Study of relationship between QTC prolongation and cardiac autonomic neuropathy in Diabetes mellitus

N Natarajan[1], M S Ramaiyah[2]

[1,2]Associate Professor, Department of General Medicine , Kerala Medical College, Palakkad, India.

Address for correspondence: Dr N Natarajan, Associate Professor, Department of General Medicine , Kerala Medical College, Palakkad, India.

Email: natarajan2016@rediffmail.com

ABSTRACT

Objective: Cardiac Autonomic neuropathy is one of the complications in diabetic patients. This study intends to detect the prevalence of QTc prolongation in diabetic patients as well as its relationship with cardiac autonomic neuropathy.

Materials & Methods: The present study was conducted on 50 diabetic patients. Cardiac autonomic neuropathy was assessed by non-invasive tests: Deep breathing test, Valsalva ratio ,Immediate heart rate response to standing 30:15,B.P rise with sustained hand grip and postural hypotension. Scoring and grading were done for cardiac autonomic neuropathy . Even QT interval and QTc interval were determined.

Results: Out of 50 diabetic patients, 22(44%) were males and 28 (56%) females. 26 patients (52%) having grade I cardiac autonomic neuropathy had no prolonged QTc interval . While, 24 patients (48%) had QTc prolonged were associated with grade II, III and IV cardiac autonomic neuropathy. The sensitivity and specificity of prolonged QTc were 46% and 100%, respectively.

Conclusion: QTc prolongation correlated positivity with degree of cardiac autonomic neuropathy in diabetic patients.

Keywords: Diabetes mellitus, Cardiac autonomic neuropathy, QTc interval

INTRODUCTION

Cardiac autonomic neuropathy (CAN) in diabetes has been called a "silent killer", because so few patients realize that they suffer from it, and yet its effect can be lethal. Early sub clinical detection of CAN and intervention are of prime importance for risk stratification in preventing sudden death due to silent myocardial infarction[1].

Prolongation of QTc as marker of Cardiac Autonomic Neuropathy was first described by Flugelman et al 1980[2]. QTc prolongation in Diabetes is associated with increased incidence of sudden cardiac death (Kahn JK et al 1987)[3]. Similar studies have observed and substantiated the role of prolonged QTc prolongation in sudden cardiac death (Jermendy et al 1994[4] and Bellavare et al 1988[5]). Moreover, prolongation of QTc interval has been shown to predict sudden cardiac death in patients with both type 1 and type 2 diabetes mellitus and also prolongation of QTc interval has also been found to be an independent risk factor for strokes in patients with type 2 diabetes mellitus[6,7]. Hence , diabetic patients having both QTc prolongation and cardiac autonomic neuropathy could be utilized for the risk stratification for cardio-vascular and cerebro-vascular morbidity and mortality.

The objective of this study to make effect on the existing knowledge that QTc prolongation in diabetes detects cardiac autonomic neuropathy.

MATERIALS & METHODS

The present study was conducted on 50 patients of diabetes mellitus admitted in medical ward , Department of Medicine, Kerala Medical College and Hospital , Palakkad from January 2015 to December 2015. Type 1 and 2 diabetes mellitus and having symptoms of autonomic neuropathy like, postural dizziness, impotence, gustatory sweating, atonic urinary bladder, gastroparesis, neuropathy, tingling sensation, hyperaesthesia and numbness were included. Cases with evidences of heart diseases, electrolyte imbalance, abnormal resting ECGs, taking drugs known to interfere with autonomic function tests were excluded

Cardiac dysautonomia was assessed by cardiovascular response to five non invasive autonomic function tests as recommended by Ewing's et al[8]. These include: Valsalva Ratio: (Heart rate response to Valsalva maneuver) , Deep Breath Test , 30:15 ratio (Immediate heart rate response to standing) , Postural Hypotension (Blood pressure response to standing) and SHGT (Blood pressure response to sustained handgrip).

Scoring was done as per criteria advocated by Bellavere et al. (1983)[9]. A score of 2 or more denoted definite cardiac autonomic neuropathy. Autonomic neuropathy was also graded as advocated by Lakhotia et al. (1997) [10]from O-IV, grade I onwards had definite cardiac autonomic neuropathy.

