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A Study of QTc interval and its association with microangiopathy in patients with type 2 diabetes mellitus.

KEYWORDS

Qtc prolongation, Type 2 DM

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ABSTRACT

Background: Knowledge regarding diabetes, diabetic care, glycemic control and lifestyle modifications is a key to successful control of diabetes and prevention of diabetic complications.

Objective: Our aim was to estimate prevalence of prolonged QTc interval as an predictor of cardiac autonomic neuropathy and to see its association with postural hypotension and microangiopathic complications (Diabetic Neuropathy, Retinopathy, Nephropathy) and other factors including duration of diabetes, metabolic control and smoking with abnormalities of the QTc interval in type 2 diabetic patients in predicting cardiac autonomic neruopathy (CAN).

Material and Method: Cross-sectional study was conducted in the Department of Medicine, Himalayan institute of medical sciences, Dehradun from December 2014 to March 2016. A total of 400 patients of type-2 diabetes mellitus of more than one year duration were studied. The QT interval was measured on electrocardiographic (ECG) recordings. The patients with HbA1c levels > or = 7.5% were considered as poorly controlled. The relationship of postural hypotension (PH) and heart rate variability with the duration and control of diabetes were also evaluated. Data was analyzed using SPSS 23.0 software. Chi-square and logistic regression tests were used. A 'p' value less than 0.05 was considered significant.

Results: The mean QTc interval was 0.49 ± 0.03 seconds, mean duration of diabetes was 10.82 ± 5.89 years and mean HbA1c in our study was 8.96 ± 1.98. Patients with long standing diabetes (>10 years) and poor metabolic control (HBA1c > 7.5) had strong correlation with QTc prolongation. QTc showed a significant correlation with the control of diabetes, postural hypotension and diabetic complications.

Conclusion: Prolonged QTc interval and postural hypotension are relatively easy, quick and inexpensive methods to measure cardiac autonomic neuropathy and is significantly associated with CAN.

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production.The two broad categories of DM are designated type 1 and type 2 . Both types of diabetes are preceded by a phase of abnormal glucose homeostasis as the pathogenic processes progresses (1).

QTC prolongation: The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.

According to Ewing's methodology various methods are illustrated such as resting heart rate, beat-to-beat variation with deep breathing (E:I ratio), orthostasis blood pressure, valsalva ratio for cardiac autonomic reflex (2).

Relation between T2DM and QTc prolongation: Cardiac autonomic neuropathy (CAN) contributes significantly to increased cardiovascular mortality and morbidity in type 2 diabetic patients. CAN is a common complication of diabetes and is associated with resting tachycardia, Postural Hypotension (PH), painless myocardial ischaemia or infarction, arrhythmias and sudden cardiac death (3).

A prolonged QTc interval indicates an imbalance between right and left sympathetic innervation. Diabetic patients with a regional sympathetic imbalance and QTc interval prolongation may be at a greater risk for arrhythmias.

This study was planned to estimate prevalence of prolonged Qtc in patients with type 2 diabetes patient and to study the association of QTc with microangiopathy (4).

AIMS AND OBJECTIVES

2. To estimate prevalence of prolonged QTc interval in patients with Type 2 Diabetes Mellitus.
3. To study association between prolonged QTc interval and microangiopathy in Type 2 Diabetes Mellitus patients.

MATERIALS AND METHODS

The study was conducted in the Department of General Medicine, Himalayan Institute of Medical Sciences (HIMS), Swami Ram Nagar, Dehradun, over a period of 12 months. Subjects was recruited amongst the patients from OPDs, medical and the surgical wards of Himalayan Hospital, with a primary diagnosis of Type 2 Diabetes Mellitus and after obtaining written informed consent. 400 diagnosed cases of type 2 diabetes more than 18 years of age were taken and patients presenting with any of the following conditions were excluded from the study i.e. H/O Previous M.I., Cardiac arrhythmia, Uncontrolled HTN (> 180/100 mm hg), Low Serum calcium levels, H/O anti arrhythmic, TCA's, antipsychotics. Thorough history and detailed clinical examination done for clinical evidence of neuropathy and retinopathy , routine lab. tests including blood sugar parametres (FBS, PPBS , HBA1c) , S. Creatinine (for eGFR) and ECG were done. Diagnosis of CAN is based on QTc Interval formula found by Bazzet (QTc = QT / (RR)1/2). QTc normal value was considered as 0.45 sec. and Orthostatic Hypotension was also examined for cardiac autonomic reflex

