JPSIM Journal of Pakistan Society of Internal Medicine

Original Article

Assessment of QTc Interval Prolongation and its Relationship with Glycemic Control in Diabetic Populations across Demographic and Clinical Spectrums

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Abstract

Objective: To assess the QTc Interval Prolongation and its Relationship with Glycemic Control in Diabetic Populations across Demographic and Clinical Spectrums.

Methods: This cross-sectional study was carried out with outpatients visiting the Department of Medicine at Quaid-e-Azam Medical College in Bahawalpur, from November 2022 to May 2023. It involved a total of 255 diabetic patients, encompassing both genders, aged between 40 and 70 years. The focus was on evaluating the prolonged QTc interval.

Results: The mean age of the patients is 54.23 ± 9.49 years, the HbA1c level is 7.32 ± 0.449, and the mean QTc interval is 439.88 ± 14.795 milliseconds, respectively. Among the 255 diabetic patients studied, prolonged QTc was noted in 98 (38%) of them. The mean HbA1c level for patients with prolonged QTc is 7.40 ± 0.374 contrasting with a slightly lower mean of 7.27 ± 0.485 in patients without prolonged QTc. The statistical significance of this difference is underscored by a P value of 0.024.

Conclusion: In conclusion, our study of 255 diabetic patients, showed a high prevalence of prolonged QTc intervals, observed in 38% of the patients. The study highlighted a significant correlation between prolonged QTc intervals and HbA1c levels, particularly pronounced in specific demographic and clinical subgroups. Elevated HbA1c levels were more frequently associated with QTc prolongation, especially in younger patients (40-55 years) and those with dyslipidemia. However, the study found no significant difference in QTc prolongation between genders.

Keywords: QTc dispersion, Glucose variability, type 2 diabetes, ECG, QT interval

How to cite this:

Noor S, Saeed R, Khan S, Bilal MH, Nayyer N, Iqbal J. Assessment of QTc Interval Prolongation and its Relationship with Glycemic Control in Diabetic Populations across Demographic and Clinical Spectrums. J Pak Soc Intern Med. 2024;5(1): 413-417

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Introduction

Diabetes mellitus (DM) is one of the metabolic conditions which is characterized by raised blood glucose levels, stemming from either enhanced insulin resistance or decreased insulin production.[1] Recognized globally as an escalating health concern, diabetes significantly impacts individuals, societies, and economies worldwide. Diabetes ranks as a major cause of death worldwide and contributes substantially to global healthcare spending.[2] In 2019, it was estimated that diabetes affected 463 million people globally, a number projected to increase by 10.2% by 2030. Unmanaged hyperglycemia, a hallmark of both Type I & II diabetes, can lead to severe health complications if not addressed promptly.[3] DM significantly increases the risk of various cardiovascular diseases (CVD), such as heart failure, myocardial infarction, arrhythmias and it significantly increases the risk of mortality.[4] Cardiovascular diseases, affecting the heart and blood vessels, are the principal cause of diabetes-related deaths and morbidities. Therefore, early screening for cardiovascular complications in diabetic patients is crucial.[5]

In individuals with diabetes, cardiac autonomic neuropathy (CAN) is a most common complication that significantly raises the mortality rate in these patients.[6] CAN in diabetic patients is identified by various symptoms, including changes in heart rate variability, postural hypotension, resting tachycardia, asymptomatic myo-

cardial infarction, and an increased risk of sudden cardiac death. Research has consistently shown a direct relationship between how long a person has had diabetes and the likelihood of developing CAN.[7] The QT interval on an ECG, indicating ventricular contraction and relaxation, when prolonged, signifies an elevated risk of arrhythmias and related complications. Increased QT interval has been linked to autonomic neuropathy.[8] Thus, any diabetic patient presenting with abnormal QT intervals during routine visits should be thoroughly evaluated for potential cardiovascular complications. The QT interval, influenced by factors like age, sex, and heart rate, must be corrected for heart rate, known as the QTc interval. Sertbaset al.[9] discovered that 21% of diabetic patients exhibit prolonged QTc intervals.

