The Relationship between QT Interval Indices with Cardiac Autonomic Neuropathy in Diabetic Patients

maryam vasheghani
Shaheed Beheshti University of Medical Sciences
Farzaneh Sarvghadi
Research Institute for Endocrine Sciences
Mohammad Reza Beyranvand (beyran4@yahoo.com)
Shahid Beheshti University of Medical Sciences School of Medicine
Habib Emami
National Research Institute of Tuberculosis and Lung Disease

Research

Keywords: Cardiac Autonomic Neuropathy, Diabetes Mellitus, Standard and Continuous Electrocardiogram, ECG, QT interval, QT minimum, QT maximum, QT dispersion, QT mean

Posted Date: July 28th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-47922/v1

Version of Record: A version of this preprint was published on November 19th, 2020. See the published version at https://doi.org/10.1186/s13098-020-00609-0.

Abstract

Introduction

Long QT interval (QT) and abnormal QT dispersion (QTd) are associated with sudden death. The relationship between cardiac autonomic neuropathy (CAN) and QT indices in diabetic patients were investigated.

Methods

Totally 130 diabetic subjects (mean age 50.87 ± 13.9 years) were included (70 individuals with and 60 individuals without CAN). All participants had sinus cardiac rhythm. The patients who had diseases or take drugs that cause orthostatic hypotension (OH), cardiac arrhythmia and QT prolongation were excluded. After interview and examination, standard and continuous ECG was taken in supine position with deep breathing and standing up position. CAN diagnosis was based on Ewing's tests. QT, QT corrected (QTc), minimum QT (QT min), maximum QT (QT max) and mean ± SD of QT (QT mean) and QTd were assessed from standard ECG. QTc was calculated by Bazett's formula. QTc > 440 msec in men and QTc > 0.46 msec in women and QTd > 80 msec were considered abnormal.

Results

In patients with CAN, 13.7% were symptomatic and 51.2% were asymptomatic. The prevalence of abnormal QTc and QTd was 11.3% and 28.7%, respectively. There was no significant difference between the patients with or without CAN in terms of long QTc and abnormal QTd. However, the mean ± SD of QT max, QT mean and QTd was higher in the patients with CAN (P_Vlue = 0.008, 0.03, 0.02, respectively).

Conclusion

The prevalence of asymptomatic CAN was twice that of symptomatic CAN. In patients with CAN the QT max, QT mean and QTd were higher than those without CAN.

Background

The QT interval (QT) indicates the time needed for ventricular myocardial depolarization and repolarization [1] and several physiological factors influence the duration of QT, such as age and sex, and more importantly, heart rate and autonomic system activity.[2] Therefore QT should be corrected based on heart rate, which is called QTc. The maximum minus the minimum QT interval between the various ECG leads is called QT dispersion (QTd). QTd can be a sign of heterogeneity in the recovery of stimulation phase, and this heterogeneity can be the cause of malignant ventricular arrhythmia.[3] Cardiac autonomic neuropathy (CAN) is prevalent in diabetic patients and increases the risk of cardiac arrhythmias and events, such as sudden death and myocardial infarction .[4] QTc prolongation has been associated with severity of CAN in diabetic patients.[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.[6] Long QTc causes serious arrhythmias and sudden death, and, along with nephropathy, increases the mortality rate of patients .[7] Increased QTd is seen in patients who have recent myocardial infarction, long QT syndrome, heart failure and diabetes mellitus with CAN. It can be a cause of malignant ventricular arrhythmias and predict mortality in diabetic patients.[8]Concerning the effect of CAN on QT, several clinical and experimental studies have shown different effects. Ukpabi OJ showed that QTc is significantly more affected by autoimmune neuropathy than other variables in diabetic patients.[9]

Increased QTd is correlated with CAN. High QTd indicates a dysfunction of the autonomic system of heart in patients with DM.[10]But, QTd have not been associated with CAN even with Holter monitoring method in some recent studies.[11]In this study the relationship between cardiac autonomic neuropathy (CAN) and QT indices in diabetic patients was investigated.

Material And Methods

This cross-sectional study was performed on type 2 diabetic patients (according to ADA criteria) referred to the internal medicine or endocrine clinic of Loghman Hakim General Hospital in Tehran, Iran.[12] From 582 diabetic patients who referred during one year, 130 patients (70 patients with autonomic cardiac neuropathy, 60 patients without autonomic cardiac neuropathy) were selected by convenient sampling according to inclusion and exclusion criteria (Figure-1).