RESULTS

Table 1: Prevalence of prolonged QTc interval in diabetes

Qtc interval	Frequency	%
Normal	281	70.3%
Prolonged	119	29.8%
Total	400	100%

Table 2 – Distribution of prolonged QTc interval according to duration and control of diabetes.

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Duration of T2DM(years)	QTc interval				P Value
	Normal		Prolonged		
	Frequency	%	Frequency	%	
<5 yrs	113	40.2%	21	17.6%	<0.001
5 - 10 yrs	109	38.8%	38	31.9%	
>10 yrs	59	21.0%	60	50.4%	
Total	281	100%	119	100%	
HBA1c					
<6.5	29	10.3%	5	4.2%	0.017
6.5 - 7.4	86	30.6%	27	22.7%	
>=7.5	166	59.1%	87	73.1%	
Total	281	100%	119	27%	

Table 3-Distribution of patients having prolonged QTc interval according to presence of complications

Postural hypotension	QTc interval				P Value	OR	95% CI
	Normal		Prolonged				
	Frequency	%	Frequency	%			
NO	266	94.7%	82	68.9%	<0.001	8.002	4.1813 to 15.3124
YES	15	5.3%	37	31.1%			
Total	281	100%	119	100%			
Presence of Neuropathy							
No	174	61.9%	41	34.5%	<0.001	3.094	1.9761 to 4.8434
Yes	107	38.1%	78	65.5%			
Total	281	100%	119	100%			
Diabetic retinopathy (NPDR+PDR)							
N	193	68.7%	53	44.5%	<0.001*	2.731	1.758 to 4.244
Y	88	31.3%	66	55.5%			
Total	281	100%	119	100%			
eGFR							
<90	154	54.8%	90	75.6%	<0.001	2.559	1.5838 to 4.1359
>=90	127	45.2%	29	24.4%			
Total	281	100%	119	100%			

Table 4 - Mean value of prolonged QTc interval according to various factors.

	Qtc interval						P Value
	Normal			Prolonged			
	Mean ±SD	Median	Min - Max	Mean ± SD	Median	Min – Max	
Duration of T2DM(years)	7.13 ± 5.73	6.00	0.03 - 25.00	10.82 ± 5.89	10.50	0.08 - 25.00	<0.001
	QTc interval						P Value
	Normal			Prolonged			
	Mean ± SD			Mean ± SD			
HBA1c(%)	8.436 ± 2.02			8.96 ± 1.98			0.018
QTc interval	N	Mean ECG QTc interval		Std. Deviation	Minimum		Median
Normal	281	.4081		.02667	.33	.45	.4100
Prolonged	119	.4985		.03905	.46	.62	.4900
Total	400	.4350		.05160	.33	.62	.4300

Table 5 - Logistic regression showing the most significant factor amongst other significant factors.

		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age	.103	.041	6.231	1	.013	1.109	1.022	1.202
	Duration of T2DM	-.110	.080	1.894	1	.169	.896	.765	1.048
	Postural hypotension	2.923	.879	11.065	1	.033	18.596	3.322	104.087
	PRESENCE OF NEUROPATHY	.239	.808	.088	1	.767	1.271	.261	6.191
	Diabetic retinopathy	.939	.739	1.616	1	.204	2.557	.601	10.876
	eGFR (<90)	-.008	.016	.252	1	.0180	.992	.960	1.024
	HBA1c	.108	.247	.192	1	.001	1.114	.687	1.808
	Constant	-5.583	3.641	2.351	1	.125	.004		

DISCUSSION

In our study the prevalence of QTc prolongation is seen to be high as 29.8% which was also seen in almost equal no. in Chinese patients in which 3156 patients were studied and 30.1 % were found to have prolonged QTc (5).