Managing blood sugar levels is crucial in treating type 2 diabetes. Prolongation of the QTc interval is linked to the severity of CAN in diabetes patients. A prolonged QTc interval can lead to severe arrhythmias and sudden death. This risk is further elevated when combined with kidney disease, increasing the mortality rate among these patients. Increasingly, research indicates that controlling blood glucose can impact cardiac repolarization, thereby affecting the likelihood of deadly ventricular arrhythmias. Data from this study would help us to determine the magnitude of problem in our population as there is paucity of local literature. Moreover, based on the outcome of this study strategies will be developed for prevention and monitoring of diabetic patients at risk of developing cardiac autonomic neuropathy. Furthermore, early detection and treatments like physical exercise, weight reduction, antihypertensive medications, and beta-blockers can mitigate the harmful effects of cardiac autonomic neuropathy (CAN).

Methods

The study, employing a cross-sectional design, was conducted at the outpatient services of the Department of Medicine, Quaid-e-Azam Medical College in Bahawalpur. It spanned from November 2022 to May 2023, involving patients who visited the outpatient department during this period. Total 255 diabetic patients of both male and female having age 40-70 were selected. The sample size of 256 patients was determined based on an assumed prevalence of prolonged QTc in diabetic patients at 21%, with a margin of error of 5% and a confidence level of 95%. Non-probability consecutive sampling was employed for patient selection.[9]

Patients with known cardiac disease (i.e Ischemic and valvular heart disease, arrhythmias, cardiomyopathies, structural heart disease etc), thyroid dysfunction, chronic lung, renal and liver diseases, patients with history of alcohol intake, any drug intake like, antipsychotic, antihistamine, macrolide or on azole antifungal which may affect QT interval were excluded.

Before the study commenced, approval was obtained from the institutional ethics review committee. Before participation, all study subjects were briefed on the possible risks and advantages associated with the study. Following this, written consent was obtained from each individual agreeing to participate. Baseline characteristics including age and gender was noted on predesigned Performa. Standard 12 lead Electrocardiography was done in out-patient department on presentation. QT interval and R-R interval was measured from standard 12 lead ECG using magnifying glass and calipers. HbA1c level was analyzed for enrolled patients from pathology department of Quaid-e-Azam Medical College Bahawalpur. All information was noted on preformed Proforma.

Data was analyzed using IBM SPSS Version 26.0 and was presented in the form of graphs and tables. Quantitative variables like, age, QTc interval and HbA1c was presented as mean ± standard deviation. Qualitative variables like, gender (Male/Female, dyslipidemia (Yes/No)and prolonged QTc interval (Yes/No) was presented as percentage and frequencies.

Comparison of HbA1C was performed using independent t test taking p-value of ≤ 0.05 as statistically significant. Stratification was done with regards to age, gender and dyslipidemia to see the effect of these on the outcome variable (prolonged QTc interval). Post stratification chi square test/Fischer test was applied taking p-value of ≤ 0.05 as statistically significant.

Results

The mean age of the patients is 54.23 ± 9.49 years, the HbA1c level is 7.32 ± 0.449, and the mean QTc interval is 439.88 ± 14.795 milliseconds, respectively. Among the 255 diabetic patients studied, prolonged QTc was noted in 98 (38%) of them (Fig. 1).

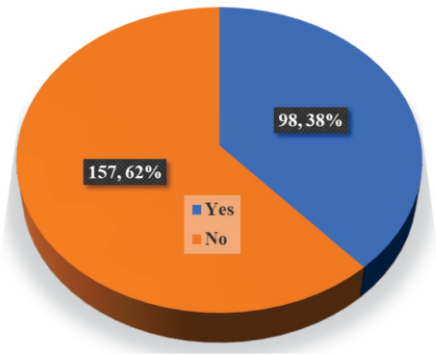

Fig. 1: *Frequency of prolonged QTC intervals (n=255)*

Data presented in Table 1 focus on the association between prolonged QTc intervals and age groups among diabetic patients attending follow-up. The patients are divided into two age brackets: 40-55 years and 56-70 years. A notable observation is made in the younger

age group (40-55 years), where 67 (51.94%) patients exhibit prolonged QTc intervals. In comparison, the older age group (56-70 years) demonstrates a lower frequency, with 31 (24.60%) patients experiencing prolonged QTc. This significant contrast in prevalence between the two age groups is statistically significant (P=0.000).

