Original Article

Prolonged QTc Interval as an Indicator of Cardiac Autonomic Neuropathy in Diabetes Mellitus Patients

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Abstract

Background: Cardiac autonomic neuropathy (CAN) is linked with increased risk of cardiac arrhythmias and sudden death from silent myocardial ischemia, and hence, it is a significant contributor to morbidity and mortality in diabetes patients. For diagnosis of CAN, there are several non-invasive diagnostic tests but take a long time and are not appropriate for screening broad population. Numerous studies have indicated that prolonged corrected QT interval (QTc) on electrocardiogram (ECG) is a specific, quick, and accurate way to identify CAN.

Objectives: Examining relationship between QTc interval and diabetic CAN is the purpose of current study.

Methods: This is cross-sectional study conducted among 70 diabetic patients aged >18 years, admitted in KIMS, Bangalore, for period of 1 year. The patients underwent cardiovascular autonomic function tests as outlined by Ewing *et al.*, 35 were diagnosed with CAN and 35 were without CAN. Twelve lead that ECG was taken in all 70 diabetic patients and QTc was calculated according to Bazett's formula and compared between both groups. Possible influences of age and duration of diabetes in relationship between prolongation of QTc and CAN were also studied.

Results: Mean QTc interval among patients with DM <5 years was 445.65, 6–10 years was 499.48, 11–15 years was 509.80, and >15 years was 530.44. Mean QTC interval among CAN + 525.43 and in CAN- was 444.46. The cutoff value of prolonged QTc interval between patients with and without CAN was >471 ms (statistically significant – *P* < 0.001) with sensitivity of 100% and specificity of 91.43%.

Conclusion: Comparing CAN+ and CAN- patients, lengthening of QTc interval was more noticeable in the former group. Among CAN+ patients, prolongation of QTc interval became longer as DM duration increased. Therefore, in DM patients, a prolonged QTc interval is a substantial risk factor and also a marker of CAN.

Key words: Cardiac autonomic neuropathy, Diabetes mellitus, Electrocardiogram, QTC interval

INTRODUCTION

Chronic hyperglycemia and abnormalities in the metabolism of carbohydrates, fats, and proteins brought on by deficiencies in insulin production, insulin action, or both are hallmarks of diabetes mellitus. By 2040, the number of persons with diabetes mellitus is expected to increase from the present estimate of 415 million to 642 million. Every country is seeing an increase in the number of persons with type 2 diabetes, and 75% of those individuals reside in developing nations.[1] Diabetes mellitus will likely be a major source of morbidity and death in the future due to its rising prevalence throughout the globe. About 50% of people with long-term type 1 and type 2 diabetes mellitus develop diabetic neuropathy. It might show signs of autonomic neuropathy, polyneuropathy, or both. A typical and often ignored complication of diabetes mellitus is Cardiac autonomic neuropathy (CAN). Damage to the autonomic nerve fibers that innervate the heart and blood vessels causes irregularities in heart rate regulation and vascular dynamics, which is what is known as CAN. In individuals

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with type 2 diabetes mellitus, the prevalence of CAN ranges from 20% to 73%. As it is linked to a high risk of cardiac arrhythmias and sudden death due to silent myocardial ischemia,[2] CAN is a significant source of morbidity and mortality in diabetes individuals. For the diagnosis of CAN, several non-invasive diagnostics have been described. These tests are time-consuming and unsuitable for screening a large number of diabetes patients, while being sensitive and repeatable. Numerous studies have indicated that prolonged corrected QT interval (QTc) in the electrocardiogram is a quick and specific way to identify CAN. Examining the relationship between the QTc interval and diabetic CAN is the purpose of the current investigation.[3]

METHODS

Study Design
The patients were chosen for the study's cross-sectional design based on inclusion and exclusion criteria.

Source of Data
Seventy type 2 diabetes mellitus patients who were hospitalized to the Department of Medicine in KIMS Hospital, Bangalore, Karnataka between September 2021 and September 2022 were chosen for the research.

Inclusion Criteria
Patients with type 2 diabetes mellitus between the ages of 20 and 75 were included in the study.