These patients who had definite cardiac autonomic neuropathy were subjected to resting ECG and QT interval , R-R interval calculated and the QTc were determinate. The QTc was calculated based on Bazett's formula; QTc=Q-T/vR-R and a value exceeding 440 msec was considered prolonged. 25 healthy volunteers were also subjected to resting ECG and their mean QTc remained below 440 msec. The sensitivity and specificity of QTc was determined.

RESULTS

Fifty cases of diabetes mellitus were subjected to a battery of 5 tests to find the incidence of cardiac autonomic neuropathy (CAN).

Table 1. Age wise distribution of Diabetic cases

Age Group	Number of Cases	Percentage
10-20	4	8
21-30	3	6
31-40	10	20
41-50	21	42
51-60	12	24
Total	50	100

As evident from table 1 ,most of the patients (42%) belonged to age group between 41-50 years . In this , 22 cases (44%) were males and 28 cases (56%) were females in this study, so the male: Female ratio was 1:1.27 (Graph 1). Besides , 41 (82%) cases were suffering from type 2 diabetes, while only 9 cases (18%) had Type 1 DM. Additionally, 30 (73.17%) patients had family history of type 2 diabetes mellitus (Table 2) and most of the patients (70%) had duration of 5-10 years (Table 3) . Regarding the symptoms of autonomic neuropathy, postural dizziness (54%) was most common symptom and next common symptom was impotence (46%), while diabetic diarrhea (12%) was the least common symptom (Table 4).
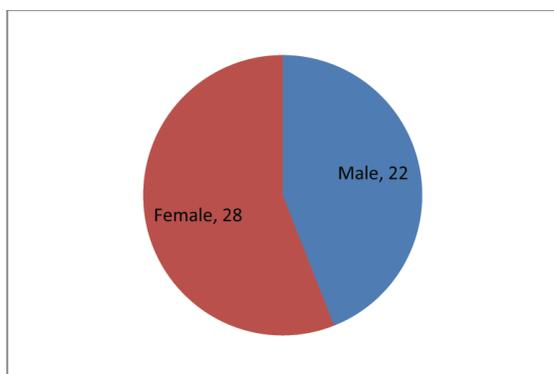
Graph 1. Sex wise distribution of cases

Table . 2 Type and family history of Diabetes mellitus (DM)

Type of DM	No. of Cases	Family history of DM
Type 2 DM	41 (82%)	30 (73.17%)
Type 1 DM	9(18%)	0 (0)

Table 3. Duration of Diabetes Mellitus

Duration of years	No. of Cases	Percentage (%)
< 5 years	7	14
5-10 years	35	70
> 10 years	8	16
TOTAL	50	100

Table 4. Frequency of symptoms of Autonomic Neuropathy

Symptoms	No. of Cases	Percentage (%)
Postural dizziness	27	54
Impotence	22	46
Gustatory Sweating	16	32
Atonic urinary bladder	9	18
Gastric atony	10	20
Constipation	9	18
Diabetic diarrhea	6	12

Table . 5 Cardiac autonomic tests in diabetic patients

Valsalva Ratio						
Sr. No	Fall in diastolic BP (mmHg)	Score	Type 2 DM	Type 1 DM	No. Cases	Percentage (%)
1	>1.21	0	13	5	18	36
2	1.11-1.20	1	16	2	18	36
3	< 1.10	2	12	2	4	28

Deep breath test						
Sr. No	E.I Ratio (beat/min)	Score	Type 2 DM	Type 1 DM	No. Cases	Percentage (%)
1	>15	0	9	4	13	26
2	11-15	1	13	1	14	28
3	< 10	2	19	4	23	46

Sr. No	30:15 ratio	Score	Type 2 DM	Type 1 DM	No. Cases	Percentage (%)
1	>15	0	9	4	13	26
2	11-15	1	13	1	14	28
3	< 10	2	19	4	23	46

Postural Hypotension

Sr. No	Fall in diastolic BP (mm Hg)	Score	Type 2 DM	Type 1 DM	No. Cases	Percentage (%)
1	>16	0	31	6	37	74
2	11-15	1	7	2	9	18
3	< 10	2	3	1	4	8

SHGT

Sr. No	Fall in diastolic BP (mmHg)	Score	Type 2 DM	Type 1 DM	No. Cases	Percentage (%)
1	>16	0	30	4	34	68
2	11-15	1	7	3	10	20
3	< 10	2	4	2	6	12

As evident from Table 5, valsalva ratio, deep breath test, 30:15 beat ratio ,postural hypotension test and SHGT were abnormal in 28%, 46%, 34%, 8% and 12 % of cases ,respectively.

