT<sub>c</sub> interval was calculated as per the Bazett's formula.

Out of 50 patients of type 2 diabetes mellitus, CAN was found in 35 patients (70%). The percentage of early, definite and severe CAN was 51.43%, 31.43% and 17.14% respectively. Patient's with CAN had mean QT<sub>c</sub> 450 ± 13.2 ms. whereas patients without CAN had mean QT<sub>c</sub> 410 ± 12.4 and this difference was found to be statistically significant (p<0.05). CAN is a common and under diagnosed complication of diabetes mellitus. Early detection of CAN helps in effective prevention of cardiovascular disease related morbidity and mortality. Prolongation of QT<sub>c</sub> interval is relatively easy, quick and reliable method for identification of CAN in diabetic patients.

### KEYWORDS

Diabetes Mellitus, Cardiac Autonomic Neuropathy, QTC interval.

### INTRODUCTION

Diabetes mellitus is characterized by chronic hyperglycaemia with disturbances in carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both.<sup>1</sup>The global figure of people suffering from diabetes mellitus is estimated to rise from current estimate of 415 million to 642 million by 2040. The number of people with type 2 diabetes mellitus is increasing in every country and 75% of people with diabetes mellitus are living in developing countries.<sup>2</sup>With an increasing incidence worldwide, diabetes mellitus will be a likely leading cause of morbidity and mortality in the future.<sup>3</sup>

Diabetic neuropathy occurs in ~50% of individuals with long-standing type 1 and type 2 diabetes mellitus. It may manifest as polyneuropathy, mononeuropathy, and/or autonomic neuropathy.<sup>4</sup> CAN is an often overlooked and common complication of diabetes mellitus.<sup>5</sup>Cardiac autonomic neuropathy(CAN) is characterized by damage to the autonomic nerve fibres that innervate the heart and blood vessels resulting in abnormalities of heart rate control and vascular dynamics.<sup>6</sup>The prevalence of CAN varies between 20%-73% in patients with type -2 diabetes mellitus.<sup>7</sup>CAN is an important cause of morbidity and mortality in diabetic patients as it is associated with high risk of cardiac arrhythmias and sudden death related to silent myocardial ischaemia.<sup>8</sup>

Numerous non-invasive tests have been described for the diagnosis of CAN.<sup>9</sup>Although sensitive and reproducible, these tests are time consuming and are not suitable for screening a large number of diabetic patients. Prolongation of the corrected QT interval (QT<sub>c</sub>) in the electrocardiogram (ECG) has been found to be a rapid and specific method for detecting CAN in many studies.<sup>10</sup>

The present study aims to evaluate the correlation between QT<sub>c</sub> interval and diabetic cardiac autonomic neuropathy.

### MATERIAL AND METHODS

#### Study design:-

The study is a cross sectional study in which the patients were selected as per the inclusion and exclusion criteria.

#### Source of Data:-

50 patients of Type 2 diabetes mellitus admitted in Department of Medicine, RMCH, Bareilly during the period of January 2016 to September 2016 were taken for the study.

#### Inclusion criteria:-

Type 2 diabetes mellitus patients in the age range of 20-75 years.

#### Exclusion criteria

1. Patients of type 2 diabetes mellitus with evidence of heart failure, hypertension, cardiac arrhythmias and other cardiovascular diseases.
2. Patients of type 2 diabetes mellitus with COPD.
3. Patients of type 2 diabetes mellitus with renal failure.
4. Patients of type 2 diabetes mellitus and liver diseases.
5. Patients of type 2 diabetes mellitus with electrolyte abnormalities.
6. Patients of type 2 diabetes mellitus and cerebrovascular diseases.
7. Patients on drugs known to interfere with autonomic function tests and QT<sub>c</sub> interval.
8. Patients on alpha blockers, beta blockers and vasodilators.
9. Patient with clinically overt neuropathy due to causes other than diabetes.
10. Anemia

**Tests for measurement of Cardiac autonomic function:-**

Cardiac dysautonomia was assessed by cardiovascular responses to five non invasive cardiac autonomic function tests as recommended by Ewing et al.7

These are as follows:-

- a. Heart rate variability during deep breathing (by doing ECG) (normal response > 15 beats/minute, borderline 11-14 beats/minute; abnormal response < 10 beats/minute).
- b. Immediate heart rate response to standing (by doing ECG) (normal response if > 1.04; borderline between 1.01 and 1.03; and abnormal if < 1.00).
- c. Heart rate response to Valsalva manoeuvre (by doing ECG) (Normal ratio is >1.21, abnormal 1.20 or less).
- d. Blood pressure response during sustained hand grip (normal response >16 mmHg, borderline response 10-15mmHg, abnormal response <10mmHg).
- e. Blood pressure response to standing (normal response <10 mmHg, borderline response 11-29mmHg, abnormal response >30mmHg).