Exclusion Criteria
The following criteria were excluded from the study:
1. People with type 2 diabetes who have heart failure, high blood pressure, cardiac arrhythmias, or other cardiovascular problems [Table 1]
2. COPD sufferers with type 2 diabetes mellitus
3. People with renal failure who have type 2 diabetes mellitus
4. People with liver problems and type 2 diabetes
5. People with type 2 diabetes who have abnormal electrolytes
6. People suffering from cerebral vascular disorders and type 2 diabetes
7. People using medications that are known to affect QT interval and autonomic function testing
8. Patients using vasodilators, beta blockers, and alpha blockers
9. A patient who has clinically obvious neuropathy from a non-diabetic etiology
10. Anemia.

Tests for Measurement of Cardiac Autonomic Function
According to Ewing *et al.*, cardiovascular responses to several non-invasive cardiac autonomic function tests were used to evaluate cardiac dysautonomia. The following are these:-

Based on the results of the above tests, the autonomic dysfunction in type 2 diabetes mellitus patients is categorized as none, early, definite, and severe.

None
All tests normal or 1 test borderline.

Early
One of three heart rate tests abnormal or two borderlines.

Definite
Two heart rate test abnormal.

Severe
Two heart rate tests abnormal with one or both blood pressure tests abnormal or both borderlines.

The QTC interval was determined by Bazett's formula (QTC = QT/$\sqrt{R\text{-}R}$), and a value exceeding 450 ms for adult men and 460 ms for adult women was considered prolonged.

Statistical Methods
Results were expressed as Mean ± Standard Deviation. Students "t" test was used to compare mean's of different groups. $P < 0.05$ was considered significant.

RESULTS

The group with CAN had a mean age of 58.86 ± 10.134 years. The group without CAN had an average age of 56.89 ± 11.3116 years. It was determined that this difference was not statistically significant.

Among CAN + patients, 2.9% had DM for <5 years, 51.4% had DM for 6-10 years, 22.9% had DM for 11-15 years and 22.9% had DM for >15 years. Among CAN - patients, 71.4% had DM for<5 years, 20.0% had DM for 6-10 years, 5.7% had DM for 11-15 years and 2.9% had DM for >15 years with p value being significant [Table 2].

Mean prolonged QTc interval was 445.65 for patients with DM for <5 years, 499.48 for 6-10 years, 509.80 for 11-15 years and 530.44 for patients with DM for >15 years. Hence with increasing duration of diabetes, the mean prolonged QTc interval also increased [Table 3].

With increasing duration of diabetes, the mean prolonged QTc interval also increases [Table 4].

Mean prolonged QTc interval among CAN + was 525.43 and among CAN - was 444.46 which was statistically significant [Table 5].

In this study, the cut-off value for prolonged QTc interval was >471ms with sensitivity of 100% and specificity of 91.43% [Table 8].

Gender Distribution

Total number of females among CAN + were 13 (37.1%) and among CAN – were 8 (22.9%).

Total number of males among CAN + were 22 (62.9%) and among CAN – were 27 (77.1%).

According to Ewing's criteria, we divided the aberrant autonomic function tests into three categories: early, definitive, and severe. Graph 1 represents percentage of CAN in different stages that is early CAN being 51.43%, definite CAN being 31.43% and severe CAN being 17.14% among the CAN positive patients. Graph 1 represents percentage of CAN in different stages that is early CAN being 51.43%, definite CAN being 31.43% and severe CAN being 17.14% among the CAN positive patients.[4-7]

Duration of DM

The results infer that for 1-year increase in the duration of diabetes, the QTC interval will be significantly prolong by 5.23 ms and this finding is statistically significant at p<0.001 and the variability in the QTC interval prolongation will be able to explain by duration of diabetes by 36% [Table 7].
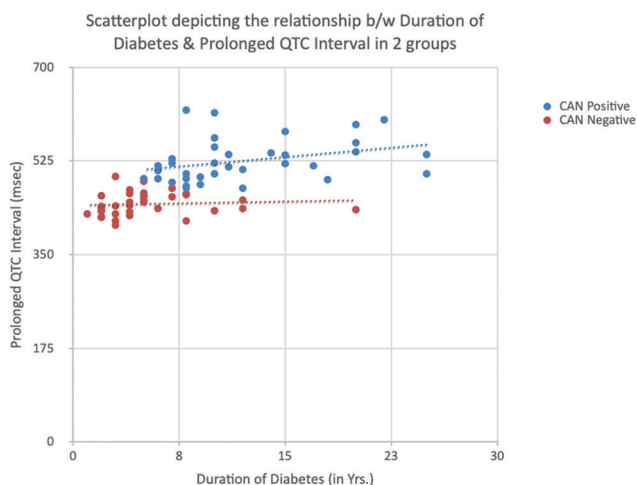
Table 1: Age and gender distribution between two groups

