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Use of Corrected QT Interval as a Diagnostic Tool for Assessment of Cardiac Autonomic Neuropathy in Diabetic Patients

KEYWORDS: Corrected QT interval Cardiac Autonomic Neuropathy Diabetes

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ABSTRACT *Objectives: Use of corrected QT interval as a diagnostic tool for assessment ofCardiac autonomic neuropathy (CAN) in diabetic patients.Methods: All diabetic patients underwent tests to detect cardiac autonomic neuropathy (CAN) and electrocardiography (ECG) to calculate corrected QT interval.Results: Out of 50 patients 38(76%) were males and 12(24%) were females, Type1 diabetes mellitus16 (32%) and Type2 diabetes mellitus34 (68%). Severe cardiac autonomic neuropathy (CAN) was seen when duration of diabetes was14.92+6.23years, early cardiac autonomic neuropathy (CAN) in 11.54+6.44years and no cardiac autonomic neuropathy (CAN) when diabetes duration was 8.9+5.45years. In severe cardiac autonomic neuropathy (CAN) QTc was 467.14+ 45.44milliseconds, early CAN QTc was420.47+ 55.33milliseconds and in no CAN was378.18+ 38.86 milliseconds.Conclusions: Patients with severe cardiac autonomic neuropathy (CAN) had longer duration of diabetes. Patients with severe CAN had higher levels of fasting blood sugar than patients without CAN. Patients with cardiac autonomic neuropathy (CAN) had significantly prolonged QTc.*

INTRODUCTION

Diabetes mellitus affects about 8% of the World's population. Diabetes mellitus is a common metabolic problem seen in clinical practice. After the advent of oral hypoglycemic drugs and insulin therapy the survival of diabetic patients is increasing. Autonomic neuropathy is a well known complication of long standing diabetes. Although insidious in onset, it may be associated with substantial morbidity and mortality. In fact, sudden death and silent myocardial ischemia has been attributed to cardiac autonomic dysfunction. The cardiovascular complications of diabetes mellitus can be classified into three groups – atherosclerotic coronary artery disease, diabetic cardiomyopathy, and cardiac autonomic neuropathy (CAN)CAN is a common form of diabetic autonomic neuropathy and causes abnormalities in heart rate control as well as central and peripheral vascular dynamics. The incidence of silent myocardial ischemia and sudden death is also high in patients with CAN. Several non-invasive tests, such as cardiac autonomic function analysis by Ewing methodology, downward tilting baroreflex sensitivity test, analysis of spontaneous beat to beat blood pressure and heart rate variabilities, time domain heart rate variability and heart-rate turbulence parameters assessed on 24 hour digital Holter recordings and new indicator test based on the measurement of sweat production after exposure to dermal foot perspiration can be used for the diagnosis of CAN.These tests, although sensitive and reproducible, are laborious and time consuming and therefore are not practical for screening large number of patients with diabetes mellitus. Prolongation of the corrected QT interval (QTc) in the electrocardiogram (EGG) has been found to be a specific, rapid and objective method for detecting cardiac autonomic neuropathy in most studies. The present study aims to evaluate the correlation between QTc interval and diabetic cardiac autonomic neuropathy.

AIM OF THE STUDY

To study the use of corrected QT interval (QTc) as diagnostic tool for assessment of cardiac autonomic neuropathy (CAN) in diabetic patients.

MATERIALS AND METHODS

SOURCE OF DATA:

All patients of Type 1 and Type 2 diabetes mellitus admitted in department of General Medicine, Gandhi Medical College, Secunderabad, during the period of 2011 to 2013 were taken into the study considering the inclusion and exclusion criteria.

STUDY DESIGN:

The study is an observational study in which patients were selected taking into consideration inclusion and exclusion criteria. Detailed history and clinical examination was done and necessary investigations were done.

