e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(11); 257-261

Original Research Article

Cardiovascular Autonomic Neuropathy in Type 2 Diabetes and Relevance of Corrected QT Interval

Gosangari Suchitra[1], Harish Kumar B[2], Neha Gala[3], Sandeep U[4]

[1]Assistant Professor, Department of Physiology, Government Medical College, Karimnagar, Telangana, India

[2]Assistant Professor, Department of Physiology, Government Medical College, Kamareddy, Telangana, India

[3]Assistant Professor, Department of Psychiatry, Apollo Institute of Medical Science, Hyderabad, India

[4]Assistant Professor, Department of Medicine, Karuna Medical College Hospital, Chittur, Palakkad Kerala, India

Received: 11-10-2023 Revised: 25-10-2023 / Accepted: 05-11-2023

Corresponding author: Dr. Sandeep U

Conflict of interest: Nil

Abstract

Background: Prolonged QT interval (QT) has been identified as risk factors for sudden cardiac death. This study aimed to explore the correlation between cardiac autonomic neuropathy (CAN) and QT interval in individuals with type 2 diabetes.

Methods: A total of 150 diabetic participants were enrolled, comprising 80 with and 70 without CAN. All subjects exhibited sinus cardiac rhythm, and those with conditions or medication usage leading to orthostatic hypotension (OH), cardiac arrhythmia, or QT prolongation were excluded. Following interviews and examinations, standard and continuous electrocardiograms (ECG) were recorded in the supine position during deep breathing and standing. CAN diagnosis relied on Ewing's tests. QT, corrected QT (QTc), minimum QT (QT min), maximum QT (QT max), and mean±SD of QT (QT mean) were evaluated from standard ECG.

Results: Among patients with CAN, 21.5% were symptomatic. The prevalence of abnormal QTc was 11.3%. No significant difference in long QTc was observed between patients with or without CAN. However, the mean±SD of QT max, QT mean, were higher in those with CAN.

Conclusion: The prevalence of asymptomatic CAN was higher than that of symptomatic CAN. Patients with CAN exhibited higher QT max, QT mean compared to those without CAN. However, there was no discernible association between CAN and prolonged QTc.

Keywords: Diabetes Mellitus, Autonomic Neuropathy, Electrocardiography, QT interval.

Introduction

The QT interval (QT) reflects the time required for ventricular myocardial depolarization and repolarization. Various physiological factors, including age, sex, heart rate, and autonomic system activity, influence QT duration. To account for heart rate variability, correction of QT, termed QTc, is essential. QT dispersion (QTd), defined as the difference between the maximum and minimum QT interval across different ECG leads, signifies heterogeneity in the recovery of the stimulation phase and may contribute to malignant ventricular arrhythmias [1-3].

Cardiac autonomic neuropathy (CAN) is prevalent in diabetic (DM) patients, elevating the risk of cardiac arrhythmias, sudden death, and myocardial infarction [4]. QTc prolongation has been linked to the severity of CAN in DM patients. Causes of prolonged QTc include long-term diabetes, ischemic heart disease, autonomic system insufficiency, and, less frequently, factors such as water and electrolyte imbalance. Long QTc poses a risk for serious arrhythmias and sudden death, thereby increasing mortality rates, especially in conjunction with nephropathy [4-7].

Elevated QTd is observed in patients with recent myocardial infarction, long QT syndrome, heart failure, and DM with CAN. It serves as a potential predictor of malignant ventricular arrhythmias and mortality in DM patients. However, the impact of CAN on QT varies across clinical and experimental studies. Ukpabi OJ demonstrated that autoimmune neuropathy significantly affects QTc more than other variables in DM patients. Increased QTd is associated with CAN, indicating autonomic system

dysfunction in the hearts of DM patients. Yet, recent studies employing Holter Monitoring have not consistently linked QTd with CAN. This study investigates the relationship between CAN and QT indices in DM patients [8-11].