Variable	Category	CAN positive		CAN negative		P-value
		Mean	SD	Mean	SD	
Age	Mean	58.86	11.50	56.89	16.43	0.32[a]
	Range	26–81		27–99		
		n	%	n	%	
Sex	Male	22	62.9	27	77.1	0.19[b]
	Female	13	37.1	8	22.95	

CAN: Cardiac autonomic neuropathy, a - Mann Whitney test, b - Chi Square test

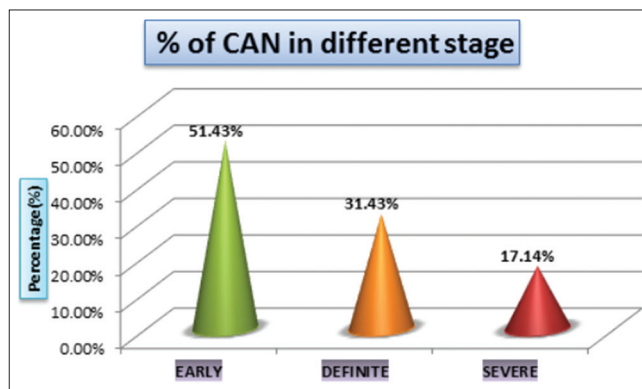### Table 2: Comparison of duration of diabetes between two groups using Chi-square test

Variable	Category	CAN positive		CAN negative		P-value
		n	%	n	%	
Duration	<5 years	1	2.9	25	71.4	<0.001*
of	6–10 years	18	51.4	7	20.0	
diabetes	11–15 years	8	22.9	2	5.7	
	>15 years	8	22.9	1	2.9	

CAN: Cardiac autonomic neuropathy, *statistically significant

Table 3: Comparison of mean prolonged QTC interval based on the duration of diabetes using Kruskal–Wallis test

Duration	n	Mean	SD	Min	Max	P-value
≤5 years	26	445.65	24.10	405	496	<0.001*
6–10 years	25	499.48	50.08	413	620	
11–15 years	10	509.80	44.04	436	580	
>15 years	9	530.44	52.49	434	602	

*statistically significant

Scatterplot depicting the relationship b/w Duration of Diabetes & Prolonged QTC Interval in 2 groups

Graph 1: %age of CAN in different stages

Table 4: Multiple comparison of mean difference in prolonged QTC interval based on the duration of diabetes using Mann–Whitney *post hoc* test

(I) Duration1	(J) Duration1	Mean Diff. (I − J)	95% CI for the Diff.		*P*-value
			Lower	Upper	
<5 years	6–10 years	−53.826	−84.54	−23.12	<0.001*
	11–15 years	−64.146	−104.94	−23.35	0.001*
	>15 years	−84.791	−127.19	−42.39	<0.001*
6–10 years	11–15 years	−10.32	−51.34	30.7	0.91
	>15 years	−30.964	−73.58	11.65	0.23
11–15 years	>15 years	−20.644	−71.02	29.73	0.70

*statistically significant

Table 5: Comparison of mean Prolonged QTC interval between two groups using Mann–Whitney test

Groups	n	Mean	SD	Mean Diff	*P*-value
CAN positive	35	525.43	39.93	80.97	<0.001*
CAN negative	35	444.46	21.35		

*statistically significant

Table 6: Spearman's rank correlation test to assess the relationship between duration of diabetes and prolonged QTC Interval

Variable	Values	CAN positive	CAN negative	Overall samples
Duration of Diabetes	Rho	0.40	0.33	0.68
	P-value	0.02 *	0.06	<0.001 *

CAN: Cardiac autonomic neuropathy, Minus sign denotes negative correlation, The correlation coefficients are denoted by rho, 0.0 – No correlation, 0.01–0.20 – Very Weak Correlation, 0.21–0.40 – Weak Correlation, 0.41–0.60 – Moderate Correlation, 0.61–0.80 – Strong Correlation, 0.81–1.00 – Very Strong Correlation*statistically significant

Table 7: Simple linear regression analysis to predict the prolonged QTC interval using duration of diabetes among study patients