Autonomic Test Scoring

A number of tests based on cardiovascular reflexes are now available for detecting even minimal dysfunction of autonomic nervous system. Ewing 75 while classifying autonomic abnormalities used three tests based on heart rate response (i.e., Sinus arrhythmia, Valsalva ratio, Postural tachycardia index) and two tests based on B.P. response (Postural drop in Systolic BP, and Rise in Diastolic BP on sustained hand grip). Patients were grouped as normal or early, definite, severe and atypical pattern of autonomic dysfunction. An alternative to this classification was suggested by some author's as to give each individual a score of 0, 1, or 2 depending upon whether the test response falls into normal, borderline or abnormal range respectively for a given autonomic function test. Sum of the scores obtained by each individual for different test would be "over all autonomic test score". Later Ewing felt this would correlate with the severity of autonomic dysfunction. This method could assess even atypical pattern and avoid such over simplification regarding autonomic dysfunction as terming it as present or absent. We have followed this scoring system in present study. . QT interval was calculated by electrocardiograph. The QTc were determined with Bazett's formula ($QTc = QT / \sqrt{RR}$) and a value exceeding 440 milliseconds were considered prolonged. The results were analyzed by appropriate statistical methods.

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Cardiac autonomic function tests
Resting heart rate
< 100 beats / min - 0 points
100 – 110 beats / min - 0.5 points
>110 beats / min - 1 point

Postural hypotension (fall in systolic B.P)
< 20 mm Hg - 0 points
20 – 30 mm Hg - 0.5 points
>30 mm Hg - 1 point

Valsalva ratio (longest RR interval: shortest RR Interval)
> 1.2 - 0 points
– 1.10 - 0.5 points
< 1.10 - 1 point

Heart rate variability on deep breathing
> 15 beats / min - 0 points
10 – 15 beats / min - 0.5 points
<10 beats / min - 1 point

Increase in diastolic blood pressure during sustained hand grip
>15 mm Hg - 0 points
10 – 15 mm Hg - 0.5 points
<10 mm Hg - 1 point

CAN SCORE
No CAN - 0 - 0.5 points
Early CAN - 1 - 2 points
Severe CAN > 2.5 points
In this study, in addition to these tests QTc interval was included.

INCLUSION CRITERIA:
Type 1 and type 2 diabetes mellitus patients in the age range of 20 to 70 years with the duration of diabetes ranging from 2 to 12 years.

EXCLUSION CRITERIA:
1. Patients with diabetes mellitus with evidence of heart diseases (acute coronary syndromes, heart failure), respiratory, renal, hepatic, and cerebrovascular disease.
2. Patients with diabetes mellitus having hypertension, electrolyte imbalance, alcoholism history.
3. Patients with diabetes mellitus with previously abnormal ECG's.
4. Patients with diabetes mellitus who are taking drugs known to interfere with autonomic function tests and QTc interval.

OTHER INVESTIGATIONS:
Hb, TC, DC, ESR, Urine Routine, FBS, PPBS, Blood urea, Serum Creatinine, Serum Electolytes, Serum Bilirubin, AST, ALT, Chest X-Ray – PAview, Echocardiography.

STASTICAL METHODS:
Results were expressed as Mean ± Standard Deviation, Students "t" test was used to compare Means of different groups, p value < 0.05 was considered significant.

OBSERVATIONS AND RESULTS
Out of the 50 patients 38 (76%) were males and 12 (24%) were females.16 (32%) patients had Type1 diabetes and 34 (68%) patients had Type 2 diabetes. 22 (44%) of patients had No CAN, 21 (42%) had Early CAN, and 7 (14%) had severe CAN.

It was also observed that severity of CAN was not related to the age of the patients. But, rather its severity was well correlating with duration of diabetes. No CAN was seen when the duration of diabetes was 8.9 ± 5.4yrs, Early CAN when the duration was 11.54 ± 6.44 yrs, Severe CAN when the duration was 14.92 ± 6.23 yrs. No CAN Vs Severe CAN, P value <0.025.

Resting heart rate was found to be more in patients with severe CAN, compared to those with either No CAN or Early CAN P value <0.0001. Valsalva ratio was less in patients with Severe CAN P value <0.0054. Heart rate variability on deep breathing was also depressed in patients with Early CAN and Severe CAN, P values <0.0001 in both cases. Postural hypotension was also significant in patients with Early CAN and Severe CAN Pvalue being <0.014 and <0.0001 respectively. Rise in diastolic BP to sustained hand grip was less than normal in patients with Severe CAN (P value <0.0001).QTc interval prolongation was significant in cases with Severe CAN (P value<0.001). QTc prolongation was not significant in patients with Early CAN (P value < 0.2).