Inclusion criteria: Type 2 diabetic patients with cardiac sinus rhythm, normal vital sign and aged 18-75 years old.

Exclusion criteria: Pregnant women, Patients who have symptoms of anemia, hypoxia, hypovolaemia, sepsis, kidney failure, or other diseases affecting the heart rhythm and orthopedic hypotension; taking medications that affect the heart rhythm, QT intervals, and blood pressure. For example: Calcium channel blockers and beta receptors, anti-hypertensives except angiotensin converting enzyme inhibitors and angiotensin receptor blocking agents; anti-arrhythmic drugs and triangular anti-psychotic drugs, Phenotyazine and abnormal difference in blood pressure or arterial pulse between the two arms of the patient.

After receiving written consent, the participants were visited and examined by a physician of internal medicine ward (Vasheghani M) in fasting state in the morning. A questionnaire was completed for demographic information. The patient rests for 15 minutes and then was examined for blood pressure and heart rate from the right hand in both sitting and standing conditions. Then standardized ECG was taken from patients with at least 10 QRS waves per lead. The CAN was assessed based on heart rate variation during physical examination (at rest tachycardia and orthostatic hypotension) and standard Ewing's tests.[13] The details of the research methodology have been published in our previous article.[14]

The QT interval demonstrates the distance between the onset of electrical activity and its recovery, which indicates the sympathetic and parasympathetic nervous systems harmony. The QT intervals were calculated based on the standard ECG tape. The QT interval was calculated from the beginning of the Q wave to the end of the T wave and expressed in milliseconds (msec). [15]

QT Minimum (QT Min): The minimum QT interval between 12 standard ECG leads.

QT Maximum (QT Max): The maximum QT interval between 12 standard ECG leads.

QT Mean (QT Mean): The mean of all QT interval s between 12 standard ECG leads.

QT Mean = ∑ QT intervals ÷ n; n = number of QT intervals

QT Corrected (QTc): QTc was calculated based on Bazett's formula. The QTc was considered long if it was more than 460 msec in women and more than 440 msec in men.[15]

Bazett's formula: QTc = QT interval ÷ square root of the RR interval (in msec)

QT dispersion (QTd): QTd was calculated from the QT Max minus QT Min. QTd was considered abnormal if it was more than 80 msec. [16]

QTd = QT Max - QT Min

This study has been scrutinized at the Ethics Committee of the Faculty of Medicine of Shahid Beheshti University of Medical Sciences and confirmed in accordance with the Helsinki Declaration. The research has been performed according to the opinions of that commission.

Statistical Analysis

All data was recorded in the questionnaires. To compare quantitative variables, independent t-test was applied. Chi-square test was applied for qualitative variables. A simple regression analysis was applied to determine the relationship between QT interval indices with each of the quantitative parameters of CAN. For statistical analysis, IBM SPSS Statistic version 22 was used and P value less than 0.05 are considered significant.

Results

Totally, 130 type 2 diabetic patients (mean age 50.87 ± 13.9 years) were included (70 individuals with and 60 individuals without CAN). The participant selection is shown in Figure 1. In patients with CAN 65,3% and in patients without CAN 75.5% were female (P-Value=0.9). In patients with CAN, 21.5 % were symptomatic and 78.5% were asymptomatic. The prevalence of abnormal QTc and QTd was 11.3% and 28.7%, respectively. Patients with CAN had a longer duration of diabetes, higher BMI and LDL-cholesterol level than those without CAN (Table 1). The Mean ± SD of QT max, QT means and QTd in Patients with

CAN were higher than those without CAN (Table 2). Prolonged QTc and Abnormal QTd were more prevalent in patients with CAN than those without CAN, but the difference is not significant (Table 3).

Discussion

Cardiac autonomic neuropathy (CAN) is a common complication of diabetes. Long QT intervals are associated with sudden death and short life-span in healthy people, and patients with diabetes or nephropathy. Increased QTd has been reported in diabetic patients with autonomic cardiac neuropathy, which has a role in its prognosis. In this study, the relationship between CAN and QT indices in type 2 diabetic patients was investigated.

About one-third of participants had abnormal QTd and about one-tenth of them had a long QTc. About one-fifth of the subjects had clinical signs (symptomatic or clinical CAN), and the rest had no obvious clinical symptoms (asymptomatic or subclinical CAN).