In our study, as the duration of diabetes increases, there is increase inincidence of QTc prolongation (cardiac autonomic dysfunction). In < 5 years it is 17.6%, 5-10 years it is 31.9%, and >10 years it is 50.4%. This is because duration of diabetes mellitus causes more autonomic dysfunction and damage to nerve fibres.

Similar observation was seen in study conducted by Pappachan JM, et al in 2008 i.e. disease duration over 10 years resulted in QTc prolongation (6). In another study by Mohan V,Sastry NG, et al in 0-5 years it is 28.2% and increases to 56.2% in 16-20 years (7). So our study correlates well with other studies.

In our study the mean duration of diabetes mellitus was 10.82 ± 5.89years. This does notmatches with the studies done by Keen et al (8) the mean duration of diabetes being 8.2 ± 2.6 years, and Noronha et al where in, the mean duration of diabetes was 7.2 ± 2 years (9). In our study the discrepancy could be explained due to poor educational and awareness of the general population. As in the patients are not aware about their diabetic status earlier and come to know later on.

The mean HbA1c in our study was 8.96. We found a significant correlation between HbA1c and the degree of cardiac autonomic neuropathy (P value 0.035). Mustonen et al showed in a 4 year follow up study of 32 subjects with type 2 diabetes that poor glycemic control was an important determinant of the progression of autonomic nerve dysfunction (10). Similarly DCCT provided extensive clinical evidence that good metabolic control of diabetes mellitus reduces diabetic complications specifically DAN (11).

In our study the control of diabetes also suggests the development of CAN. 73.1% patient were found to have CAN who were having poorly controlled diabetes (HbA1c > 7.5) which correlates well with Nayak Ub et al (12). Postural hypotension (i.e. difference in systolic blood pressure by 20 mm hg and 10 mm hg in diastolic blood pressure) was also found to be significant in our study as in 31.1% was found to have in diabetic patients having prolonged QTc as compared to patients having normal QTc (5.3 %) which also correlates well with Khoharo et al (13) and as in AW K et all in which 186 type-2 diabetes mellitus patients with a QTc value of > 440 ms were studied and prolonged QTc interval, heart rate variation and postural hypotension as relatively easy, quick and inexpensive methods to measure cardiac autonomic neuropathy was suggested (14).

In several studies (15,16,17,18) there is association of CAN with neuropathy and retinopathy. In our study out of 185 cases of peripheral neuropathy 78 cases had QTc interval prolongation (CAN) which accounts to 65.5% which is significant. Out of 154 cases of retinopathy 66 cases had QTc prolongation (CAN) which accounts to 55.5%. This is due to same pathogenic mechanisms (microvascular complications) involved in the causation of these conditions. Similar observation was also found to be in prevalence of nephropathy as calculated by decreased eGFR (<90 ml/min.). in diabetic patients with prolonged QTc. 75.6 % were found to have decreased eGFR in patients with prolonged QTc as in studied by Yun Js et al in which there is correlation between QTc and diabetic nephropathy (19).

Though, an interesting fact came into notice that 15% of patients

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with prolonged QTc were not found to have any associated diabetic complications.

CONCLUSION

On the basis of observations made and their analysis, the following conclusions are drawn from the present study:

- Type 2 diabetic patients had a great risk of having CAN which can be estimated by calculating QTc interval. The prevalence of QTc prolongation is seen to be high as 29.8% amongst diabetic patients and mean prolonged QTc interval was found to be 0.49 seconds. Significant association of QTc prolongation with –
  - Prolonged duration of diabetes.
  - Poor control of diabetes.
  - Postural hypotension (another marker for autonomic neuropathy).
  - Microangiopathy.

On Multivariate assessment, control of diabetes, diabetic nephropathy and postural hypotension were found to be the most significant individual factors amongst all other significant factors. The measurement of QTc interval is suggested as a sensitive, non-invasive, and simple predictor of cardiac dysautonomia. Early diabetic assessment and diagnosis along with good control of diabetes is helpful in preventing Cardiac autonomic Neuropathy. Diabetic awareness is the cornerstone of prevention against diabetic complications and helps in achieving glycemic targets along with prevention of complication.

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