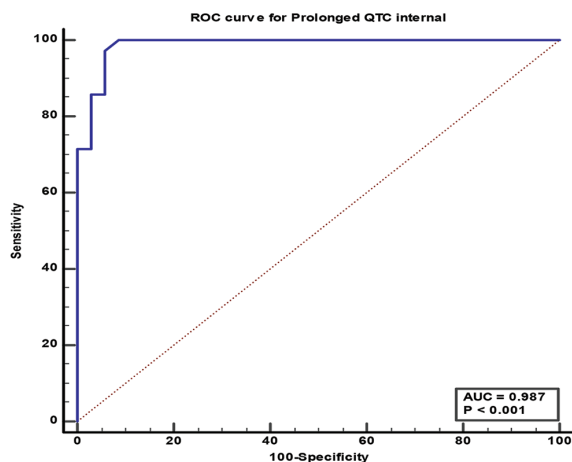| Independent variable	Unstandardized coefficients		t	*P*-value	R^2
	b	Std. Error			
Constant	439.68	8.92	49.275	<0.001*	0.36
Duration	5.23	0.85	6.123	<0.001*	

*statistically significant

Table 8: ROC curve analysis for prolonged QTC INTERVAL for determining the cutoff between patients with and without cardiac autonomic neuropathy

Variable	AUC	Std. Error	95% Conf. Interval		P-value	Cutoff	Sn (%)	Sp (%)
			Lower	Upper				
Prolonged QTC interval	0.987	0.010	0.926	1.000	<0.001*	>471	100.00	91.43

*Statistically significant, ROC is a plot of the true positive rate against the false positive rate for the different possible cutoff points of a diagnostic test. Accuracy is measured by the area under the ROC curve. An area of 1 represents a perfect test; an area of 0.5 represents a worthless test. A rough guide for classifying the accuracy of a diagnostic test is the traditional academic point system: 0.90–1 = excellent (A), 0.80–0.90 = good (B), 0.70–0.80 = fair (C), 0.60–0.70 = poor (D), and 0.50–0.60 = fail (F)

Table 9: Similar comparable studies

Researcher	CAN	Early	Definite	Severe
Present study	50%	51.43%	31.43%	17.14%
Low et al.[12]	73%	NA*	NA	NA
Khandelwal et al.[13]	80%	11	0	20
Aggarwal et al.[14]	69.23	46	30	24
Manjula et al.[15]	74	56	6	0
Hassan et al.[16]	72.8	NA	NA	NA
Domuschiev[17]	59.5	NA	NA	NA

CAN: Cardiac autonomic neuropathy, *NA: Not available
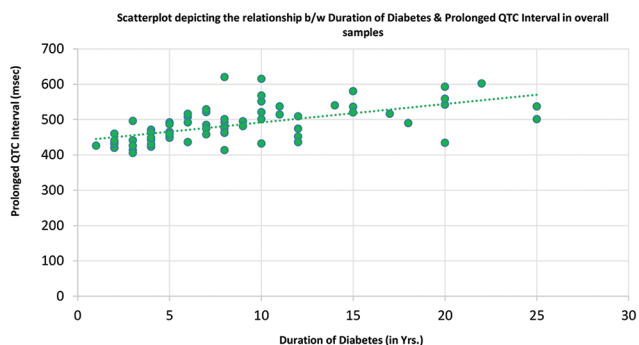
DISCUSSION

There was no discernible difference in the mean and SD of QTc between the two groups. The findings of Orosz and Stern investigation, which showed that the QT interval

in DM and pre-DM persons was not longer than normal individuals, are compatible with this observation.[8] Other studies, however, came up with different findings. QTc was substantially longer in DM patients with CAN compared to those without CAN, and this relationship was directly correlated with the severity of CAN. In comparison to our research, the sample size and mean age of their patients were smaller, and their BMI and glycosylated hemoglobin levels were greater.[9] Both sexes met the same standards for long QT distances. The diabetes patients and healthy individuals have been contrasted.[7,10-13] Even in the pre-diabetic stage, long QT intervals might be seen. A change in lifestyle that begins while a person is still in the pre-diabetic stage has a greater impact on the autonomic nervous system's performance. The connection between the QT interval and the CAN is quite intricate. Physicians initially just took into account the relationship between CAN and the prolonged QTc interval.[14] It is unclear if DM or CAN alone are the only causes of extended QT. They both could extend QT and have a synergistic impact.[15-18] With further investigation into the relationship between the QTc prolongation and sympathetic and parasympathetic system activity, the QT distance was established as a measure for the diagnosis of CAN and its severity. This association is controversial, and other research does not support these conclusions.[19] The prolonged QTc interval can be a risk factor for CAN or one of its unfavorable effects. There have been a few isolated reports of people with DM and aberrant heart rate variability with short QTc intervals.[20-22]