Patients with CAN had a longer duration of diabetes, higher BMI and LDL-cholesterol than those without CAN. In patients with CAN the QT max, QT mean and QTd were longer than those without CAN. There were no significant differences in the Mean ± SD of age, sex, QT min and QTc between the two groups. Although the prevalence of prolonged QTc and abnormal QTd was higher in patients with CAN than those without CAN, but their differences were not statistically significant.

CAN is one of the most common complications of diabetes. Its prevalence varies from 2% to 91% in type 1 diabetes (T1DM) and 25% to 75% in type 2 diabetes (T2DM). CAN is classified as “early involvement”,”definite involvement” and “severe involvement”. Other classification is symptomatic and asymptomatic CAN. In our study 21% of patients with CAN were symptomatic or have severe involvement . Symptomatic CAN, with orthostatic hypotension presentation, is seen in 6% to 32% of patients with DM.[17]

QT interval is longer in diabetic patients and long QT is more prevalent among them especially whom have cardiac autonomic neuropathy. Patients with CAN have a longer QT interval than normal individuals. It is not clear whether long QT is caused solely by diabetes or simply due to cardiac autonomic neuropathy. Both diabetes and neuropathy may have a synergistic effect and together cause long QT. In this study, because all patients were diabetic, it was not possible to compare diabetics with non-diabetics.

Long QT and DM:

The prevalence of long QTc was 11.3% in this study. Its prevalence range from 12% in black patients of Nigeria [9], 17.1% in yellow race of China [18] to 44.1% in Caucasian patients from Serbia [16]. Large multinational study such as EURODIAB showed 17% of diabetic patient have long QTc (>440 msec). [19] Diabetic patients have a longer QT interval than non-diabetics (433.89 ± 30.37 vs. 421.2± 24.6 ms, p=0.03). In diabetic patients with CAN, QTc was significantly higher than diabetic patients without CAN

(442.4 +/- 32.69 vs. 424.48 +/- 23.45 ms, p) and Prolonged QTc had direct relation to the severity of CAN.[20,21] Long QT intervals are seen in both women (453.17 ± 8.53 vs. 436.79 ± 1.44, P=0.014) and men (447.37 ± 14 vs. 420.60 ± 0.82, P=0.0109), even from the pre-diabetic stage.[22] However, other researchers have found different results in their studies. The QT interval in diabetic and pre-diabetic individuals was no longer than normal individuals or if it was longer, this difference was not significant.[23,24]

Long QT and CAN:

The relationship between QT interval and CAN is very complex. In this study the mean ± SD of QTc in diabetic patients with CAN was longer than those without CAN (415±34 vs. 406±32 msec; P-Value=0.15) but this difference was not significant. Initially, the researchers only suggested the association of CAN with the long QTc interval.[25] In some studies, QTc prolongation has been linked to sympathetic and para-sympathetic system activity, and the researchers have suggested that the index be used as a predictive or diagnostic criterion for CAN. [26,27] Researchers have shown that long QTc intervals is more prevalent in diabetic patients with CAN, but this has not been correlated with the severity of CAN.[28]Some studies have suggested the long QTc interval as a risk factor for CAN[29], while others consider long QTc interval as one of the negative consequences of CAN.[30] There are rare reports of short QTc intervals in diabetic patients with abnormal heart rate variability.[31]

The relationship of long QT interval with CAN has been observed in non-diabetic patients including sickle cell anemia. This may suggest a relationship between long QTc and CAN that is independent of diabetes. In addition to the QTc, the QT dispersion (QTd) was also higher in these patients. [32]

Over time, researchers have used other measures, such as QTd, QT Min, QT Max, QT Mean and T wave angle, to clarify the relationship between QT interval and CAN.