Materials and Methods

This cross-sectional study was conducted on patients with Type 2 Diabetes Mellitus (T2DM) based on ADA criteria, attending the medicine department of a hospital in India [12]. Among 456 DM patients, 150 individuals (80 with CAN, 70 without CAN) were selected through convenient sampling, following specific inclusion and exclusion criteria.

Inclusion Criteria:

- T2DM patients with cardiac sinus rhythm, normal vital signs, and aged 18–75 years old.

Exclusion Criteria:

- Pregnant women, individuals with symptoms of anemia, hypoxia, hypovolemia, sepsis, lower extremity amputation, renal failure, or other conditions affecting heart rhythm and orthostatic hypotension.

Those taking medications affecting heart rhythm, QT intervals, and blood pressure, such as calcium channel blockers, beta-receptor blockers, anti-hypertensive drugs (excluding angiotensin-converting enzyme inhibitors and angiotensin receptor blocking agents), anti-arrhythmic drugs, triangular anti-psychotic drugs, Phenothiazine, and those with abnormal blood pressure or arterial pulse difference between the two arms.

After obtaining written consent, participants underwent examination in a fasting state. A questionnaire capturing demographic information was completed. Participants rested for 15 minutes and underwent blood pressure and heart rate examination from the right hand in both sitting and standing positions. Standard ECGs were obtained from patients with at least 10 QRS waves per lead. CAN assessment relied on heart rate variation during physical examination (resting tachycardia and orthostatic hypotension) and standard Ewing's tests [13, 14].

The QT interval, reflecting the duration between the onset of electrical activity and its recovery, was calculated from standard ECGs. QT minimum (QT min), QT maximum (QT max), QT mean (QT mean), and QT corrected (QTc) were computed. QTc was considered prolonged if it exceeded 460 ms in women and 440 ms in men [15, 16].

Quantitative variables were compared using the independent t-test, while qualitative variables were assessed using the chi-square test. Simple regression analysis was applied to determine the relationship between QT interval indices and quantitative CAN parameters. Variables' normality was tested by the Shapiro–Wilk test. Parametric tests (independent t-test) were used for age and BMI, while non-parametric tests (Mann–Whitney test) were employed for variables without a normal distribution. To determine the best cut off, Receiver Operating Characteristic (ROC) curves for QTc were constructed. IBM SPSS Statistic version 20 was used for statistical analysis, with a significance level set at $P < 0.05$

Results

The incidence of female gender was 60% in individuals with CAN compared to 70% in those without CAN, yielding a p-value of 0.86. Among patients with CAN, 22% displayed symptoms, while 78% were asymptomatic. Individuals with CAN exhibited an extended duration of diabetes mellitus, increased BMI, and elevated levels of total and LDL-cholesterol in comparison to those without CAN, as detailed in Table 1.

The frequency of abnormal QTc 12%. The Mean ± SD values of QT max, and QT mean among patients with CAN were elevated compared to those without CAN, as outlined in Table 2.

The Area under the Curve (AUC) for QTc with the existing cut-off was 0.61 (95% CI: 0.52–0.73, P = 0.03), indicating statistical significance. Using the current QTc cut-offs, it demonstrated a sensitivity of 31% and specificity of 78% for identifying the occurrence of CAN in DM patients. In the multivariable regression analysis, only total cholesterol exhibited a correlation with CAN, as delineated in Table 3.

Table 1: Demographic and clinic-biochemical parameters in study population

Parameters	Gorup with CAN	Group without CAN	p-value
Age (in years)	47.25 ± 14.20	55.10 ± 10.80	0.35
Duration of Diabetes (months)	85.20 ± 66.40	75.80 ± 76.50	<0.05
BMI (kg/m²)	26.50 ± 4.80	29.10 ± 3.60	<0.05
FBS (mg/dl)	142.80 ± 76.20	167.40 ± 73.50	0.06
PP2BS (mg/dl)	198.50 ± 105.80	217.60 ± 95.90	0.08
HbA1C (%)	7.80 ± 1.50	7.90 ± 1.30	0.21
Triglyceride (mg/dl)	150.70 ± 86.40	155.30 ± 133.10	0.06
Total cholesterol (mg/dl)	230.90 ± 41.80	201.30 ± 44.80	<0.05
LDL-C (mg/dl)	155.40 ± 90.10	125.60 ± 35.20	<0.05
HDL-C (mg/dl)	49.30 ± 29.40	52.60 ± 20.20	0.45

