QT Dispersion in Patients of Diabetes Mellitus without Manifest Cardiac Dysautonomia.

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***Abstract**: The present study is aimed to detect this complication in diabetic individuals by measuring QT interval and its dispersion. 50 patients of diabetes mellitus were selected for the study. Cardiac dysautonomia was detected in 25 out of 50 patients. Further subgroup analysis revealed the fact that more the QT interval and dispersion severe was the cardiac dysautonomia.*

INTRODUCTION

Autonomic neuropathy is a well recognized complication of diabetes mellitus, with reported incidence from 20-40%. However, symptomatic cardiac autonomic neuropathy (CAN) manifests in about 5% of diabetic patients,[1,2] but when present, it is associated with the increased mortality attributed to prolonged QT interval predisposing to ventricular arrhythmias, silent ischaemia, and cardiac arrest.[3-4] Hence, its early detection and early prevention is essential. A battery of tests such as heart rate response to Valsalva manoeuver, B.P. response to standing and handgrip, are available but these are cumbersome and not easy to perform in every patient. Therefore, there was a need of simple, non-invasive bed side test to detect early autonomic involvement in diabetes.[3] In 1980, for the first time, an association of prolonged QT interval with cardiac autonomic neuropathy was established which opened the possibility of rapid objective method to detect cardiac dysautonomia. Since then, great emphasis has been laid down on the QT interval and QTc as an indices of autonomic dysfunction in diabetes. Since the QTc interval is considered as a measurement of myocardial depolarization and repolarization, influenced by central autonomic neural tone and kinetics of myocardial cells,[4] therefore, QT dispersion (QTd) with correction of QT with heart rate (QTc) is considered better than QTc in evaluation of cardiac dysautonomia. Since it has been hypothesised that irregular and regional cardiac autonomic denervation in diabeties mellitus leads to increased QT dispersion,[6] hence, this study was carried out.

MATERIAL AND METHODS

***Patients Selection**:* 50 diagnosed cases of diabetes mellitus (WHO, 1999) irrespective of type, age and sex attending the diabetic clinic at Pt.BD Sharma PGIMS, Rohtak from 2000-2002, were enrolled in this study after application of exclusion criteria i.e. patients with clinical, radiological or electrocardiographic evidence of heart disease, hypertension, thyrotoxicosis, severe respiratory disease, electrolyte imbalance, renal dysfunction, stroke, parkinsonism, retinopathy, chronic liver disease, alcoholism, congenital prolongation of QT interval. 10 healthy volunteers served as controls.

After obtaining detailed history and complete clinical examination, all the cases and controls were subjected to standard 12 lead surface ECG at paper speed of 50mm/sec. Following five conventional cardiovascular autonomic function tests (mentioned with score values shown in table 1) were performed on the same day after ensuring that there was no fasting hyperglycaemia.

Patient's Groups And Control : Based on the test score on a scale of 10 (each abnormal value of test was given a score of 2), the patients were divided into two groups i.e. group 1 and group 2. **Group-1** included 25 patients of diabetes mellitus with autonomic system involvement as indicated by one or more of five abnormal cardiovascular function tests (tests score 2-10)

***Table 1 :** Normal, borderline, and abnormal values of cardiovascular autonomic function tests with scores*

Name of the test	Normal (Score 0)	Borderline (Score 1)	Abnormal (Score 2)
1. Heart rate response to valsalva manoeuver (valsalva ratio)	≥ 1.21	1.11-1.20	≤ 1.10
2. R-R interval variation during deep breathing (Expiration : Inspiration ratio)	≥ 1.21	1.11-1.20	≤ 1.10
3. Immediate heart rate response to standing (30^{th}:15^{th} beat ratio)	≥ 1.04	1.01-1.03	≤ 1.00
4. Blood pressure response to standing	≤ 10 mmHg	11-29 mmHg	≥ 30 mmHg
5. Blood pressure response to sustained hand-grip	≥ 16 mmHg	11-15 mmHg	≤ 10 mmHg

Group-2 included 25 patients of diabetes mellitus without autonomic system involvement as indicated by normal response to all the five cardiovascular function tests or just one borderline test result (test score 0-1)

Controls It included 10 healthy volunteers with normal QT interval.

Measurement of QTc and QTd interval : All the measurements were done on 12 leads ECG manually using a scale by single observer. The QT interval was measured from the onset of QRS complex to the point of T-wave offset. The QT interval was corrected for the heart rate and final calculations were done for corrected QT interval i.e. QTc. The QTc dispersion (QTd) was determined as the difference between the maximum and minimum value of QTc interval calculated in 9 selected leads except lead aVR of the same recording.

Statistical analysis: The data was analyzed using the SPSS software programme. All the data were expressed as mean±95% confidence interval. The significance of differences between groups was tested by students unpaired 't' test. The correlation of QTc dispersion with individual autonomic function test was expressed by Pearson's Correlation Coefficient 'r'. A p value <0.05 was considered statistically significant.

RESULTS

The study included 50 patients of diabetes mellitus equally divided into two groups of 25 each. Patients in both the groups were matched with respect to age, gender, BMI, heart rate and blood pressure. However, there was significant difference in duration of diabetes in two groups.

Cardiovascular reflex responses in patients of diabetes are shown in Table: 2.

The heart rate response to deep breathing and immediate heart rate response to standing were abnormal in most of the patients (25 out of 30) in Group **1** patients, while Group **2** patients showed no abnormality (Table 2).