CAN score for severity of Autonomic Neuropathy
Table 5: Distribution of patients according to CAN score

No CAN (0 – 0.5)	22 (44%)
Early CAN (1 – 2)	21 (42%)
Severe CAN (> 2.5)	7 (14%)

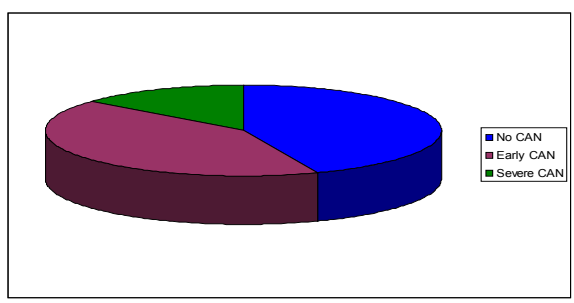

Figure 10: Distribution of patients according to CAN Score

CATEGORISATION OF PATIENTS AGE, BASED ON CAN SCORE
Table 6: Categorization of patients age, based on CAN Score

CAN SCORE	Age (years)
No CAN	46.18 ± 15.20
Early CAN	48.85 ± 14.16
Severe CAN	41.71 ± 18.12

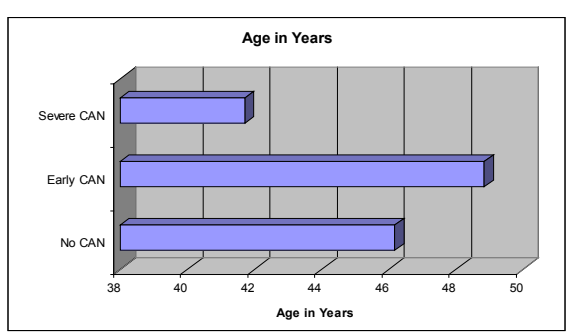

Figure 11: Categorization of patient's age, based on CAN Score

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CORRELATION BETWEEN DURATION OF DIABETES AND CAN SCORE

Table 7: Correlation between duration of DM and CAN Score

CAN SCORE	Duration of Diabetes (Years)
No CAN	8.90 ± 5.45
Early CAN	11.54 ± 6.44
Severe CAN	14.92 ± 6.23

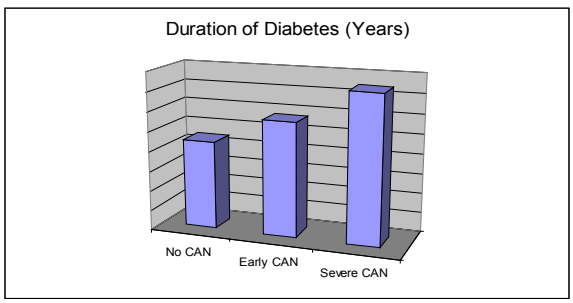

Figure 12: Correlation between duration of DM and CAN Score

Table 8: Students 't' test – Test of Significance for the Correlation between duration of DM and CAN Score

CAN SCORE	P value	
No CAN Vs Early CAN	= 0.2	Not significant
No CAN Vs Severe CAN	< 0.025	Significant

QTc - INTERVAL

Table-19: QTc interval in diabetic patients

CAN SCORE	QTc (ms)
No CAN	378.18 ± 38.86
Early CAN	420.47 ± 55.33
Severe CAN	467.14 ± 45.44

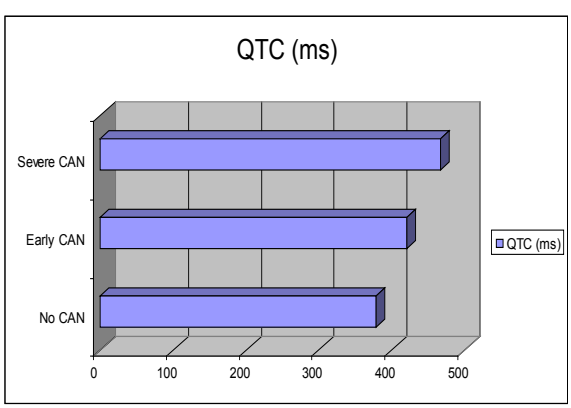

Figure 18: QTc – intervals in diabetic patients

Table 20: Students 't' test – Test of Significance for QTc interval prolongation in CAN

CAN SCORE	P value	
No CAN Vs Early CAN	< 0.2	Not Significant
No CAN Vs Severe CAN	< 0.001	Significant

DISCUSSION

Diabetic autonomic neuropathy is also one of the major complications of longstanding diabetes. It is difficult to ascertain the exact prevalence of diabetic autonomic neuropathy since it is often asymptomatic or presents with vague symptoms.

