Association of QT interval indices with cardiac autonomic neuropathy in diabetic patients

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Abstract. Background. Cardiovascular autonomic neuropathy (CAN) is a severely debilitating yet underdiagnosed condition in patients with diabetes mellitus. The prevalence can range from 2.5 % (based on the primary prevention cohort in the Diabetes Control and Complications Trial) to as high as 90 % of diabetic patients. Clinical manifestations range from orthostasis to myocardial infarction. The diagnosis is made using multiple autonomic function tests to assess both sympathetic and parasympathetic function. This study was conducted to assess the relationship between Cardiac autonomic neuropathy and QT interval. Material and methods. This was a cross-sectional study conducted in 100 patients attending a tertiary care hospital in India. Deep breathing test, Valsalva ratio, immediate heart rate response to standing 30 : 15, BP rise with sustained hand grip and postural hypotension were evaluated. Scoring was done for cardiac autonomic neuropathy. QT interval and QTc interval were determined and association with CAN was obtained. Results. Out of 100 type 2 diabetic patients, 60 % were males and 40 % were females. 25 patients having no cardiac autonomic neuropathy and had no prolonged QTc interval. While, 75 patients had QTc prolonged were associated with early and severe CAN cardiac autonomic neuropathy. The prolonged QTc was significantly associated with CAN in diabetic patients when compared without CAN and controls (P < 0.0001). The grading score for CAD showed that 75 % cases were having score > 2 were 25 % of cases had score < 2. Out of 75 patients 44 were between score 2–4 and 31 were above score 4. A significant association between QTc and Diabetic CAN patients observed when compared non CAN and controls. Conclusions. Diabetic cardiac autonomic neuropathy is associated with increase in prolongation of QTc intervals. Hence, there is need for regular checkup of autonomic nervous system in diabetic patient to prevent further complications.

Keywords: type 2 diabetes mellitus; cardiac autonomic neuropathy; ECG; QTc interval

Introduction

Diabetes-associated cardiovascular autonomic neuropathy (CAN) damages autonomic nerve fibers that innervate the heart and blood vessels, results in causing abnormalities in heart rate and vascular dynamics. It is well known fact that affect multiple organ systems and is a major cause of morbidity and mortality in patients with diabetes [1].

An association between cardiac autonomic neuropathy and QT interval prolongation was shown in many previous studies and it may predispose to sudden death in diabetes due to cardiac death or myocardial ischemia [2, 3]. CAN treatment is a complex process which includes modification in lifestyle, exercise. Most of the existing data regarding QT interval and diabetic CAN are in type 1 diabetes while only few studies in type 2 diabetes [4, 5].

The main causes of QTc prolongation are long-term diabetes, ischemic heart disease, and autonomic system insufficiency; with less frequency, etiologies such as water and electrolyte imbalance which is associated with CAN and diabetes [6, 7].

The purpose of the present study was to find out the relationship of corrected QT (QTc) interval and QTc dispersion with diabetic cardiac autonomic neuropathy in type 2 diabetes so that we can identify a subset of diabetic patients who are at high risk for sudden cardiac death.

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Material and methods

This cross sectional study was conducted on 100 patients of type 2 diabetes mellitus attending OPD of K.D. Medical College and Hospital, Mathura, India, from January 2019 to March 2020.

Ethical clearance was taken from IEC and informed consent was taken from all the participants.

Inclusion criteria

Type 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.

Exclusion criteria

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 noninvasive autonomic function tests as recommended by D.J. Ewing 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 hand grip). Scoring was done as per criteria advocated by F. Bellavere et al. [9] and M. Lahotia et al. [10]. A score of 2 or more denoted definite cardiac autonomic neuropathy.

The 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/√R–R and a value exceeding 440 msec was considered prolonged. Fifty healthy volunteers were also subjected to resting ECG and their mean QTc remained below 440 msec.

Statistical analysis: data was entered in MS-Word and expressed in numbers. Analysis of data was done by SPSS-23 latest version. Students t-test were applied to test the significance.