They consider other features of QTc interval, such as QT interval variability, as a diagnostic index and or severity index for CAN. The ratio of QTc variation to heart rate variation determines a criterion that provides the balance between QT variation and heart rate variation. QTc variation index was more sensitive for the diagnosis of CAN and determining the degree of progression of the disease. [33,34]

QTd and CAN in Diabetic Patients:

In this study QTd was longer in patients with CAN than those without CAN (69 vs. 58 msec, p= 0.02 respectively). Statsenko et al. who compared QTd in patients with chronic heart failure and diabetic cardiac autonomic neuropathy, also showed QTd was longer in diabetic patients with CAN than those without CAN.[35] Other researchers showed QTd is longer in patients with type 2 diabetes, but could not find this relation with type 1 diabetes and CAN.[36] In a study to compare QT interval between diabetic and healthy individuals they found long QTd (>65 msec) in 0.9% of diabetic patients, but no cases were seen in non-diabetic patients.[37]

QTd increase with disorder in the sympathetic and parasympathetic branches of the autonomic system.[38] In a study, those who had sensory neuropathy, QTd had a direct correlation with the severity of neuropathy. QTd in diabetic patients was higher than control group and during the stand-up maneuver; this difference will be greater.[39] Other factors, such as high blood pressure, may affect the results and cause differences in the results of studies. Each of the QT indices may be affected by a part of the nervous autonomic system, such as the sympathetic or parasympathetic branch, and one index alone may not show the full function of the autonomic system.

QT mean, QT max, QT min and CAN or DM:

The diabetic patients have significantly higher QTc max and QTc mean than non-diabetic group ($p < 0.001$ for all). However, QTc min was longer in diabetic patient, but this difference was not significant ($p = 0.083$). [37]

Patients with CAN also have higher QTc max and QTc mean than those without CAN.[38]

Bankers and colleagues compared QT interval parameters in patients with none—ST elevation myocardial infarction in two groups, patients with type 2 diabetes and non-diabetics. QTc and QTd were higher in the diabetic group, especially those who needed coronary artery surgery or had ventricular arrhythmias. In patients who died during hospitalization, QTd and QT max was higher.[40]

Other factors, such as high blood pressure, may affect the results and cause differences in the results of studies. Each of the QT indices may be affected by a part of the nervous autonomic system, such as the sympathetic or parasympathetic branch, and one index alone may not show the full function of the autonomic system. For example, QTd is higher in patients with CAN and is more affected by the parasympathetic branch and systolic blood pressure regardless of CAN.[41]

In this study, there was no difference in age and sex between the two groups with and without CAN. Heart rate varies depending on the circadian cycle, so all measurements were done in the 9:00 AM- 4:00 PM and two hours after waking up. These reduce the difference between precipitants.

The difference in the results of studies may be due to several aspects:

1. Sample size
2. Differences in the investigated groups
3. Differences in CAN identification method and criteria for diagnosis. In some groups, precise methods or a combination of different methods were used.
4. Differences in long QTc criteria or abnormal QTd. In some studies, QTc> 440 msec have been considered long for both gender.

The limitations of our study are: First, the study was performed in a single center with a small number of patients. Therefore, the external validity of the study is lower. Second, The QT interval was measured and

calculated manually. Therefore, there is a possibility of operator error and the measurements are less accurate than the measurements with computer software. Third, other factors which affect QT interval such as electrolyte imbalance (hypo or hyper-kalemia, hypo or hyper-calcemia) were not evaluated.

This study has some strength: First, In order to increase the internal validity of the research, all examinations and measurements were performed by an internal specialist and with one device in all patients. All indexes that can be manually measured for QT distance have been evaluated.

The prevalence of CAN in different studies varies depending on the criteria used to define the disease, the diagnostic criteria, the population studied, diagnostic methods and their accuracy and whether or not it depends on the operator, the duration of diabetes, the stage of diabetes and CAN and many other factors. On the other hand, many factors also affect heart rate variability, cardiac repolarization-depolarization and QT interval.

Regardless of the factors we mentioned as interfering and confounder factors affecting the relationship between QT distance with neuropathy or diabetes, it is very difficult to determine the relationship between QT distance with neuropathy and diabetes, either alone or together.

Declarations

Acknowledgment

The authors are grateful to the colleagues and patients of the endocrine and cardiac clinics who helped with the project. They thank Dr. Niloufar Alizadeh, a PhD student in biostatistics, who re-analyzed the data.

Recommendation

To better and more accurately understanding the relationship between QT distance with diabetes and neuropathy, it is recommended that it is recommended that the study be performed with a larger sample size in four groups: group I or control, individuals without diabetes and neuropathy; group II, individuals with diabetes; group III, individuals with neuropathy; and group IV, individuals with both diabetes and neuropathy.