PREVALENCE OF DIABETIC – CAN

In our study CAN was present in 28 patients (54%) out of 50 patients. This correlated with prevalence of CAN as stated by other studies, i.e., Nijhawan et al 78 60%, Lakhotia et al79 64%, Barthwal et al 80 36%, Kumar et al 8160%, Krishna et al82 48%, and Veglio et al 83 63%

AGE

Age of the patients does not correlate with severity of CAN. This was also seen in other studies. Correlation between age of the patients and severity of CAN , found in the study was No CAN 46.18 ± 15.20yrs, Early CAN 48.85± 14.16yrs and Severe CAN 41.71 ±18.12yrs.

DURATION OF DIABETES

We found that the duration of diabetes correlates with the severity of CAN, i.e., in the study done by Kumar et al the duration of diabetes was, Without CAN 8.13.19 ± 2.81yrs; With CAN 8.52 ±6.26yrs respectively, Barthwal et al (Without CAN 8.03.51 ± 2.81yrs; With CAN 7.11 ±3.49yrs) Shimbakuro et al (Without CAN 8.45.3 ± 2.1yrs; With CAN 9.6 ±1.1yrs) Present study(Without CAN 8.90 ± 5.45yrs; With CAN 13.23 ±7.10yrs) .

EFFECT OF GLYCEMIC CONTROL

Our study shows that diabetics with CAN have a higher fasting blood glucose levels than diabetics without CAN, i.e., No CAN 233± 90.19 mg/dl, Early CAN 223.90 ± 87.30 mg/dl; and Severe CAN 271±44.47 mg/dl. Student't' test showed significant P value (<0.05) when it was done to know the effect of glycemic control on CAN. No CAN Vs Early CAN -Not Significant (0.2 P value) and No CAN Vs. Severe CAN - Significant (<0.05 P value.)

SYMPTOMS OF AUTONOMIC NEUROPATHY

32 out of 50 diabetics had one or the other symptoms referable to autonomic neuropathy. Sweating abnormalities were noted in 32% of our patients. This is in comparison with other studies Lakhotia et al 26%, Krishna et al 38%, Balachander et al 38%. Fullness of stomach was noted in 30% of our patients. Similar results were obtained in other studies Lakhotia et al 16%, Krishna et al 34%, Balachander et al 20% Constipation was noted in only 8% of our patients which is similar to that mentioned by Lakhotia et al ie 12%. Diarrhea as a complaint was noted in only 12% of our patients which is lesser when compared to other studies mentioned. Lakhotia et al 18%, Krishna et al 28%, Balachander et al 38% .Similarly impotence was also present in only 8% when compared to other studies. . Lakhotia et al 54%, Krishna et al 9%, Balachander et al 22.2%. Postural dizziness was noted in 30% of our patients. Similar results were noted in other studies. Lakhotia et al 44%, Krishna et al 58%, Balachander et al 46% .

QTc INTERVAL PROLONGATION

There is a well described association between abnormalities of autonomic function and QTc prolongation. Bellavers et al, in their study mentioned that diabetic cardiac autonomic neuropathy should be included among long QT syndromes.In our present study QTc interval was more prolonged in diabetic patients with severe CAN (467.14 ± 45.44 ms P value < 0.001, significant) when compared to patients with early CAN (420.47 ± 55.33 ms P value < 0.2, Not significant) and No CAN (378.18 ± 38,86 ms P < 0.2 Not significant).Similar observations were made by Barathwal et al 80 (426 ± 24.4 ms), Veglio etal (421 ± 26ms) Kumar et al (423 ± 22 ms), Shimbakuro et al (449 ± 13 ms), Mathur CP et al (449.31 ± 21.9) and Pappachan JM et al.

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CONCLUSIONS

The duration of diabetes, and fasting blood sugar values were significantly higher in patients with diabetes with severe CAN. Prolongation of QTc interval correlates well with degree of cardiac autonomic neuropathy in diabetics.QTc prolongation may be considered as pointer towards diabetic cardiac autonomic neuropathy in the busy outpatient setting where it is not possible to perform the conventional battery of tests. Recognition of QTc prolongation may help identify diabetics with risk of sudden cardiac death.

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