In terms of gender, 61 out of 142 male patients (42.96%) exhibit prolonged QTc intervals. Conversely, a slightly lower frequency is observed in female patients, with 37 out of 113 (32.74%) experiencing prolonged QTc. Although there is a noticeable difference in the frequency of prolonged QTc between genders, the P value of 0.096 suggests that this difference is not statistically significant. This indicates that, while there is a trend towards a higher prevalence of prolonged QTc in males compared to females, the difference is not conclusive in our study.

The study also investigates the relationship between extended QTc intervals and the occurrence of dyslipidemia in patients with diabetes. Patients are categorized based on their dyslipidemia status. Among those with dyslipidemia, a significant proportion, 48 out of 102 (47.06%), exhibit prolonged QTc intervals. In contrast, patients without dyslipidemia show a lower incidence of prolonged QTc, with 50 out of 153 (32.68%) having this condition. The P value of 0.021 indicates a statistically significant association between dyslipidemia and prolonged QTc in this sample.

Table 1: *Association of prolonged QTC interval with different variables*

Variables	Prolonged QTC		Total	P value
	Yes (%)	No (%)		
Age group				
40-55 years	67 (51.94)	62 (48.06)	129	
56-70 years	31 (24.60)	95 (75.40)	126	0.000
Total	98 (38)	157 (62)	255	
Gender				
Male	61 (42.96)	81 (57.04)	142	
Female	37 (32.74)	76 (67.26)	113	0.096
Total	98 (38)	157 (62)	255	
Dyslipidemia				
Yes	48 (47.06)	54 (52.94)	102	
No	50 (32.68)	103 (67.32)	153	0.021
Total	98	157	255	

Table 2 offers a detailed comparative analysis of mean HbA1c levels among diabetic patients, highlighting differences between those with and without prolonged QTc intervals. Notably, the mean HbA1c level for patients with prolonged QTc is 7.40 (standard deviation: 0.374), contrasting with a slightly lower mean of 7.27 (standard deviation: 0.485) in patients without prolonged QTc. The statistical importance of this difference is highlighted by a P value of 0.024, indicating a possible association between elevated HbA1c levels and the likelihood of QTc interval prolongation in patients with diabetes.

Table 2: *Comparison of mean HBA1C between with and without prolonged QTC*

Prolonged QTC	N	Mean	Std. Deviation	P value
Yes	98	7.40	0.374	0.024
No	157	7.27	0.485	

Further stratification of the data reveals age-related trends. In the 40-55 years age group, those with prolonged QTc exhibit a mean HbA1c of 7.31 (standard deviation: 0.402), significantly higher than the 7.17 (standard deviation: 0.310) seen in counterparts without prolonged QTc (P value: 0.0295). In the older age group of 56-70 years, this disparity is even more evident; patients with prolonged QTc have a mean HbA1c of 7.60 (standard deviation: 0.196), compared to 7.34 (standard deviation: 0.562) in those without (P value: 0.0130). These results clearly indicate an association between higher HbA1c levels and prolonged QTc intervals across different age groups.

When examining the data by gender, interesting patterns emerge. Male patients with prolonged QTc have a mean HbA1c level of 7.62 (standard deviation: 0.297), slightly higher than the 7.47 (standard deviation: 0.541) in males without prolonged QTc, though this difference is not statistically significant (P value: 0.0527). In contrast, female patients show nearly identical mean HbA1c levels regardless of QTc status: 7.04 (standard deviation: 0.109) for those with prolonged QTc and 7.05 (standard deviation: 0.289) for those without, highlighted by a non-significant P value of 0.8394. This suggests that, unlike in males, HbA1c levels in females do not vary significantly in relation to QTc prolongation.