In addition, it is hypothesized that the majority of research have been conducted on individuals with DM and CAN and that the long QT interval is more closely related to DM than CAN. Long QT has, however, also been seen in CAN, as well as other illnesses such cirrhosis and sickle cell anemia. This may imply that extended QTc and CAN have separate relationships.[23]

One of the most significant and under recognized complications of diabetes is CAN. After taking into account the numerous inclusion and exclusion criteria, 70 individuals who were determined to have type 2 diabetes mellitus based on ADA criteria in total were included in this research. In this investigation, CAN was ruled out in 50% of the 70 type 2 diabetes. This study's autonomic neuropathy prevalence was quite comparable to the prevalence that has been reported in various previous research.[21]

The mean age of patients with CAN in this research was 58.86 and 56.89 ± 10.134 years, which was comparable to the study done by Hassan et al.[16] (50.6 ± 7.8 years), although the mean age in studies done by Motataianu et al.[18] and Manjula et al.[15] was 59.4 ± 7.9 years and 42 ± 8.9 years, respectively. About 51.43% of the patients in this research had early CAN, 31.43% had definite CAN, and 17.14% had severe CAN. Aggarwal et al.[14] discovered early CAN in 46% of patients, four definite in 30%, and severe CAN in 24% of patients. In a similar manner, Ekta et al.[13] discovered early CAN in 11% of patients, severe CAN in 20% of patients, and could not classify 69% of patients.[22] Nayak et al. discovered that 50% of patients had early CAN and 50% had severe CAN. Early CAN was discovered in 56% of patients and definite CAN in 6%, according to Manjula et al.[15] QTc prolongation and cardiac dysautonomia in diabetes mellitus have a well-established relationship. In their research, Bellavere et al.[20] suggested that the long QT syndromes should include diabetic CAN. In this research, diabetic individuals with CAN had a longer mean QT interval than those without CAN (525.43 ± 39.93 ms vs. 444.46 ± 21.35 ms). Shimabukuro et al. (449 ± 13 ms), Barthwal et al. (426 ± 24.4 ms), and Mathur et al. (449 ± 21.9 ms) all reported similar findings [Table 9].[19]

Hence, the mean age of CAN positive patients was 58.86 and CAN negative was 56.89. Mean prolonged QTC interval among patients with DM <5 years was 445.65, 6–10 years was 499.48, 11–15 years was 509.80, and >15 years was 530.44.

Mean QTC interval among CAN+ 525.43 and in CAN – was 444.46.

The cutoff value of prolonged QTc interval between patients with and without CAN was >471 ms (statistically significant – $P < 0.001$) with a sensitivity of 100% and specificity of 91.43%.

CONCLUSION

It was discovered that 50% of type 2 diabetics had CAN, and that this incidence was connected with the length of diabetes. A frequent and poorly recognized consequence of diabetes mellitus is CAN. In the development of silent myocardial ischemia, CAN is crucial. Effective prevention of cardiovascular disease-related morbidity and death depends on the early diagnosis of CAN. Cardiovascular autonomic function testing is straightforward yet time-consuming, according to Ewing et al. To identify CAN in diabetic individuals, a reasonably simple, rapid, and reliable way is to prolong the QTc interval. Hence,
- The prolongation of QTC interval was more significant among CAN + patients when compared to CAN
- Among CAN+ patients, the prolongation of QTC interval increased with increasing duration of DM
- Hence, prolonged QTC interval is a significant risk factor and also an indicator for CAN among DM patients.

