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RESEARCH ARTICLE
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ASSOCIATION OF CORRECTED QT INTERVAL WITH MICROVASCULAR COMPLICATIONS OF TYPE 2 DIABETES MELLITUS

Dr. Tejashree Pasumarthy[1], Dr. Fareeha Afreen[2*], Dr. Pooja Rajesh Naik[3], Dr. Seetha VSR Prashanthi[4], Dr. Javeria Afshan[5]

[1]Post graduate, Department of General Medicine, Vydehi Institute of Medical Sciences and Research Centre, Bangalore- 560066, Email- teja.sree94@gmail.com
[2*]Post graduate, Department of General Medicine, Vydehi Institute of Medical Sciences and Research Centre, Bangalore- 560066, Email- faru_053@yahoo.co.in
[3]Assistant professor, department of general medicine, KLE JGMMMC,Hubli, Kle academy of Higher education and Research", Email - pjnaik12@gmail.com
[4]Post graduate, Department of General Medicine, Vydehi Institute of Medical Sciences and Research Centre,Bangalore- 560066, Email - drprashanthiseetha@gmail.com
[5]Senior Resident, Department of General Medicine Bangalore Medical College and Research Institute, afsjaveria@gmail.com

***Corresponding Author -** Dr. Fareeha Afreen
*Email: faru_053@yahoo.co.in

ABSTRACT

Background and Objectives: There is a rising incidence of type 2 diabetes mellitus, and hyperglycaemia is known to cause microvascular complications and macrovascular complications like ischemic heart disease and sudden cardiac death. Each microvascular complication is an independent risk factor for sudden cardiac death. QT interval, corrected for heart rate, is a simple electrocardiogram (ECG)-based method indicating cardiac repolarization abnormality. Prolonged QTc lowers the threshold for life-threatening cardiac arrhythmias. The present study examines the association of QTc interval with microvascular complications in diabetes mellitus.

Methods: A cross-sectional study was conducted from January 2020 to June 2021. A total of 117 patients with type 2 diabetes mellitus were enrolled after obtaining informed consent. All participants underwent clinical examination and laboratory investigations. Statistical analysis was performed to correlate the QTc interval with microvascular complications using SPSS software. Unpaired t-test and chi-square test were applied.

Results: Out of 117 patients, 45 were female and 72 were male. Prolonged QT interval was found in 12% of participants ($p < 0.001$). There was no significant difference in age, duration of diabetes, or glycemic control between those with and without prolonged QT. QT prolongation was significantly associated with diabetic retinopathy (20.3%), nephropathy (22.9%), and neuropathy (29.0%).

Conclusion: There is a significant association between QT interval prolongation and the severity and multiplicity of diabetic microvascular complications. QTc interval serves as a simple and cost-effective method for early detection of cardiovascular risk in patients with type 2 diabetes mellitus.

Keywords: Type 2 diabetes mellitus, microvascular complications, QTc interval

INTRODUCTION

Diabetes mellitus (DM) is a common metabolic disorder characterized by chronic hyperglycemia resulting from an absolute or relative deficiency in insulin secretion and/or action, leading to widespread pathophysiological changes across multiple organ systems [1]. Complications of DM are broadly categorized into vascular and nonvascular types. Vascular complications include macrovascular disease such as coronary heart disease, cerebrovascular events, and peripheral arterial disease and microvascular disease, encompassing diabetic retinopathy, nephropathy, and neuropathy. Nonvascular complications often involve recurrent infections, hearing impairment, and various dermatological manifestations [4].

Globally, the prevalence of diabetes has risen dramatically over recent decades. Estimates grew from approximately 30 million affected individuals in 1985 to 537 million adults aged 20–79 years in 2021; projections suggest this figure will reach 643 million by 2030 and 783 million by 2045 [2,3]. Such an upward trend underscores the growing public health burden posed by DM and its sequelae.

Diabetic nephropathy (DN) represents a leading cause of chronic kidney disease and end-stage renal disease (ESRD), frequently necessitating renal replacement therapy. Notably, up to 20% of patients with type 2 DM already exhibit nephropathy at the time of diagnosis [5]. Diabetic retinopathy (DR), a major cause of adult blindness, is classified into non-proliferative (NPDR) and proliferative (PDR) forms, and is often accompanied by other ocular conditions such as cataracts and glaucoma, which occur earlier and more frequently in diabetic patients [4].

Diabetic neuropathy encompasses a heterogeneous group of disorders affecting both peripheral and autonomic nerves. The most common presentation is distal symmetric polyneuropathy, which can cause sensory loss and pain. Of particular concern is cardiac autonomic neuropathy (CAN), which may lead to subclinical cardiac dysfunction and substantially elevate the risk of sudden cardiac death, even in the absence of overt ischemic heart disease [5].