Table 2: QT interval variables in study patients

Parameters	Group with CAN (Mean ± SD)	Group without CAN (Mean ± SD)	p-value
QT min	345 ± 28	330.5 ± 29	0.76
QT max	402 ± 31	389 ± 32	0.04
QT mean	368 ± 27	359 ± 31	0.06
QTc	421 ± 33	412 ± 31	0.12

Table 3: Multivariate regression analysis of CAN and various parameters

Variables	B	Sig	Exp(B)	Lower 95% CI for Exp(B)	Upper 95% CI for Exp(B)
HbA1C	-0.045	0.72	0.955	0.745	1.215
Triglyceride	0.002	0.198	1.002	0.998	1.005
LDL-C	-0.002	0.536	0.998	0.991	1.007
Total cholesterol	0.016	0.021	1.016	1.004	1.028
QT max	-0.463	0.494	-3.389	0.661	1.374
QT mean	0.467	0.505	3.243	0.642	1.034
QTc	-0.07	0.982	0.931	0.007	127.21

Discussion

Long QT interval is a recognized factor linked to sudden death, prevalent not only in healthy individuals but also in those with DM or CAN. Hence, this study delved into investigating the association between QT indices and CAN in patients with T2DM. In this investigation, no statistically significant disparities were observed between the two groups concerning age, sex, HbA1C, and blood sugar levels. However, patients with CAN exhibited an extended duration of DM, higher BMI, and elevated levels of total and LDL-cholesterol. Notably, one-fifth of the subjects presented clinical signs indicative of symptomatic CAN. Furthermore, approximately one-third and one-tenth of the participants displayed long QTc. However, the prevalence of long QTc did not exhibit a significant difference between the two groups. The values of QT max, and QT mean were notably prolonged in patients with CAN, whereas no significant differences were observed in the values of QT min and QTc between the two groups. The prevalence of long QTc observed in this study is comparatively lower than in other investigations. Similar to our study, Ninkovic VM conducted a study involving over 500 Caucasian patients with T2DM [17]. It's noteworthy that long QT is more commonly found in females, individuals with T1DM, those with prolonged diabetes duration, and patients experiencing chronic complications of diabetes mellitus [10, 17, 18]. Certain factors such as race have not received specific attention in this context. The prevalence of long QT in different racial groups has been reported as 12% in blacks, 17% in yellows [19], and 44% in Caucasians [17]. However, a large multicenter study with diverse nationalities conducted by EURODIAB in 2017 reported an overall prevalence of 17% [20].

In individuals with DM) and CAN, the QTc interval exhibited a significant elevation compared to those without CAN [21]. Moreover, there exists a direct correlation between the prolongation of QTc and the severity of CAN [22]. The relationship between the QT interval and CAN is intricate. Initially, physicians primarily considered the association between CAN and prolonged QTc interval [23]. The exact etiology of long QT is ambiguous, raising the question of whether it is solely attributed to DM or is a consequence of CAN. It is plausible that both factors exert a synergistic effect leading to prolonged QT. The prolongation of QTc has been associated with the activity of the sympathetic and parasympathetic systems. Subsequent research has introduced QT dispersion as an index for diagnosing CAN and assessing its severity [24,25]. In this study, it was observed that the QT min, QT max, and QT mean durations in individuals with DM and CAN were notably prolonged compared to those without CAN. This finding aligns with the outcomes reported in earlier studies [26-28].