REFERENCES

1. Bennett HP, Knowler WC. Definition, classication of diabetes mellitus and glucose homeostasis. In: Kahn CR, Weir GC, King GL, Moses AC, Smith RJ, Jacobson AM, editors. Joslin's Diabetes Mellitus. Philadelphia: Lippincott Williams and Wilkins; 2003. p. 31.
2. Diabetes: Facts and Gures. International Diabetes Federation. Available from: https://www.idf.org/about-diabetes/facts-gures [Last accessed on 2016 Jul 14].
3. Powers AC, Diabetes mellitus: Complications. In: Kasper DL, Fauci AS, Longo DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. New York: McGraw-Hill Education; 2015. p. 2399.
4. Powers AC, Diabetes mellitus: Complications. In: Kasper DL, Fauci AS, Longo DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. New York: McGraw-Hill Education; 2015. p. 2426.
5. Dimitropoulos G, Tahrani AA, Stevens MJ. Cardiac autonomic neuropathy in patients with diabetes mellitus. World J Diabetes 2014;5:17-39.
6. Vinik AL, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation 2007;115:387-97.
7. Ewing DJ, Clarke BF. Autonomic neuropathy: Its diagnosis and prognosis. Clin Endocrinol Metab 1986;15:855-88.
8. Maser R, Lenhard MJ. Cardiovascular autonomic neuropathy due to diabetes mellitus: Clinical manifestations, consequences, and treatment. J Clin Endocrinol Metab 2005;90:5896-903.
9. Ewing DJ, Martyn CN, Young RJ, Clark BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care1985;8:491-8.
10. Pappachan JM, Sebastian J, Bino BC, Jayaprakash K, Vijaykumar K, Sujathan P, et al. Cardiac autonomic neuropathy in diabetes mellitus: Prevalence, risk factors, and utility of corrected QT interval in the ECG for its diagnosis. Postgrad Med J 2008;84:205-10.
11. Brwone KF, Prystowsky E, Heger JJ, Chilson DA, Zipes DP. Prolongation of the Q-T interval in man during sleep. Am J Cardiol 1983;52:55-9.
12. Low PA, Benrud-Larson LM, Sletten DM, Opfer-Gehrking TL, Weigand SD, O'brien PC, et al. Autonomic symptoms and diabetic neuropathy: A population-based study. Diabetes Care 2004;27:2942-7.
13. Khandelwal E, Jaryal AK, Deepak KK. Pattern and prevalence of cardiovascular autonomic neuropathy in diabetics visiting a tertiary care referral center in India. Indian Physiol Pharmacol 2011;55:119-27.
14. Aggarwal S, Tonpay PS, Trikha S, Bansal A. Prevalance of autonomic neuropathy in diabetes mellitus. Curr Neurobiol 2011;2:101-5.
15. Manjula SR, Viswabharti N, Siddhartha K, Neeraja, Sudhakar K. Study of clinical evaluation of autonomic dysfunction in Type 2 DM. IOSR J Pharm Biol Sci 2015;10:55-61.
16. Hassan ZF, Ajeena IM, Abbase AH. The prevalence of cardiac autonomic neuropathy in pure type II diabetic patients. J Nat Sci Res 2014;4:147-55.
17. Domuschiev I. Cardiac autonomic neuropathy and its correlation with retinopathy in Type 2 diabetics. Biotechnol Biotechnol Equip 2005;19:180-3.
18. Moţăţăianu A, Bălaşa R, Voidăzan S, Bajkó Z. Cardiovascular autonomic neuropathy in context of other complications of Type 2 diabetes mellitus. Biomed Res Int 2013;2013:507216.
19. Nayak UB, Acharya V, Jain H, Lenka S. Clinical assessment of the autonomic nervous system in diabetes mellitus and its correlation with glycemic control. Indian J Med Sci 2013;67:13-22.
20. Bellavere F, Ferri M, Guarini L, Bax G, Picolli A, Cardone C, et al. Prolonged QT period in diabetic autonomic neuropathy: A possible role in sudden cardiac death? Br Heart J 1988;59:379-83.
21. Mathur CP, Gupta D. QTC prolongation in diabetes mellitus-an indicator of cardiac autonomic neuropathy. J Indian Acad Clin Med 2006;7:130-2.
22. Barthwal SP, Agarwal R, Khanna D, Kumar P. QTC prolongation in diabetes mellitus-an indicator of cardiac autonomic neuropathy. JAPI 1997;45:15-7.
23. Shimabukuro M, Chibana T, Yoshida H, Nagamine F, Komiya I, Takasu N. Increased QT dispersion and cardiac adrenergic dysinnervation in diabetic patients with autonomic neuropathy. Am J Cardiol 1996;78:1057-9.