**Table 6. Scoring and grading of Cardiac Autonomic neuropathy**

Scoring of CAD		
Score	No of Cases	Percentage (%)
2	9	18
3	12	24
4	14	28
5	6	12
6	6	12
7	2	4
8	1	2

Grade	I	II	III	IV	No of Cases
Type 2	21	12	1	7	41
Type 1	5	-	-	4	9

Grading of CAD

The scoring for CAD showed that 28% cases were having score 4 and 2% of cases had score 1, whereas 28% cases had score 4. Regarding grading, 52%, 24%, 2%, 22% had grade I, II,III and IV CAN ,respectively (Table 6). Our study also showed that 23 (46%) cases had QTc>440 msec , while the remaining 27 (54%) cases had QTC < 440 msec (Table 7).

Table 7. QTc interval in Diabetic Patients

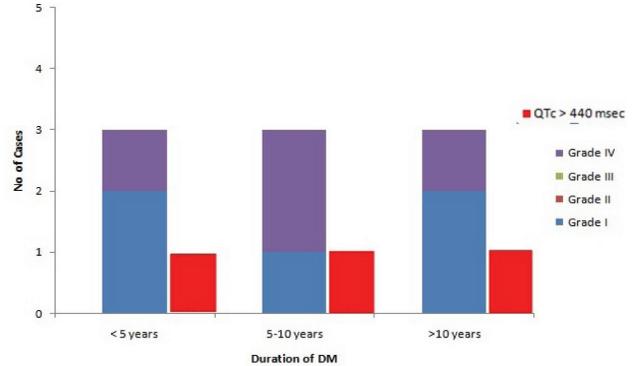| QTc	<440 msec	>440 msec
Type 2	21	20
Type 1	6	3
Total	27	23
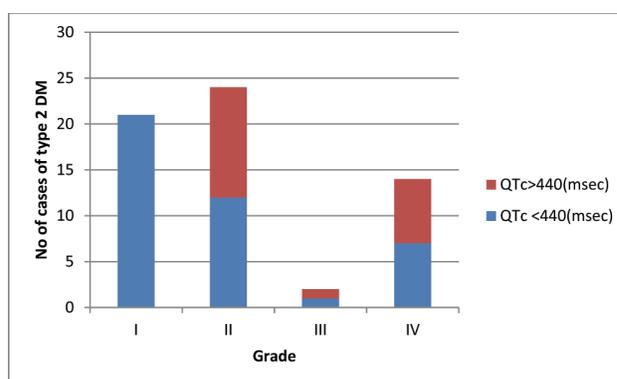
Graph 2. Relationship between grading of CAN and QTc in Type 2 DM

In type 2 DM, 21 cases were having grade I CAD and none of them had QTc > 440 msec. 12 patients having grade II CAD were associated with QTc > 440 msec. One case with grade III CAD was having QTc > 440 msec and also one patient had grade IV CAD and all of these patients had QTc > 440 msec (Graph 2).

Regarding type 1 DM, 5 cases were of grade I autonomic neuropathy and none had QTc > 440 msec. There was no case of grade II and III CAD, but had 4 cases of grade IV autonomic neuropathy with QTc > 440 msec (Graph 3). There was no case with score 2 or 3 having QTc > 440 msec. But 50% having score 4 had QTc > 440 msec, whereas all those cases who were having score > 5 had QTc > 440 msec (graph 4).

7 cases of type 2 DM having < 5 years of duration belonged to grade I autonomic neuropathy with QTc > 440 msec. 50 % of patients with 5-10 years duration having grade I,II and IV CAD respectively, had QTc > 440 msec. 7 cases with > 10 year of duration , had grade II, III,IV CAN ,respectively had prolonged QTc (Graph 5).