Formatting of funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. 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; 25(4);2002,p:702-707

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 Dec;35(12):1928-1933. doi: 10.1016/j.ajem.2017.08.044.
3. Lederman YS, Balucani C, Steinberg LR, Philip C, Lazar JM, Weedon J, Mirchandani G, Weingast SZ, Viticchi G, Falsetti L, Silvestrini M, Gugger JJ, Aharonoff D, Piran P, Adler Z, Levine SR. Does the Magnitude of the Electrocardiogram QT Interval Dispersion Predict Stroke Outcome? J Stroke Cerebrovasc Dis. 2019 Jan;28(1):44-48. doi: 10.1016/j.jstrokecerebrovasdis.2018.09.006.
4. 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 Oct 14;11(10):e0164807. doi: 10.1371/journal.pone.0164807.
5. Dimova R, Tankova T, Guergueltcheva V, Tournev I, Chakarova N, Grozeva G, Dakovska L. Risk factors for autonomic and somatic nerve dysfunction in different stages of glucose tolerance. J Diabetes Complications. 2017 Mar;31(3):537-543. doi: 10.1016/j.jdiacomp.2016.11.002.
6. Mahmud R, Gray A, Nabeebaccus A, Whyte MB. Incidence and outcomes of long QTc in acute medical admissions. Int J Clin Pract. 2018 Nov;72(11):e13250. doi: 10.1111/ijcp.13250.
7. 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 Dec;12(2):112-120. doi: 10.15420/ecr.2017:16:1.
8. 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. 2018 Nov 9:e12619. doi: 10.1111/anec.12619.
9. Ukpabi OJ, Onwubere BJ. QTc prolongation in Black diabetic subjects with cardiac autonomic neuropathy. Afr Health Sci. 2017 Dec;17(4):1092-1100. doi: 10.4314/ahs.v17i4.1.
10. 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 Oct;56(5):675-80. doi: 10.1111/ped.12329.
11. 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 Mar;29(2):256-62. doi: 10.1007/s00380-013-0356-8.
12. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018 Jan;41(Suppl 1):S13-S27. doi: 10.2337/dc18-S002
13. 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 Nov;96(45):e8296. doi: 10.1097/MD.0000000000008296.
14. Vasheghani M, Sarvghadi F, Beyranvand MR. The association between cardiac autonomic neuropathy and diabetes control. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2019, 12:581-

15. 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 Sep-Oct;19(5):611-5. doi: 10.4103/1119-3077.188707.
16. 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 Oct;53(5):737-44. doi: 10.1007/s00592-016-0864-y.
17. Agashe S, Petak S. Cardiac Autonomic Neuropathy in Diabetes Mellitus. Methodist Debakey Cardiovasc J. 2018 Oct-Dec;14(4):251-256. doi: 10.14797/mdcj-14-4-251. PMID: 30788010
18. 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 Aug 28;12(8):e0183055. doi: 10.1371/journal.pone.0183055. PMID: 2884672
19. 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 Sep;54(9):871-876. doi: 10.1007/s00592-017-1018-6.
20. Matel D, Chiochină AD, Stratone A. Utility of QTc interval for the diagnosis of cardiac autonomic neuropathy in type 2 diabetes mellitus. Rev Med Chir Soc Med Nat Iasi. 2010 Jan-Mar;114(1):282-6. PMID: 20509317
21. Kuzu F. The effect of type 2 diabetes on electrocardiographic markers of significant cardiac events. Pak J Med Sci. 2018 May-Jun;34(3):626-632. doi: 10.12669/pjms.343.14562
22. 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. 2019 Jul 30:e12678. doi: 10.1111/anec.12678.
23. Orosz A, Baczkó I, Nyiraty S, Körei AE, Putz Z, Takács R, Nemes A, Várkonyi TT, Balogh L, Ábrahám G, Kempler P, Papp JG, Varró A, Lengyel C. Increased Short-Term Beat-to-Beat QT Interval Variability in Patients with Impaired Glucose Tolerance. Front Endocrinol (Lausanne). 2017 Jun 13;8:129. doi: 10.3389/fendo.2017.00129
24. Stern K, Cho YH, Benitez-Aguirre P, Jenkins AJ, McGill M, Mitchell P, Keech AC, Donaghue KC. QT interval, corrected for heart rate, is associated with HbA1c concentration and autonomic function in diabetes. Diabet Med. 2016 Oct;33(10):1415-21. doi: 10.1111/dme.13085.
25. 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 Oct;27(7):639-53. doi: 10.1002/dmrr.1239
26. Serhiyenko VA, Serhiyenko AA. Cardiac autonomic neuropathy: Risk factors, diagnosis and treatment. World J Diabetes. 2018 Jan 15;9(1):1-24. doi: 10.4239/wjd.v9.i1.1.