Results

Hundred cases of type 2 diabetic cardiac autonomic neuropathy (CAN) were selected. As evident from table 1, most of the patients 39 % belonged to age group between 41–50 years, 41 % belonged to age group between 51–60 years and 20 % belonged to age group between 61–70 years. In this study 61 cases were males and 39 cases were females given in table 1.

Besides, most of the patients (14 %) had duration of < 5 years (70 %) had duration of 5–10 years (16 %) had duration of > 10 years (table 2). Regarding the symptoms of autonomic neuropathy, postural dizziness (52 %) was most common symptom in males next common symptom was impotence (17 %) and infertility in females was (13 %), while diarrhea (10 %) was the least common symptom (table 3). As evident from table 3, Valsalva ratio, deep breath test, 30 : 15 beat ratio, postural hypotension test and SHGT were abnormal.

The grading score for CAD showed that 75 % cases were having score > 2 were 25 % of cases had score < 2. Out of 75 patients 44 were between score 2–4 and 31 were above score 4 mentioned in table 4. QTc interval in diabetic patients were given in table 5.

Associations of CAD and QTc interval in diabetic patients were done in table 6. A significant association between QTc and Diabetic CAN patients observed when compared non CAN and controls.

Discussion

Diabetic CAN is most common in chronic complication in diabetic patients. 100 diabetic patients were assessed CAN and establish the relationship between CAN and QTc interval. Out of the 100 patients studied, the majority of the patients i.e., 39 % belonged to age group 41–50 years, 41 % belonged to age group 51–60 years and 20 % belonged to age group 61–70 years. Out of the 100 patients, 39 patients were females and 61 were males. The majority 71 % of patients had diabetes of 5–10 years duration, 16 % of patients had diabetes of > 10 years duration and 14 % of patients had diabetes of < 5 years duration. In S.P. Bathwal [11] study, the mean duration of diabetes was 6.5 years. 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

20 % of cases had an abnormal response (i.e. < 1.10). Previous studies by D.J. Ewing et al. [12], S.P. Bathwal [11] and M. Lahotia et al. [10] had abnormal response of 26 %, 22.3 % and 20 %, respectively.
**Table 3. Cardiac autonomic tests in diabetic patients**

| Sr. No. | Valsalva ratio (Fall in BP (mm Hg)) | Score | No. of cases | Percentage (%) |
|---------|-----------------------------------|-------|--------------|----------------|
|         |                                   |       | Male         | Female         |
| 1       | > 1.21                            | 0     | 38           | 46             | 54             |
| 2       | 1.11–1.20                         | 1     | 42           | 48             | 52             |
| 3       | < 1.10                            | 2     | 20           | 51             | 49             |

| Sr. No. | E/I ratio (beat/min) | Score | No. of cases | Percentage (%) |
|---------|----------------------|-------|--------------|----------------|
|         |                      |       | Male         | Female         |
| 1       | > 15                 | 0     | 25           | 55             | 45             |
| 2       | 11–15                | 1     | 35           | 60             | 40             |
| 3       | < 10                 | 2     | 40           | 40             | 60             |

| Sr. No. | 30 : 15 ratio | Score | No. of cases | Percentage (%) |
|---------|---------------|-------|--------------|----------------|
|         |               |       | Male         | Female         |
| 1       | > 1.04        | 0     | 20           | 62             | 38             |
| 2       | 1.01–1.03     | 1     | 30           | 61             | 39             |
| 3       | < 1.0         | 2     | 50           | 70             | 30             |

**Deep breath test**

**Postural Hypotension**

**SHGT (Blood pressure response to sustain hand grip)**

| Sr. No. | Postural Hypotension (Fall in BP (mm Hg)) | Score | No. of cases | Percentage (%) |
|---------|-------------------------------------------|-------|--------------|----------------|
|         |                                           |       | Male         | Female         |
| 1       | < 10                                       | 0     | 65           | 70             | 30             |
| 2       | 11–29                                      | 1     | 20           | 65             | 35             |
| 3       | > 30                                       | 2     | 15           | 63             | 37             |

| Sr. No. | SHGT (Fall in BP (mm Hg)) | Score | No. of cases | Percentage (%) |
|---------|---------------------------|-------|--------------|----------------|
|         |                           |       | Male         | Female         |
| 1       | > 16                      | 0     | 75           | 68             | 32             |
| 2       | 11–15                     | 1     | 15           | 56             | 44             |
| 3       | < 10                      | 2     | 10           | 60             | 40             |

| Score    | No. of cases | Percentage (%) |
|----------|--------------|----------------|
|          | Male         | Female         |
| 0–1 (No Autonomic Neuropathy) | 25 | 52 | 48 |
| 2–4 (Early Autonomic Neuropathy) | 44 | 53 | 47 |
| > 5 (Severe Autonomic Neuropathy) | 31 | 49 | 51 |