Regarding type 1 DM , 2 out of 3 cases with < 5 years of duration had grade I CAD and one case had grade IV CAD with QTc > 440 msec. 3 cases with 5-10 years of duration; 1 case had grade 1 CAD and 2 cases had grade IV CAD and in this one case had prolonged QTc. 3 cases with >10 years duration of these 2 were of grade II autonomic neuropathy and 1 case had grade 1 autonomic neuropathy and only 1 case in them had QTc> 440 msec (Graph 6). Considering QTc prolongation as an indicator of CAN, it was observed to have sensitivity of 46% and specificity of 100% with no false positive response.

Graph 3 Relationship between CAN and QTc in Type 1 DM

Graph 4.   QTc interval and Cardiac autonomic neuropathy

Graph 5. Relationship between the duration of type 2 DM, CAD and QTc interval.

Graph 6. Relationship between the duration of type 1 DM , CAD and QTc interval

DISCUSSION

50 diabetic patients were subjected to a battery of standard tests to determine cardiac autonomic neuropathy (CAN) and also to establish the relationship between CAN and QTc interval.

Out of the 50 patients studied, the majority of the patients i.e. 21 (42%) belonged to age group 41-50 years. A study by Bathwal et al. in 1996 had   mean age studied was 41.6 years [11]. In Lakhotia et al. study the mean age studied was 45 years [10]. Whereas in Ewings study [13] the cases belonged to age group between 24-63 years.

Out of the 50 patients, 28 patients were females. Thus females dominated the males in this study and there were patients of type 2 diabetes mellitus   grossly outnumbered the type I diabetics. The former being 82% and latter being only 18% and majority of type II diabetics had a family history of diabetes while the reverse was true for type I diabetics.

The majority (70%) of patients had diabetes of 5-10 years duration. In Bathwal et al. (1996) study, the mean duration of diabetes was 6.5 years [11].   19 (38%) patients had nephropathy (as indicated by urine albumin) and these patients were having duration of diabetes of > 7 years. Thus there is direct relationship of nephropathy with the duration of diabetes. QTc is prolonged in majority of cases (14 out of 19 cases), who had nephropathy

Valsalva Ratio: 28% of cases had an abnormal response (i.e. <1.10). Previous studies by Ewing's [12], Bathwal et al [11] and Lakhotia et al [10] had abnormal response of 26% , 22.3 % and 20 % , respectively .
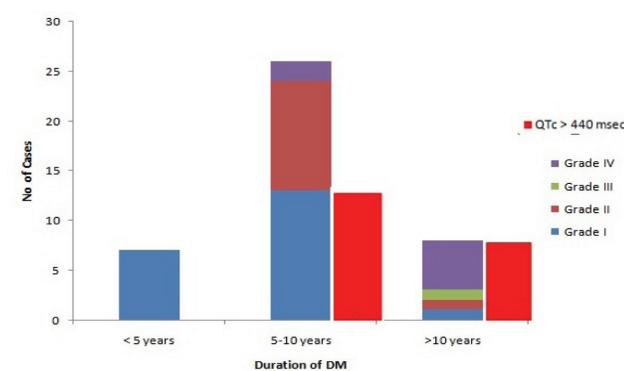
Deep Breath Test: 23 (46%) patient had abnormal response in this study. In Ewing's study [12], it was 42%, Bathwal et al study [11], it was 38.3% and in Lakhotia et al. study [10], the abnormal response was 42% abnormal with 20% borderline cases.
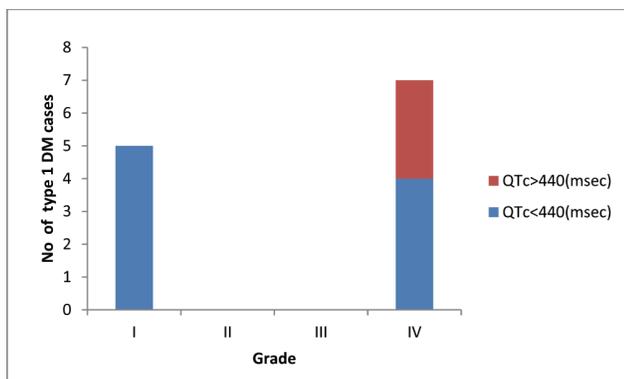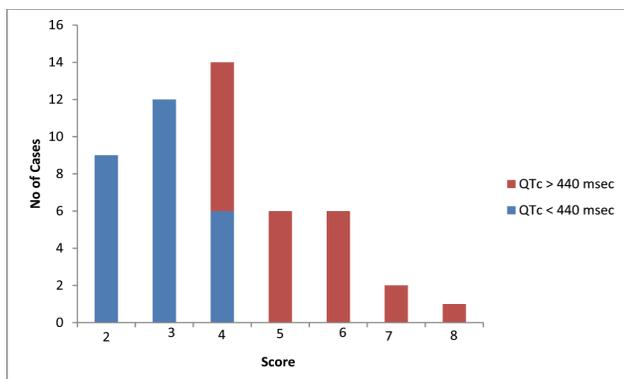
30:15 Ratio : Our study had 38% cases with abnormal response in this study. In Ewing's study [12], it was 38% abnormal cases, In Bathwal et al study [11] it had 17% abnormal cases , where as in Lakhotia et al [10] study it was 42% abnormal with 2% border line cases.