Prolongation of the heart-rate–corrected QT interval (QTc) on electrocardiogram is a recognized marker of CAN and has been independently associated with increased cardiovascular mortality in type 2 DM. Early identification of QTc prolongation enables timely interventions such as tailored physical activity programs, weight management, optimized blood pressure control, and beta-adrenergic blockade to mitigate arrhythmic risk and improve outcomes [6].

OBJECTIVES OF THE STUDY

- To measure the corrected QT interval in patients with type 2 diabetes mellitus.
- To determine the association of corrected QT interval with the microvascular complications of type 2 diabetes mellitus.

MATERIALS AND METHODS

Study Design and Setting

A hospital-based, cross-sectional study was conducted at Vydehi Institute of Medical Sciences and Research Centre, Bengaluru. The study was carried out over a period of one and a half years, from January 2020 to June 2021.

Study Population and Source of Data

The study population consisted of patients diagnosed with type 2 diabetes mellitus, who were either visiting the outpatient department or admitted to the Department of General Medicine and the Department of Endocrinology. Eligible patients were recruited consecutively after providing informed written consent.

Sample Size Calculation

The required sample size was estimated using the formula:

$N=Z^2\ \sigma^2/d^2$

n" Sample Size , where $Z = 1.96$ for 95% confidence level, σ = standard deviation of QT interval (22 ms), and d = margin of error (4 ms). The calculated sample size was 117 participants.

Inclusion Criteria
Patients were included if they were:
- Known cases of type 2 diabetes mellitus
- Aged between 30 and 65 years
- Of either sex
- Willing to provide informed consent for participation in the study

Exclusion Criteria
Patients were excluded if they had any of the following:
- Cardiovascular autonomic neuropathy (e.g., orthostatic hypotension, resting tachycardia >100 bpm)
- History of ischemic heart disease, myocarditis, cerebrovascular accidents, subarachnoid hemorrhage, encephalitis, or head injury
- Presence of pacemaker, hypothyroidism, or electrolyte imbalance
- Atrial fibrillation, major ventricular conduction defects (QRS duration >120 ms), or left ventricular hypertrophy
- Use of QT-prolonging medications, such as anti-arrhythmic agents (e.g., amiodarone, quinidine), antipsychotics (e.g., haloperidol, ziprasidone), antidepressants (e.g., amitriptyline, sertraline), digoxin, ketoconazole, and fluoroquinolones (e.g., ciprofloxacin)
- History of alcohol consumption or gestational diabetes mellitus

Ethical Considerations
Ethical approval for the study was obtained from the Institutional Ethics Committee. Written informed consent was obtained from all participants before enrollment.

Data Collection and Clinical Evaluation
Participants underwent comprehensive clinical evaluation using a structured proforma. Demographic details, duration and treatment history of diabetes, past medical and drug history were recorded. General physical examination included assessment of height, weight, BMI, pulse rate, and blood pressure. Systemic examination was performed in all cases.

Electrocardiographic and Clinical Assessments
A 12-lead electrocardiogram (ECG) was recorded on the day of admission. The QT interval was measured manually in lead II from the onset of the QRS complex to the end of the T wave as it crossed the isoelectric line. The RR interval was determined by counting the number of small boxes between two R wave peaks in the same lead. The QTc interval was calculated using Bazett's formula.
Fundoscopic examination was performed by an ophthalmologist to evaluate for diabetic retinopathy. Diabetic neuropathy was assessed using the Semmes-Weinstein monofilament test applied at 10 random points on the foot. Diabetic nephropathy was determined by relevant laboratory investigations, including urine albumin levels.

Statistical Analysis
Data were analyzed using SPSS version 22. Categorical variables were presented as percentages, while continuous variables were expressed as mean ± standard deviation. The unpaired t-test was used to compare mean QTc intervals between groups. The chi-square test was employed to assess associations between QTc prolongation and presence of microvascular complications. A p-value <0.05 was considered statistically significant.

Results:
Participant Characteristics and Disease Duration

Category	Subcategory	Frequency	Percentage (%)
Sex	Female	45	38.5
	Male	72	61.5
Age group	31 – 40 years	7	6
	41 – 50 years	36	30.8
	51 – 60 years	47	40.2
	61 – 65 years	27	23.1
Duration of diabetes	< 1 year	16	13.7
	1 – 5 years	36	30.8
	6 – 10 years	34	29.1
	11 – 15 years	19	16.2
	> 15 years	12	10.3
Microvascular complications	Retinopathy	59	50.4
	Nephropathy	48	41
	Neuropathy	31	26.5
Multiple microvascular complications	Retinopathy + nephropathy	41	35.04
	Nephropathy + neuropathy	24	20.51
	Retinopathy + neuropathy	22	18.8
	All three complications	21	17.95

Table 1. Demographic and Clinical Characteristics of Study Participants

The study enrolled 117 patients with type 2 diabetes mellitus, of whom 61.5% were male and 38.5% female. The largest age group was 51–60 years (40.2%), followed by 41–50 years (30.8%), 61–65 years (23.1%), and 31–40 years (6.0%). Diabetes duration varied: 13.7% of participants had been diagnosed for less than one year, 30.8% for 1–5 years, 29.1% for 6–10 years, 16.2% for 11–15 years, and 10.3% for over 15 years.