**Table 4. Scoring of cardiac autonomic neuropathy**

**Table 5. QTc interval in diabetic patients**

| QTc      | Diabetics with autonomic neuropathy (n = 75) | Diabetics without autonomic neuropathy (n = 25) | Control (n = 50) |
|----------|---------------------------------------------|------------------------------------------------|-----------------|
| < 440 (msec) | 418 ± 26                                    | 394 ± 21*                                       | 372 ± 15*       |
| > 440 (msec) |                                              |                                                |                 |

**Table 6. Relation between QTc interval and diabetic autonomic neuropathy**

**Note:** * — indicates significant P-value < 0.0001.
Deep Breath test
20% patient had abnormal response in this study. In D.J. Ewing et al. study [12] it was 42%, in S.P. Bathwal [11] it was 38.3% and in M. Lakhotia et al. [10], the abnormal response was 42% abnormal with 20% borderline cases.

30 : 15 ratio
Our study had 42% cases with abnormal response in this study. In D.J. Ewing et al. study [12] it was 38% abnormal cases, in S.P. Bathwal [11] it had 17% abnormal cases, where as in another study it was 42% abnormal with 2% borderline cases [10].

Postural hypotension
This study had 15% cases with abnormal response. In D.J. Ewing et al. study [12] it was 16% abnormal cases and in S.P. Bathwal study [11] it was 4.4% abnormal cases and in M. Lakhotia et al. study [10] it was 16% abnormal.

SGHT
10% cases had an abnormal response in this study. In D.J. Ewing et al. study [12] it was 14% abnormal cases and in S.P. Barathwal studies [11] it was 14.9% and in M. Lakhotia et al. studies [10] it was 26% abnormal cases. Previous studies by D.J. Ewing [12] and S.P. Barathwal [11] had not mentioned the borderline cases, however M. Lakhotia et al. study [10] had stated about borderline cases. Our study had higher score when compared to M. 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 correlated with the previous studies [10–12]. 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, 14]. Our study shows that 25 patients had no CAN with no QTc prolongation, these patients had average duration of type 2 DM between 5–6 years.

Further, patients having early and chronic CAN had QTc prolongations in the range of >440. Hence it strongly indicates that severity of cardiac autonomic neuropathy and QTc prolongation appears to have a relationship with duration of type 2 diabetes mellitus.

Based on our findings, QTc prolongation was noticed in cardiac autonomic neuropathy also by many other investigators [15, 16]. 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 [17].

The study has shown that QTc prolongation is an easy and reliable testing method for diabetic cardiac autonomic failure and enables routine measurements for physicians in clinical practice. 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 suggest that autonomic dysfunction depends on the duration of diabetes.

Study limitation: the study have limitations of small populations which can be extended with larger population. Study did not include clinical follow-up on cardiac mortality of patients.

Conclusions
CAN the results of the investigation indicate there was prolongation of QTc in type 2 diabetic patients with different degree of 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. The prevalence of CAN in diabetics is high.