This study exhibits several strengths. Firstly, to enhance internal validity, a single individual conducted all examinations and measurements using a consistent device. Secondly, the manual measurement of all QT interval-related indices was employed. Thirdly, the study exclusively focused on patients with T2DM, maintaining uniformity in factors like age, gender, and DM control between the two groups. Fourthly, novel cut-off values for QTc were proposed for identifying CAN in T2DM. However, certain limitations should be acknowledged. Firstly, the study was conducted in a single center with a relatively small patient cohort, diminishing the external validity. Secondly, the sample size calculation was specifically tailored for QTc, potentially limiting the exploration of the relationship of other indices with CAN. Thirdly, the manual measurement and calculation of the QT interval introduce the possibility of operator error, rendering the measurements less precise than those obtained through computer software. Lastly, factors influencing the QT interval, such as electrolyte

imbalances (hypo- or hyperkalemia, hypo- or hypercalcemia), were not systematically assessed.

Conclusion

Asymptomatic CAN was found to be more prevalent than symptomatic CAN. Patients with CAN exhibited a prolonged duration of diabetes, higher BMI, and elevated levels of LDL cholesterol. The values for QT max, QT mean, were notably higher in patients with CAN. To further elucidate the relationship between QT distance, diabetes, and CAN, it is advised that multinational and multicentre studies be undertaken.

References

1. Lederman YS, Balucani C, Steinberg LR, Philip C, Lazar JM, Weedon J, Mirchandani G, Weingast SZ, Viticchi G, Falsetti L, Silvestrini M, Gugger JJ, Aharonof D, Piran P, Adler Z, Levine SR. Does the magnitude of the electrocardiogram QT interval dispersion predict stroke outcome? J Stroke Cerebrovasc Dis. 2019;28(1):44–8.
2. Pourmand A, Mazer-Amirshahi M, Chistov S, Sabha Y, Vukomanovic D, Almulhim M. Emergency department approach to QTc prolongation. Am J Emerg Med. 2017;35(12):1928–33.
3. Veglio M, Giunti S, Stevens LK, Fuller JH, Cavallo-Perin P, et al. Prevalence of Q-T interval disparison in type I diabetes and its relation with cardiac ischemia. Diabetes Care. 2002;25(4):702–7.
4. Mahmud R, Gray A, Nabeebaccus A, Whyte MB. Incidence and outcomes of long QTc in acute medical admissions. Int J Clin Pract. 2018;72(11):e13250.
5. Antoniou CK, Dilaveris P, Manolakou P, Galanakos S, Magkas N, Gatzoulis K, Tousoulis D. QT prolongation and malignant arrhythmia: how serious a problem? J Eur Cardiol. 2017;12(2):112–20.
6. Cha SA, Yun JS, Lim TS, Min K, Song KH, Yoo KD, Park YM, Ahn YB, Ko SH. Diabetic cardiovascular autonomic neuropathy predicts recurrent cardiovascular diseases in patients with type 2 diabetes. PLoS ONE. 2016;11(10):e0164807.
7. Dimova R, Tankova T, Guergueltcheva V, Tournev I, Chakarova N, Grozeva G, Dakovska L. Risk factors for autonomic and somatic nerve dysfunction in diferent stages of glucose tolerance. J Diabetes Complicat. 2017;31(3):537–43.
8. Uysal F, Ozboyaci E, Bostan O, Saglam H, Semizel E, Cil E. Evaluation of electrocardiographic parameters for early diagnosis of autonomic dysfunction in children and adolescents with type-1 diabetes mellitus. Pediatr Int. 2014;56(5):675–80.
9. Tanaka K, Yodogawa K, Ono T, Yana K, Miyamoto M, Atarashi H, Kato T, Mizuno K. Greater insulin resistance indicates decreased diurnal variation in the QT interval in patients with type 2 diabetes. Heart Vessels. 2014;29(2):256–62.
10. Ukpabi OJ, Onwubere BJ. QTc prolongation in Black diabetic subjects with cardiac autonomic neuropathy. Afr Health Sci. 2017;17(4):1092–100.
11. Cekirdekci EI, Bugan B. Can abnormal dispersion of ventricular repolarization be a predictor of mortality in arrhythmogenic right ventricular cardiomyopathy: the importance of Tp-e interval. Ann Noninvasive Electrocardiol. 2019;24(3):e12619.
12. American Diabetes Association. Classifcation and diagnosis of diabetes: standards of medical care in diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S13–27.
13. Vasheghani M, Sarvghadi F, Beyranvand MR. The association between cardiac autonomic neuropathy and diabetes control. Diabetes Metab Syndr Obes Targets Ther. 2019;12:581.
14. Lin K, Wei L, Huang Z, Zeng Q. Combination of Ewing test, heart rate variability, and heart rate turbulence analysis for early diagnosis of diabetic cardiac autonomic neuropathy. Medicine (Baltimore). 2017;96(45):e8296.
15. Ninkovic VM, Ninkovic SM, Miloradovic V, Stanojevic D, Babic M, Giga V, Dobric M, Trenell MI, Lalic N, Seferovic PM, Jakovljevic DG. Prevalence and risk factors for prolonged QT interval and QT dispersion in patients with type 2 diabetes. Acta Diabetol. 2016;53(5):737–44.
16. Batmaz G, Aksoy AN, Aydın S, Ay NK, Dane B. QT interval changes in term pregnant women living at moderately high altitude. Niger J Clin Pract. 2016;19(5):611–5.
17. Ninkovic VM, Ninkovic SM, Miloradovic V, Stanojevic D, Babic M, Giga V, Dobric M, Trenell MI, Lalic N, Seferovic PM, Jakovljevic DG. Prevalence and risk factors for prolonged QT interval and QT dispersion in patients with type 2 diabetes. Acta Diabetol. 2016;53(5):737–44.