Prevalence of Microvascular Complications

Complication	< 1 yr	1–5 yrs	6–10 yrs	11–15 yrs	>15 yrs	Total	P-value
Retinopathy Absent	11 (68.8%)	22 (61.1%)	13 (38.2%)	8 (42.1%)	4 (33.3%)	58 (49.6%)	0.103
Retinopathy Present	5 (31.3%)	14 (38.9%)	21 (61.8%)	11 (57.9%)	8 (66.7%)	59 (50.4%)	
Nephropathy Absent	12 (75.0%)	25 (69.4%)	20 (58.8%)	9 (47.4%)	3 (25.0%)	69 (59.0%)	0.039
Nephropathy Present	4 (25.0%)	11 (30.6%)	14 (41.2%)	10 (52.6%)	9 (75.0%)	48 (41.0%)	
Neuropathy Absent	15 (93.8%)	29 (80.6%)	26 (76.5%)	10 (52.6%)	6 (50.0%)	86 (73.5%)	0.017
Neuropathy Present	1 (6.3%)	7 (19.4%)	8 (23.5%)	9 (47.4%)	6 (50.0%)	31 (26.5%)	

Table 3. Association of Diabetes Duration with Microvascular Complications

Half of the cohort (50.4%) exhibited diabetic retinopathy, 41.0% had nephropathy, and 26.5% had neuropathy. Multiple complications were common: 35.0% had both retinopathy and nephropathy, 20.5% had nephropathy and neuropathy, 18.8% had retinopathy and neuropathy, and 17.9% had all three.

	Minimum	Maximum	Mean	Std. Deviation
QTc interval	330.0	520.0	407.650	26.1301

Table 4. Descriptive Statistics of QTc Interval

Category	Mean	SD	Mean	SD	P values
Age	53.05	8.41	51.50	8.95	0.522

Duration of diabetes (years)		5.98	7.54		
FBS (mg/dl)	202.97	97.85	193.93	139.40	0.759
PPBS (mg/dl)	281.67	111.95	276.00	160.24	0.867
HbA1c	9.40	2.49	9.52	3.71	0.877
CHL (mg/dl)	183.91	61.80	181.93	55.25	0.909
TGL (mg/dl)	202.80	163.23	163.93	83.69	0.384
HDL (mg/dl)	36.84	12.42	35.62	8.12	0.723
LDL (mg/dl)	109.92	45.53	100.45	32.88	0.454
Spot Urine ACR	80.39	317.86	279.16	451.51	0.040
Monofilament test	1.39	2.78	4.93	4.10	<0.001

Table 5. Association of QTc Prolongation (≥440 ms) with Clinical and Laboratory Parameters

The prevalence of nephropathy and neuropathy increased significantly with longer diabetes duration. Nephropathy rose from 25.0% among those with disease duration under one year to 75.0% in those with more than 15 years of diabetes (p=0.039). Neuropathy similarly increased from 6.3% to 50.0% over the same intervals (p=0.017). Although retinopathy prevalence climbed from 31.3% to 66.7%, this did not reach statistical significance (p=0.103).

Complication	**QTc < 440 ms**	**QTc > 440 ms**	**Total**	**P-value**
Retinopathy Absent	56 (96.6%)	2 (3.4%)	58 (49.6%)	0.005
Retinopathy Present	47 (79.7%)	12 (20.3%)	59 (50.4%)	
Nephropathy Absent	66 (95.7%)	3 (4.3%)	69 (59.0%)	0.002
Nephropathy Present	37 (77.1%)	11 (22.9%)	48 (41.0%)	
Neuropathy Absent	81 (94.2%)	5 (5.8%)	86 (73.5%)	0.001
Neuropathy Present	22 (71.0%)	9 (29.0%)	31 (26.5%)	
Total	**103 (88.0%)**	**14 (12.0%)**	**117 (100.0%)**	

Table 5. Distribution of QTc Categories (<440 ms vs. ≥440 ms) According to Microvascular Complication Status

QTc Interval Findings and Associations

QTc intervals ranged from 330 to 520 ms, with a mean of 407.7 ± 26.1 ms. Prolonged QTc (≥440 ms) was observed in 12.0% of patients. Those with nephropathy and neuropathy had significantly higher rates of QTc prolongation (22.9% and 29.0%, respectively) compared to those without these complications (4.3% and 5.8%; p=0.002 and p=0.001). Retinopathy was also associated with QTc prolongation (20.3% vs. 3.4%; p=0.005). No significant differences in age, glycemic indices, lipid profile, diabetes duration, or treatment modality were observed between QTc groups. However, spot urine albumin-creatinine ratio and monofilament scores were significantly elevated in the prolonged-QTc group (p=0.040 and p<0.001), supporting a link between QTc prolongation and the severity of microvascular damage.