In Group **2** patients, only 2 patients showed borderline heart rate

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response to deep breathing and 30th to 15th beat ratio. None of these patients satisfy the criteria of autonomic dysfunction. This group formed a contrast group with no or minimal autonomic dysfunction as compared to Group **1.**

Table 2: *Cardiovascular autonomic function tests in patients with diabetes mellitus*

Test Result	Group 1(n=25)	Group 2(n=25)
A) Heart rate response to deep breathing		
1) Abnormal	18	0
2) Borderline	7	2
3) Normal	0	23
B) Immediate heart rate response to standing		
1) Abnormal	13	0
2) Borderline	12	2
3) Normal	0	23
C) Valsalva ratio		
1) Abnormal	9	0
2) Borderline	11	0
3) Normal	5	25
D) BP response to sustained hand grip		
1) Abnormal	4	0
2) Borderline	9	0
3) Normal	12	25
E) BP response to standing		
1) Abnormal	2	0
2) Borderline	10	0
3) Normal	13	25

Categorization of Autonomic Dysfunction in Group 1 patients

Group **1** patients were further categorized into two subgroups **1A.** Mile to moderate involvement (Test Score £ 4). 12 patients of group **1** had mild to moderate involvement. **1B.**Moderate to severe involvement (Test Score ³ 4) 13 patients had moderate to severe involvement.

QTc indices and QTc dispersion analysis

QTc intervals in both group of patients and controls are presented in Table No. 3. Depending on the grading of group 1 patients into A & B, the QTc in both the subgroups is presented in Table 4.

The QTc min was comparable in all the groups while QTc max was significantly prolonged in group 1 patients. The QTc dispersion i.e. difference between QTc max and QTc minimum, was found significantly higher in group 1 patients indicating its direct relation with cardiac dysautonomia.

The QTc dispersion, though significantly prolonged in both the subgroups, was found to be more prolonged in patients of group 1B i.e., patients in which autonomic dysfunction was severe, indicating the direct correlation between severe dysautonomia and QTc dispersion.

DISCUSSION

Autonomic neuropathy is a microvascular complication known to occur in both types of diabetes mellitus and remains one of the most challenging problem.[1] Development and severity of cardiac autonomic neuropathy (CAN) is not all or none phenomenon but represent a continuous progression of disease, hence, it's severity is directly related to duration and degree of hyperglycemia. Ewing *et al*[3] have advocated five autonomic function tests out of which at least two must be abnormal for a definite diagnosis of CAN. Exact mechanism of QTc prolongation is not defined clearly, but it has been suggested that some non-quantifiable sympathetic imbalance is responsible for QTc prolongation as parasympathetic have little influence on QTc modulations. Cardiovascular autonomic involvement can manifest clinically as postural hypotension, resting tachycardia, exercise intolerance or may be just silent, detected on autonomic function tests.[3] Due to asymptomatic and debilitating nature of the autonomic nervous system involvement and increased sudden death observed in these patients, its early detection is essential to reduce mortality. With the advent of simple, non-invasive cardiovascular reflex test, it has become possible to detect it early and even to classify its severity. Recently ADA and American Academy of Neurology, considered the QTc interval to be a specific, reproducible and standardized early test for autonomic function. Various studies conducted so far suggested an unconfirmed relationships between prolonged QT dispersion and autonomic system involvement in diabetes.

Table 3 : *QTc intervals in patients and controls*

	Group 1	Group 2	Controls	p-value		
	Mean±SD (n=25)	Mean±SD (n=25)	mean±SD (n=10)	Gr.1 vs Gr.2	Gr.1 vs Con.	Gr.2 vs Con.
QTcmax(ms)	442.4±17.06	407±9.95	409.2±15.46	<0.001	<0.001	NS
QTcmin(ms)	384.92±15.34	379.80±12.64	379±13.15	NS	NS	NS
QTd(ms)	57.48±8.06	27.20±7.14	29.8±6.57	<0.001	<0.001	NS
QTd(%)	14.95±2.20	7.20±2.01	7.85±1.72	<0.001	<0.001	NS

Table 4 : *QTc intervals in subgroups (i.e. group 1A and 1B)*

	Mild to moderate dysfunction **(Gr 1A)**	Moderate to severe dysfunction **(Gr 1B)**	p-value
	Mean±SD (n=12)	Mean±SD (n=13)	
QTcmax(ms)	435.58±14.72	448.69±69±17.16	<0.05
QTcmin(ms)	384.16±15.29	385±15.99	NS
QTd(ms)	51.41±4.81	63.07±6.18	<0.001
QTd(%)	13.41±1.48	16.38±1.76	<0.001

The analysis of QTc indices and QTd in these subgroups showed statistically significant higher mean QTd in **Gr 1B** patients as compared to Gr **1A** patients (Table 5) going in accordance with results of other workers.[6-7] This observation indicated that QT dispersion occurred early in autonomic dysfunction and then became prolonged with severe autonomic involvement. Based on these observations, we hypothesise that QTd constitute an excellent parameter to detect cardiac dysautonomia early and its further prolongation indicates severe autonomic neuropathy, therefore, serial QTd values are more useful for evaluation of severity of cardiac dysautonomia than single abnormal value.

In our study the mean QTc max was 442.4±17.06 ms in group I patients which was significantly higher than the corresponding value in group 2 patients and control subjects, directly, correlating it with cardiac dysautonomia. On the other hand QTc minimum was more or less comparable in all the three groups suggesting that cardiac dysautonomia has no effect on it. The QTc dispersion was also significantly much higher in Group **1** patients (57.48 ±8.06ms) as compared to group **2** patients and controls. This analysis suggested that cardiac dysautonomia can be picked up at the earliest by calculating QTc dispersion. Here we agree with the other Here we agree with other authors who have made similar observations.[8,9]

To determine whether QTd manifests early or late in patients of diabetes with autonomic dysfunction, subcategorization of Group **1** into two subgroups i.e. early **(Gr1A)** and severe **(Gr1B)** involvement of autonomic system was done as discussed earlier.

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