Postural Hypotension: This study had 8% cases with abnormal response In Ewing study [12] it was 16% abnormal cases and in Bathwal et al study [11], it was 4.4% abnormal cases and in Lakhotia et al study [10], it was 16% abnormal .

SHGT : 12% cases had an abnormal response in this study. In Ewing's study [12], it was 14% abnormal cases and in Barthwal et al study [11] it was 14.9% and in Lakhotia et al study [10] it was 26% abnormal cases.

Previous studies by Ewing's [12] and Barthwal et al [11] had not mentioned the borderline cases, however Lakhotia et al study [10] had stated about borderline cases. Our study had higher score when compared to Lakhotia et al study [10] , it might be due to less sample size in their study .

Our study shows that the abnormal result (%) for deep breath test was highest among other tests, which was also corroborated with the previous studies [10,11,12]. The 30:15 ratio and Valsalva ratio stood 2nd and 3rd position respectively, while the postural hypotension and SHGT are less commonly affected. This clearly demonstrates that the development of autonomic neuropathy typically involves the parasympathetic fibers before the sympathetic nerve fibers [13]. Our study shows that 26 patients had grade 1 CAN with no QTc prolongation, these patients had average duration of type 2 DM between 5-6 years. Even type 1 DM patients (duration more than 10 years) having grade 1 CAD had no QTc prolongation, .

Further, 12 patients having grade II CAN had mean duration of diabetes of 7-8 years. Moreover, all these patients had QTc prolongations in the range of 446-470msec. While the maximum 470 msec QTc being observed in a patient having 12 years of duration. The minimum 446 msec QTc was observed in a patient with 7.5 year duration of diabetes. Hence it strongly indicates that severity of cardiac autonomic neuropathy and QTc prolongation appear to have a relationship with duration of type 2 diabetes mellitus .

There was only one patient with grade III cardiac autonomic neuropathy of whom QTc was 472 msec but this patient had duration of diabetes of 16 years.

11 patients had grade IV cardiac autonomic neuropathy of which 7 cases were of type 2 DM and 4 cases were of type 1 DM group. The mean duration of diabetes mellitus in type 2 group was 13-15 years and the range of QTc was 454-480msec. However in the type 1 DM group the duration of disease ranged from 3 to 14 years.

Interestingly the one case with the 3 years duration had QTc of 470 msec. Whereas another case with 14 years duration had QTc of 460 msec. Finally the duration of type 2 DM had a definitive predictive value for both CAN and QTc prolongation while the reverse was true for type 1 DM .

Considering QTc prolongation as an indicator of CAN, it was observed to have sensitivity of 46% and specificity of 100% with no false positive response. Our study was comparable with Gonin JM et al.(1990) [14] , which showed 89% specificity with sensitivity of 57%. Veglio et al (1995)[15] has found specificity to be 89% with sensitivity as low as 15%. However, Bartwal et. al. (1996) study [11] had sensitivity as high as 79% and specificity of almost 100%. This predictive value of prolonged QTc in detection of cardiac autonomic neuropathy was not comparable with any the earlier studies.