Based on the results of the above tests, the autonomic dysfunction in Type -2 diabetes mellitus patients is categorized as none, early, definite and severe.11

**None :-** all tests normal or 1 test borderline.

**Early:-** one of 3 heart rate tests abnormal or 2 borderline.

**Definite:-** two heart rate test abnormal.

**Severe :-** 2 heart rate tests abnormal with one or both blood pressure tests abnormal or both borderline.

The QTC interval was determined by Bazett's formula ( $QTC = QT/\sqrt{R-R}$ ), and a value exceeding 440 msec. was considered prolonged.12

**Statistical Methods**

Results were expressed as Mean ± Standard Deviation. Students "t" test was used to compare mean's of different groups. P value < 0.05 was considered significant.

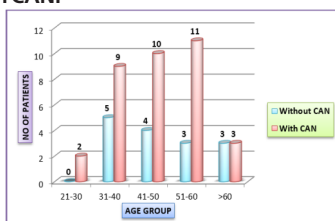
**Results:-**

The mean age of diabetic patients was  $48.76 \pm 10.27$  years (range: 20-70 years). Majority of the cases were in the age group of 30-60 years. Mean age in the group with CAN was  $48.657 \pm 10.134$  years. The mean age in the group without CAN was  $48.66 \pm 11.3116$  years. This difference was found to be statistically insignificant ( $P=0.9975$ ).

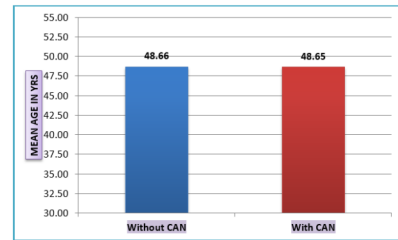
**Table no. 1:- Age group distribution of patient without CAN and with CAN.**

Age Group	Without CAN	With CAN	Total
21-30	0	2	2
31-40	5	9	14
41-50	4	10	14
51-60	3	11	14
>60	3	3	6
Total	15	35	50

**Graph no. 1:- Age group distribution of patients without CAN and with CAN.**



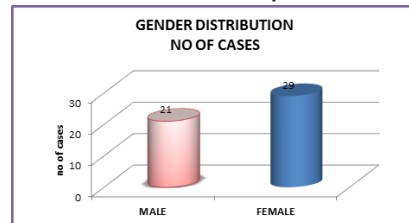
**Graph no. 2:- Mean age (in years) of patients without CAN and with CAN.**



**Gender distribution**

Total no of females were 29(58%).  
Total no of males were 21(42%).

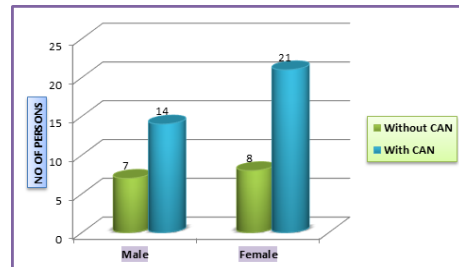
**Graph no. 3:- Gender distribution of patients.**



**Table no. 2:- Gender distribution of patients without CAN and with CAN.**

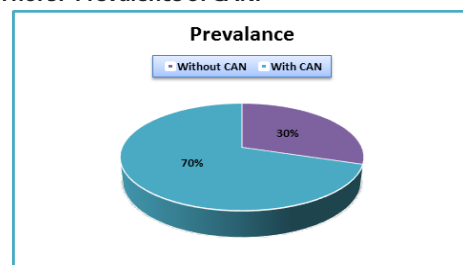
	Male	Female
Without CAN	7	8
With CAN	14	21

**Graph no. 4:- Gender distribution of patients without CAN and with CAN.**



Out of 50 patients CAN was found in 35 patients .

**Graph no. 5:- Prevalence of CAN.**

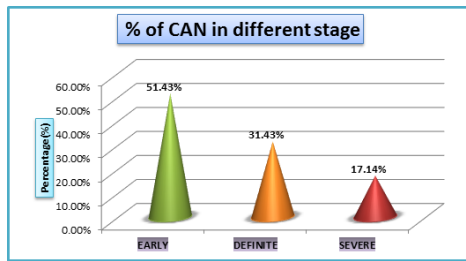


We categorized the abnormal autonomic function tests as per Ewing's criteria where the abnormality was sub-grouped as early, definite and severe.

The observation revealed that 51.43% of our diabetic patients had early, 31.43% had definite and 17.14% had severe CAN.