Variable	**QTc < 440 ms**	**QTc > 440 ms**	**Total**	**P-value**
Duration of Diabetes				
< 1 year	14 (87.5%)	2 (12.5%)	16	**0.668**
1 – 5 years	30 (83.3%)	6 (16.7%)	36	
6 – 10 years	32 (94.1%)	2 (5.9%)	34	
11 – 15 years	16 (84.2%)	3 (15.8%)	19	
> 15 years	11 (91.7%)	1 (8.3%)	12	
Total	**103 (88.0%)**	**14 (12.0%)**	**117**	
Treatment History				
Oral	77 (86.5%)	12 (13.5%)	89	**0.457**
Injection	10 (100.0%)	0 (0.0%)	10	

Both	16 (88.9%)	2 (11.1%)	18	
Total	**103 (88.0%)**	**14 (12.0%)**	**117**	
Fundoscopy Findings				
No DR	56 (96.6%)	2 (3.4%)	58	**0.005**
NPDR	42 (82.4%)	9 (17.6%)	51	
PDR	5 (62.5%)	3 (37.5%)	8	
Total	**103 (88.0%)**	**14 (12.0%)**	**117**	

DISCUSSION

The risk of sudden cardiac death is higher in individuals with prolonged corrected QT interval [6]. Hence, monitoring the QTc interval in patients with type 2 diabetes mellitus is crucial. Several studies have explored the relationship between diabetes-associated microvascular complications and QTc prolongation [7]. This study aimed to investigate the association between multiple microvascular complications and QTc duration.

In our cohort of 117 patients (45 females, 72 males) aged 30–65 years, the mean QTc was 407.65 ms. A QTc >440 ms is universally considered prolonged, though gender differences exist, and the average age of QTc prolongation in our sample was 51.5 ± 8.95 years. Veglio et al. reported QTc prolongation in as many as 26% of type 2 diabetics [8], whereas we observed a 12% prevalence, with higher rates in men than women. Our participants' mean age was over 50 years, contrasting with the younger cohort studied by Jobe et al. [9], likely reflecting the loss of premenopausal hormonal protection among women in our sample [10].

Brown et al. identified multiple determinants of QTc prolongation including age, fasting glucose, female sex, and glycemic control [11,12] although Cardoso et al. did not confirm these associations [13]. In our study, QTc duration did not differ significantly by age, diabetes duration, or glycemic indices, suggesting other mechanisms at play.

Although not statistically significant, patients on insulin (versus oral agents) tended toward longer QTc, consistent with reports that insulin therapy can lengthen QT via sympathetic activation and shifts in serum potassium [14,15]. Hypoglycemia induced by insulin or sulfonylureas has likewise been implicated in QTc prolongation [16], reflecting its role within the insulin-resistance syndrome [17].

We found QTc prolongation in 20.3% of patients with retinopathy, 22.9% with nephropathy, and 29.0% with neuropathy. Hyperglycemia-induced reductions in nitric oxide can impair Ca^{2+}-ATPase and Na^{+}/K^{+}-ATPase activity in cardiomyocytes, prolonging repolarization [18]. Endothelial dysfunction, oxidative stress, and chronic inflammation key drivers of microvascular damage share these pathophysiological pathways [19]. Thus, our findings support a common etiological link between diabetic microvascular complications and QTc prolongation.

Furthermore, the severity and multiplicity of microvascular complications were independently associated with prolonged QTc. These results underscore QTc interval as a simple, cost-effective marker for identifying diabetic patients at elevated cardiovascular risk.

CONCLUSION

In this cross-sectional study of 117 patients with type 2 diabetes mellitus, QTc interval prolongation showed a clear, independent association with the presence, severity, and multiplicity of microvascular complications namely diabetic retinopathy, nephropathy, and neuropathy. Patients exhibiting more advanced or multiple microvascular lesions were significantly more likely to have prolonged QTc, placing them at elevated risk for potentially life-threatening cardiac arrhythmias. Given its simplicity, reproducibility, and low cost, routine measurement of the QTc interval in diabetic patients particularly those with established microvascular disease can serve as an effective screening tool to identify individuals at increased cardiovascular risk and guide early preventive interventions.

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