References
1. Khandoker AH, Jelinek HF, Palaniswami M. Identifying diabetic patients with cardiac autonomic neuropathy by heart rate complexity analysis. Biomed Eng Online. 2009 Jan 29;8:3. doi: 10.1186/1475-925X-8-3.
2. Flugelman MY, Kantor Y, Abinader EG, Lewis BS, Barzilai D. Electrocardiographic patterns in diabetics without clinical ischemic heart disease. Isr J Med Sci. 1983 Mar;19(3):252-5.
3. Kahn JK, Sisson JC, Vinik AI. QT interval prolongation and sudden cardiac death in diabetic autonomic neuropathy. J Clin Endocrinol Metab. 1987 Apr;64(4):751-4. doi: 10.1210/jcem-64-4-751.
4. Takebasyahi K, Aso Y, Sugita R, Takemura Y, Inukai T. Clinical usefulness of corrected QT intervals in diabetic autonomic neuropathy in patients with type 2 diabetes. Diabetes Metab. 2002 Apr;28(2):127-32.
5. Bellavere F, Ferri M, Guarini L, et al. Prolonged QT period in diabetic autonomic neuropathy: a possible role in sudden cardiac death? Br Heart J. 1988 Mar;59(3):379-83. doi: 10.1136/ hrt.59.3.379.
6. Pillai JN, Madhavan S. Cardiac Autonomic Neuropathy and QTc Interval in Type 2 Diabetes. Heart India 2015;3(1):8-11. doi: 10.4103/2321-449X.153279.
7. Astrup AS, Tarnow I, Rossing P, Hansen BV, Hilsted J, Parving HH. Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy. Diabetes Care. 2006 Feb;29(2):334-9. doi: 10.2337/ diacare.29.02.06.dc05-1242.
8. Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy: Q J Med. 1980 Winter;49(193):95-108.
9. Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. Br Med J (Clin Res Ed). 1982 Oct 2;285(6346):916-8. doi: 10.1136/bmj.285.6346.916.
10. Lakhotia M, Shah PK, Vyas R, Jain SS, Yadav A, Parikh MK. Clinical dysautonomia in diabetes mellitus—a study with seven different autonomic reflex function tests. J Assoc Physicians India. 1997 Apr;45(4):271-4.
11. Bathwal SP. QTc prolongation is diabetes mellitus — an indicator of Cardiac autonomic neuropathy. Journal of the Association of Physicians of India. 1997;45(1):15-17.
12. Ewing DJ, Campbell IW, Clarke BF. Assessment of car-
Перехресне дослідження

Взаємозв’язок показників інтервалу QT з кардіальною автономною нейропатією у хворих на цукровий діабет

Резюме. Актуальність. Кардіальна автономна нейропатія належить до тяжких, але недостатньо діагностованих ста́нів у хворих на цукровий діабет. Поширеність кардіальної автономної нейропатії перебуває в межах від 2,5 (на основі профілактичного обстеження когорти хворих у дослідженні Diabetes Control and Complications Trial) до 90 % пацієнтів із цукровим діабетом 2-го типу. Кардіальна автономна нейропатія є різноманітним аж до розвитку інфаркту міокарда. Клінічні прояви кардіальної автономної нейропатії є різноманітними аж до розвитку інфаркту міокарда. Клінічні прояви кардіальної автономної нейропатії є різноманітними аж до розвитку інфаркту міокарда. Клінічні прояви кардіальної автономної нейропатії є різноманітними аж до розвитку інфаркту міокарда.

Мета. Дане дослідження було проведено для оцінки взаємозв’язку між кардіальною автономною нейропатією та показником інтервалу QT. Матеріали та методи. Перехресне дослідження проведено за участю 100 пацієнтів, які відвідували лікарню у хворих на цукровий діабет незалежно від інших серцево-судинних ускладнень. У 25 пацієнтів наведені дані для аналізу, а у решті 75 пацієнтів наведено дані для контролю.

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Результати. Серед 100 пацієнтів із цукровим діабетом 2-го типу було 60 % чоловіків і 40 % жінок. 25 пацієнтів мали кардіальну автономну нейропатію. Водночас у 75 пацієнтів з подовженим інтервалом QTc був пов’язаний з наявністю кардіальної автономної нейропатії. Серед 100 пацієнтів із цукровим діабетом 75 % мали пов’язані з наявністю кардіальної автономної нейропатії.

Висновки. Діабетична кардіальна автономна нейропатія пов’язана з подовженим інтервалом QTc та зумовлює кардіальну автономну нейропатію в еквівалентному та еквівалентному статусі кардіальної автономної нейропатії.

Ключові слова: цукровий діабет 2-го типу; цукровий діабет 1-го типу; показники QT; інтервал QTc; кардіальна автономна нейропатія.