18. Delhey L, Jin J, Thapa S, Delongchamp R, Faramawi MF. The association of metabolic syndrome and QRS|T angle in US adults (NHANES III). Ann Noninvasive Electrocardiol. 2020;25(1):e12678.
19. Su JB, Yang XH, Zhang XL, Cai HL, Huang HY, Zhao LH, Xu F, Chen T, Cheng XB, Wang XQ, Lu Y. The association of long-term glycaemic variability versus sustained chronic hyperglycaemia with heart rate-corrected QT interval in patients with type 2 diabetes. PLoS ONE. 2017;12(8):e0183055.
20. Amione C, Giunti S, Fornengo P, Soedamah-Muthu SS, Chaturvedi N, Fuller JH, Barutta F, Gruden G, Bruno G. Incidence of prolonged QTc and severe hypoglycemia in type 1 diabetes: the EURODIAB Prospective Complications Study. Acta Diabetol. 2017;54(9):871–6.
21. Kuzu F. The effect of type 2 diabetes on electrocardiographic markers of significant cardiac events. Pak J Med Sci. 2018;34(3):626–32.
22. Agarwal G, Singh SK. Arrhythmias in type 2 diabetes mellitus. Indian J Endocrinol Metab. 2017;21(5):715–8.
23. Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R, Stevens M, Kempler P, Hilsted J, Tesfaye S, Low P, Valensi P, Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev. 2011;27(7):639–53.
24. Serhiyenko VA, Serhiyenko AA. Cardiac autonomic neuropathy: risk factors, diagnosis, and treatment. World J Diabetes. 2018;9(1):1–24.
25. Fisher VL, Tahrani AA. Cardiac autonomic neuropathy in patients with diabetes mellitus: current perspectives. Diabetes Metab Syndr Obes. 2017;10:419–34.
26. Clemente D, Pereira T, Ribeiro S. Ventricular repolarization in diabetic patients: characterization and clinical implications. Arq Bras Cardiol. 2012;99(5):1015–22.
27. Takahashi N, Nakagawa M, Saikawa T, Watanabe M, Doie T, Yufu X, et al. Regulation of QT indices mediated by autonomic nervous function in patients with type 2 diabetes. Int J Cardiol. 2004;96(3):375–9.
28. Takebayashi K, Sugita R, Tayama K, Aso Y, Takemura Y, Inukai T. The connection between QT dispersion and autonomic neuropathy in patients with type 2 diabetes. Exp Clin Endocrinal Diabetes. 2003;111(6):351–7.