The stratified analysis also includes dyslipidemia status. Among patients with dyslipidemia, those with prolonged QTc have a mean HbA1c of 7.72 (standard deviation: 0.199), slightly higher than the 7.65 (standard deviation: 0.542) in those without prolonged QTc. However, the lack of statistical significance (P value: 0.400) indicates that HbA1c levels are not markedly different between groups within the dyslipidemia category. A similar pattern is observed in the non-dyslipidemia group, with no significant difference in mean HbA1c levels between those with (7.10, standard deviation: 0.213) and without prolonged QTc (7.07, standard deviation: 0.304), as indicated by a P value of 0.5318. These findings collectively suggest that the presence or absence of dyslipidemia does not significantly impact the relationship between HbA1c levels and prolonged QTc intervals in diabetic patients.

Table 3: *Stratification in relation to different groups*

Prolonged QTC	N	Mean	Std. Deviation	P value
Age group 40-55 years				
Yes	67	7.31	0.402	0.0295
No	62	7.17	0.310	
Age group 56-70 years				
Yes	31	7.60	0.196	0.0130
No	95	7.34	0.562	
Male gender				
Yes	61	7.62	0.297	0.0527
No	81	7.47	0.541	
Female gender				
Yes	37	7.04	0.109	0.8394
No	76	7.05	0.289	
dyslipidemia				
Yes	48	7.72	0.199	0.400
No	54	7.65	0.542	
Non-dyslipidemia				
Yes	50	7.10	0.213	0.5318
No	103	7.07	0.304	

Discussion

In our study assessing QTc interval prolongation and its relationship with glycemic control in diabetic populations, we observed that 38% of the 255 diabetic patients had prolonged QTc intervals. This was particularly evident in the younger age group (40-55 years), with a higher prevalence (51.94%) compared to the older group (56-70 years) at 24.60%. The study also uncovered a gender-related trend, where a higher incidence of prolonged QTc was noted in male patients (42.96%) than in female patients (32.74%), although this difference was not statistically significant. Furthermore, an association between prolonged QTc intervals and dyslipidemia was identified, alongside a potential link between elevated HbA1c levels and QTc prolongation, particularly in younger diabetic patients.

When contextualized with similar studies, our findings are both corroborated and contrasted. For example, Lu Z et al.[10] highlighted the significant impact of Tyrosine Kinase Inhibitors (TKIs) on QTc prolongation in diabetic patients, underscoring the influence of specific treatments on cardiac health. Noori NM et al.'s[11] study, which compared cardiac electrophysiological parameters between diabetic patients and healthy controls, aligns with our observations of higher QT intervals in diabetic patients. In contrast, Sertbas Y et al.'s9 research found a lower prevalence of prolonged QTc (21%) but noted a significant correlation with glycemic variability, which our study did not specifically evaluate.

The study by Sivieri R et al.[12] further enriches this context by demonstrating that QT prolongation is more common in diabetic patients than in non-diabetic controls and is particularly higher in patients with autonomic neuropathy. Yang XH et al.'s[13] findings on the negative correlation between QTc interval and insulin sensitivity also provide an important perspective, suggesting that reduced insulin sensitivity is associated with increased QTc interval risk.

The study by Taubel J and colleagues,[14] which focuses on the increased risk of sudden cardiac death in diabetic patients and the complex factors contributing to QTc prolongation, underscores the importance of comprehensive cardiovascular care in the management of diabetes. Finally, the study by Lafqih MB et al.[15] offers insights into smoking and diuretic usage as risk factors for QTc prolongation, underscoring the multifaceted nature of this cardiac risk in diabetic populations.

Conclusion

In conclusion, our study of 255 diabetic patients, showed a high prevalence of prolonged QTc intervals, observed in 38% of the patients. The study highlighted a significant correlation between prolonged QTc intervals and HbA1c levels, particularly pronounced in specific demographic and clinical subgroups. Elevated HbA1c levels were more frequently associated with QTc prolongation, especially in younger patients (40-55 years) and those with dyslipidemia. However, the study found no significant difference in QTc prolongation between genders. These findings underscore the importance of rigorous glycemic control in diabetic patients, especially considering the potential risk of QTc prolongation and its implications on cardiac health. This study contributes to a better understanding of the cardiac risks in diabetic patients and underscores the need for targeted interventions based on demographic and clinical characteristics.

Conflict of Interest: None

Funding Source: None

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