Based on our findings, QTc prolongation is not an accurate indicator for diagnosis of cardiac autonomic neuropathy, based on high specificity and low sensitivity. Hence this test could be used as a supportive test to detect CAN, however the patients should also be subjected to a battery of standard tests to find the incidence of CAN. QTc has been clearly established as a predictor of sudden cardiac death. Considering the above fact it is prudent that diabetic patients must have an optimal control of blood glucose , since prolonged QTc has been clearly established as a predictor of sudden cardiac death. So diabetic patients should be screened for cardiac autonomic neuropathy regularly and those with abnormal QTc should be closely monitored. Hence, there is a strong need for earlier and regular evaluation of autonomic nervous system in type 2 diabetics to prevent further complications. The data from the current study demonstrated that diabetics had cardiac sympathetic and cardiac parasympathetic nervous system involvement. The presence of symptoms and the involvement of the autonomic nervous system suggests that autonomic dysfunction depends on the duration of diabetics.

In conclusion, the results of the investigation indicate there was prolongation of QTc in DM patients with different degree of CAN. A battery of standard tests could be effective in detecting CAN. Further research on a large sample size is required to further elucidate the findings of this study and effectiveness of QTc prolongation may be taken as a direct evidence of cardiac autonomic neuropathy in diabetics.

REFERENCES

1. Khandoker AH, Jelinek HF, Palaniswami M. Identifying diabetic patients with cardiac autonomic neuropathy by heart rate complexity analysis. Biomed Eng Online. 2009 ;8:3. doi: 10.1186/1475-925X-8-3.

2. Flugelman MY, Kauher Y, Abinader EG, Barzilai D. Rest. ECG patterns in diabetics without evidence of IHD. Diabetes1980; 29 (suppl 2): 76A

3. Kahn JK, Sisson JC, Vinik AI. QT interval prolongation and sudden cardiac death in diabetic autonomic neuropathy. J Clin Endocrinol Metab. 1987 ;64(4):751-4.

4. Jermendy G. QT prolongation and sudden unexpected death. Lancet. 1994 19;343(8899):742.

5. Bellavere F, Ferri M, Guarini L, Bax G, Piccoli A, Cardone C, and Fedele D .Prolonged QT period in diabetic autonomic neuropathy: a possible role in sudden cardiac death? Br Heart J. 1988 ; 59(3): 379–383.

6. Hilsted J. Pathology in diabetic autonomic neuropathy. Diabetes.1982; 31:730.

7. Astrup AS, Tarnow L, Rossing P, Hansen BV, Hilsted J, Parving HH. Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in TYPE 1diabetics patients with diabetic nephropathy. Diabetes care 2006; 29:334-9.

8. Ewing DJ, Campbell IW, Clark BF. The natural history of diabetic autonomic neuropathy. QJ Med 1980; 49:95-108.

9. Bellavere F, Bosello G, Fedele D, Cardone C, and Ferri M. Diagnosis and Management of diabetic autonomic neuropathy Br. Med. J. 1983:287:61.

10. Lakhotia M, Shah PK, Vyas R, Jain SS, Yadav A, Parihar MK. Clinical dysantonomia in DM – a study with seven autonomic reflex function test. J Assoc Physicians India. 1997;45:271-274.

11. Bathwal S.P. et al. QTc prolongation is diabetes mellitus – an indicator of Cardiac autonomic neuropathy. JAPI1997;45(1):15-17.

12. Ewing DJ, Campbell IW, Clarke BF. Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. Ann Intern Med. 1980 ;92(2 Pt 2):308-11.

13. Sucharita S, Ganapathi Bantwal, Jyothi Idiculla, Vageesh Ayyar, and Mario Vaz. Autonomic nervous system function in type 2 diabetes using conventional clinical autonomic tests, heart rate and blood pressure variability measures. Indian J Endocrinol Metab. 2011; 15(3): 198–203.

14. Gonin JM, Kadrofske MM, Schmaltz S, Bastyr EJ 3rd, Vinik AI.Corrected Q-T interval prolongation as diagnostic tool for assessment of cardiac autonomic neuropathy in diabetes mellitus. Diabetes Care. 1990;13(1):68-71.

15. Veglio M, Chinaglia A, Borra M, Perin PC. Does abnormal QT interval prolongation reflect autonomic dysfunction in diabetic patients? QTc interval measure versus standardized tests in diabetic autonomic neuropathy. Diabet Med. 1995 ;12(4):302-6.