27. Khoharo HK, Halepoto AW. QTc-interval, heart rate variability and postural hypotension as an indicator of cardiac autonomic neuropathy in type 2 diabetic patients. J Pak Med Assoc. 2012 Apr;62(4):328-31.
28. Imam MH, Karmakar CK, Jelinek HF, Palaniswami M, Khandoker AH. Detecting Subclinical Diabetic Cardiac Autonomic Neuropathy by Analyzing Ventricular Repolarization Dynamics. IEEE J Biomed Health Inform. 2016 Jan;20(1):64-72. doi: 10.1109/JBHI.2015.2426206.
29. Arif ZA, Shaikh IA, Masood N. Cardiovascular autonomic neuropathy (CAN) in patients of type 2 diabetes mellitus: a tertiary care hospital based study. Indian Heart J. 2014 Nov-Dec;66(6):751-4. doi: 10.1016/j.ihj.2014.10.417.
30. Fisher VL, Tahrani AA. Cardiac autonomic neuropathy in patients with diabetes mellitus: current perspectives. Diabetes Metab Syndr Obes. 2017 Oct 6;10:419-434. doi: 10.2147/DMSO.S129797
31. Kittnar O. Electrocardiographic changes in diabetes mellitus. Physiol Res. 2015;64 Suppl 5:S559-66.
32. Kolo PM, Sanya EO, Olanrewaju TO, Fawibe AE, Soladoye A. Cardiac autonomic dysfunction in sickle cell anaemia and its correlation with QT parameters. Niger Med J. 2013 Nov;54(6):382-5. doi: 10.4103/0300-1652.126288.
33. Imam MH, Karmakar CK, Khandoker AH, Jelinek HF, Palaniswami M. Heart rate independent QT variability component can detect subclinical cardiac autonomic neuropathy in diabetes. Conf Proc IEEE Eng Med Biol Soc. 2016 Aug;2016:928-931. doi: 10.1109/EMBC.2016.7590853.
34. Khandoker AH, Imam MH, Couderc JP, Palaniswami M, Jelinek HF. QT variability index changes with severity of cardiovascular autonomic neuropathy. IEEE Trans Inf Technol Biomed. 2012 Sep;16(5):900-6.
35. Statsenko ME, Turkina SV, Shalaeva SS, Vinnikova AA. Impaired cardiac structural and functional parameters in patients with chronic heart failure and diabetic cardiac autonomic neuropathy. Ter Arkh. 2013;85(10):23-8.
36. Psallas M, Tentolouris N, Cokkinos A, Papadogiannis D, Cokkinos DV, Katsilambros N. QT dispersion: comparison between diabetic and non-diabetic individuals and correlation with cardiac autonomic neuropathy. Hellenic J Cardiol. 2006 Sep-Oct;47(5):255-62.
37. Clemente D, Pereira T, Ribeiro S. Ventricular repolarization in diabetic patients: characterization and clinical implications. Arq Bras Cardiol. 2012 Nov;99(5):1015-22. doi: 10.1590/s0066-782x2012005000095
38. Takahashi N, Nakagawa M, Saikawa T, Watanabe M, Doie T, Yufu X, et al. Regulation of QT indicies mediated by autonomic nervous function in patients with type 2 diabetes. Int J Cardiol. 2004 Sep;96(3):375-9. doi: 10.1016/j.ijcard.2003.07.026.
39. Tanikawa T, Abe H, Tanaka Y, Nakashima X. "cardiac autonomic balance and QT dispersion during head-up tilt testing in diabetics with and without sensory neuropathy. Clin Exp Hypertens. 2004 Feb;26(2):137-44. doi: 10.1081/ceh-120028551.
40. Bonakdar HR, Aslanpour M, Moladoust H, Sadeghipour P, Mohamadi F, Rad 1, Jalal Kheirkhah MA. Comparison between QT Interval Parameters in Type 2 Diabetic and Nondiabetic Patients with Non-

ST Elevation Myocardial Infarction. J Tehran Heart Cent. 2014;9(4):166-73. PMID: 25870641