**Table no. 3:- Percentage of CAN in different stages.**

	NO OF CASES	Percentage
<b>EARLY</b>	18	51.43%
<b>DEFINITE</b>	11	31.43%
<b>SEVERE</b>	6	17.14%

**Graph no. 6:- Percentage of CAN in different stages.****Duration of DM**

The mean duration of diabetes was found to be  $4.24 \pm 3.9779$  years (range 1-15 years.)

**Table no. 4:- Duration of diabetes and CAN.**

Duration of diabetes	With CAN	Without CAN
1-5 yrs	21	15
6-10yrs	8	0
>10yrs	6	0
Total	35	15

**QT<sub>c</sub> Interval In Diabetic Patients**

Patients with CAN had mean QT<sub>c</sub>  $450 \pm 13.2$  ms whereas patients without CAN had mean QT<sub>c</sub>  $410 \pm 12.4$  ms and this difference was found to be statistically significant (P value < 0.05).

**Table no.5:-QT<sub>c</sub> Interval In Diabetic Patients**

CAN	QT <sub>c</sub> INTERVAL
Diabetics without CAN	$410 \pm 12.4$ ms
Diabetics with CAN	$450 \pm 13.2$ ms

**Discussion:-**

Cardiac Autonomic Neuropathy is one of the most important and underdiagnosed complication of diabetes. A total of 50 patients who were diagnosed to have type 2 diabetes mellitus based on ADA criteria were included in this study after considering the various inclusion and exclusion criteria. In this study out of 50 type 2 diabetics (21 males, 29 females) 70% were defined as having cardiac autonomic neuropathy (CAN). The prevalence of autonomic neuropathy in this study was very similar to the reported prevalence in some other studies (table no 6)

**Table no 6:-**

Researcher	CAN	EARLY	DEFINITE	SEVERE
Present study	70%	51.43%	31.43%	17.14%
Low et al <sup>13</sup>	73%	NA*	NA	NA
Ekta et al <sup>14</sup>	80%	11	0	20
Aggarwal et al <sup>15</sup>	69.23	46	30	24
Manjula et al <sup>16</sup>	74	56	6	0
Zainab et al <sup>17</sup>	72.8	NA	NA	NA
Domuschiev et al <sup>18</sup>	59.5	NA	NA	NA

\*NA:- not available

The mean age of patients with CAN in this study was found to be  $48.657 \pm 10.134$  years which was similar to the study conducted by Zainab et al ( $50.6 \pm 7.8$  years)<sup>17</sup>, whereas mean age was  $59.4 \pm 7.9$  years and  $42 \pm 8.9$  years in study conducted by Anca Motaitianu<sup>19</sup> and S.R Manjula et al<sup>16</sup> respectively.

In this study early CAN was found in 51.43% patients, 31.43% patients had definite CAN and 17.14% patients had severe CAN. Similarly, Aggarwal et al<sup>15</sup> found early CAN in 46% patients, definite in 30% and severe CAN in 24% patients, Ekta et al<sup>14</sup> found early CAN in 11% patients, severe CAN in 20% patients, 69% patients could not be classified. Uday. B. Nayak et al<sup>20</sup> found early CAN in 50% patients and severe CAN in 50% patients. S.R Manjula et al<sup>16</sup> found early CAN in 56% patients and definite CAN in 6% patients.

There is a well described association between QT<sub>c</sub> prolongation and cardiac dysautonomia in diabetes mellitus. Bellavere et al<sup>21</sup> in their study mentioned that diabetic cardiac autonomic neuropathy should be included among the long QT syndromes. In this study, mean QT<sub>c</sub> interval was prolonged in diabetic patients with CAN ( $450 \pm 13.2$ ms) when compared to patients without CAN ( $410 \pm 12.4$ ms). Similar observations were made by Mathur CP et al ( $449.31 \pm 21.9$ ms)<sup>22</sup>, Barthwal et al ( $426 \pm 24.4$ ms)<sup>23</sup> Shimabukuro et al ( $449 \pm 13$ ms)<sup>24</sup>.

**Conclusion:-** The prevalence of cardiac autonomic neuropathy (CAN) in type 2 diabetics was found to be 70% and it correlated with the duration of diabetes.

CAN is a common and under diagnosed complication of diabetes mellitus. CAN plays an important role in the development of silent myocardial ischaemia. Early detection of CAN helps in effective prevention of cardiovascular disease related morbidity and mortality. Cardiovascular autonomic function tests as described by Ewing et al are simple yet time consuming. Prolongation of QT<sub>c</sub> interval is relatively easy, quick and reliable method for identification of CAN in diabetic patients.

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