41. 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. doi: 10.1055/s-2003-42726

Tables

Table 1 - Basic characteristics of diabetic patients with and without CAN

Variables (Mean ± SD)	**Patients with CAN**	**Patients without CAN**	**P_Value**
Age (Years)	51.73±13.24	50.41±14.43	0.5
Duration of DM (Month)	**94.83±34.38**	**68.16 ± 35.15**	**0.01**
FBS (mg/dl)	178.13±86.78	158.59±81.44	0.3
BS 2 Hours Post Prandial (mg/dl)	220.6±104.51	222.4±114.63	0.7
HbA1C (%)	8.14±2.09	7.74±10.77	0.2
BMI (kg/m^2)	**28.06±5.36**	**27.37±4.22**	**0.05**
Total Cholesterol (mg/dl)	209±39.84	203.72±48.26	0.2
Triglyceride (mg/dl)	205.26±152.35	189.4±104.71	0.3
HDL (mg/dl)	44.56±13.52	51.77±30.44	0.5
LDL (mg/dl)	**165.52±95.56**	**119.78±40.41**	**0.008**

Table 2 - The QT intervals indices (Mean ± SD) in diabetic patients with and without CAN

Variables (Mean ± SD, msec)	**Patients with CAN**	**Patients without CAN**	**P_Value**
QT min	340±32	334.7±31	0.8
QT max	**400.9±34**	**395±34**	**0.03**
QT mean	**375±29**	**365±32**	**0.05**
QTc	415±34	406±32	0.15
QTd	**69±24**	**58±19**	**0.02**

Table 3 – The prevalence of prolonged QTc and abnormal QTd in diabetic patients with and without CAN

Variables	Patients with CAN	Patients without CAN	P_Value
QTc			1
Prolonged	12%	10%	
(>440 msec in male; >460 msec in female)			
Normal	88%	90%	
QTd			0.13
Abnormal (>80msec)	20%	15%	
Normal	80%	85%	

Figures

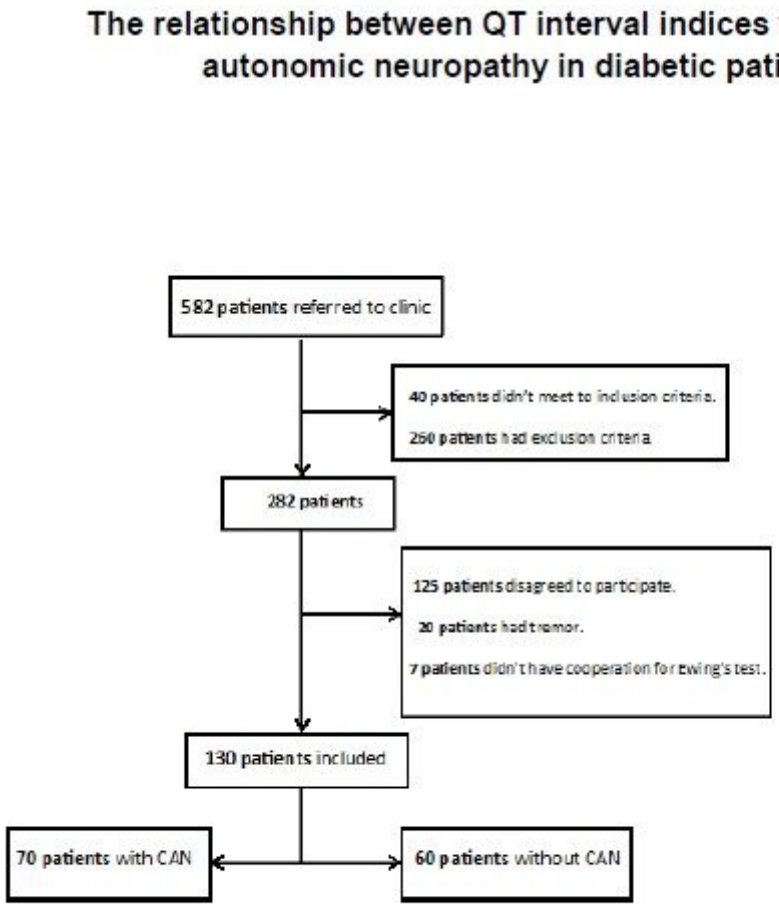

Figure 1- Study Design Diagram

Figure 1

Study Design Diagram