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ASSOCIATION BETWEEN PROLONGED QTc INTERVAL AND MICROALBUMINURIA IN PATIENTS OF TYPE II DIABETES MELLITUS

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ABSTRACT

Autonomic neuropathy and nephropathy are common but severe complications of diabetes. QTc prolongation is a predictor of CAN (Cardiac autonomic neuropathy) and microalbuminuria is a predictor of nephropathy. This study was done to find the association between QTc interval prolongation and microalbuminuria in patients of type II diabetes mellitus. This cross sectional study was conducted in sree balaji medical college and hospital with 60 patients of type 2 diabetes mellitus. A complete History and thorough clinical examination were recorded in these patients at the time of admission. All these patients were tested for microalbuminuria and QTc interval prolongation in ECG. Study analysed by chi square test from two sample proportion. Most of the patients were in 50 to 70 years of age group. There is a significant association between QTc prolongation and microalbuminuria as evidenced by (67.76% Vs 24.13%, P<0.0001) more number of cases with microalbuminuria having prolonged QTc interval. Male to female ratio is 1.15:1. In addition to this it was noted that there is increase in incidence of QTc interval prolongation and microalbuminuria as the duration of diabetes increased. There was a significant association between cardiac autonomic neuropathy (i.e. QTc prolongation) and microalbuminuria. Microalbuminuria doesn't directly cause QTc prolongation but it can be used as an indicator for patients who are prone to develop cardiac autonomic neuropathy and hence are at higher risk of having fatal arrhythmias.

KEY WORDS: QTc interval prolongation; Microalbuminuria; Cardiac autonomic neuropathy; Diabetic nephropathy;

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INTRODUCTION

India is the diabetic capital of the world. Diabetes is rapidly gaining the status of a potential epidemic in India with more than 62 million1 individuals currently diagnosed with the disease. Most of the diabetic population is undiagnosed and even those who are diagnosed are not receiving proper treatment. People with diabetes have an increased risk of developing a number of serious complications including cardiovascular diseases, nephropathy, neuropathy and retinopathy etc. Diabetic neuropathy is one of the most common among the complications of diabetes. Yet, it is the least investigated and has a poorly understood pathogenesis. Diabetic nephropathy is a leading cause of diabetes related mortality and morbidity. Microalbuminuria is an early marker of glomerular disease that has been shown to predict glomerular injury in early diabetic nephropathy.2 It has been demonstrated that cardiac dysfunction can occur in diabetic patients without any evidence of ischemic heart disease, caused by Cardiac Autonomic Neuropathy (CAN) and this increases the risk of sudden unexpected death. Prolonged QTc interval is found to be a specific indicator for CAN. For all cardiovascular mortality in type 2 diabetes, QTc-max was found to be an independent predictor. By virtue of early detection and therapeutic interventions such as physical training, weight loss, anti-hypertensives and beta blockade the delirious effects of CAN might be reduced. In type 1 diabetics, QTc interval abnormalities have been shown to be associated with microalbuminuria indicating the relation between Cardiac Autonomic Neuropathy and diabetic nephropathy3. But there are very few such reports in type 2 diabetes. The aim of this study is to evaluate CAN, as predicted by prolonged QTc interval and to check its association with microalbuminuria in type 2 diabetic patients, and correlate it to the severity and duration of diabetes.

Aim and objectives

The aim of this study is to find the association between prolonged QT_C Interval and Microalbuminuria in type 2 diabetes patients.

MATERIALS AND METHODS

60 patients of type 2 Diabetes Mellitus attending Sree Balaji medical college and Hospital and were studied over a period of one year (January 2015-January 2016).Ethical committee approval obtained – Refno002/SBMC/IHEC/2014-103.Informed consent obtained from all the patients.The study subjects are those who fulfill the inclusion and exclusion criteria.

Inclusion criteria

All type 2 DM patients (Irrespective of patients age and duration of diabetes) attending Sree Balaji medical college and Hospital over a period of one year.

Exclusion criteria

The patients with the following abnormalities are excluded from the study as these could also be the reason for causing the comparative parameters

- History of MI/Angina
- Clinical evidence of heart failure
- Left bundle branch block
- Atrial fibrillation
- Uncontrolled hypertension (>180/100 mm of Hg)
- Febrile illness/Urinary tract infection
- H/o drug intake like ACE/ARB's/NSAIDS
- Acute poor metabolic control
- Smoking
- High serum calcium levels

From the selected patients, detailed history was obtained and a thorough physical examination was done. History including age, sex, age of onset and duration of diabetes and details regarding presenting complaints were noted. Past history of any other disease is noted, the total duration of diabetes, drugs taken by the patients, regularity and dosage was also noted. A family history was taken. Personal history like smoking, alcohol consumption, drug intake were duly noted. Then, a complete clinical examination is carried out in each patient with particular reference to complications of diabetes like micro and macro vascular complications. The following investigations are done in these patients

- CBC
- FBS, PPBS
- Blood urea, Serum creatinine
- Urine routine and microscopy
- Test to detect microalbuminuria (MICRAL test).
- ECG (To calculate QTc interval- Average of 3 QT and RR intervals from the leads where QT interval is easily identified to calculate this by BAZZET's formula- QT /√RRms).
- Special investigations if required.

Sample size

60 cases of type 2 diabetes mellitus patients were taken as the total sample size. In a study11 out of 86 patients (43 microalbuminuric, 43 normoalbuminuric) the proportion of patients with prolonged QTc interval was 67% in microalbuminuric and 38% in normoalbuminuric group. Using this study as a reference, 2 sample groups – microalbuminuric and normoalbuminuric were made of 30 each and sample proportion is calculated.

STATISTICAL ANALYSIS

Study design

Cross sectional study which is an observational study that analyzes data collected from a population. Our population is diabetic patient. We analyse the urine microalbumin levels and Qtc interval in all patients and try to correlate the same Descriptive statistics was done for all data and suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired t test and categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS Version 16 and charts generated using Microsoft Excel 2010.

RESULTS

Table1
Age distribution

Age (in years)	No. of cases	Percentage
50-59	26	43.33
60-69	22	36.66
70-79	7	11.66
>80	5	8.33
Total	**60**	**100**

Most of the patients selected were between 50 to 70 years of age

Graph 1
Age Distribution

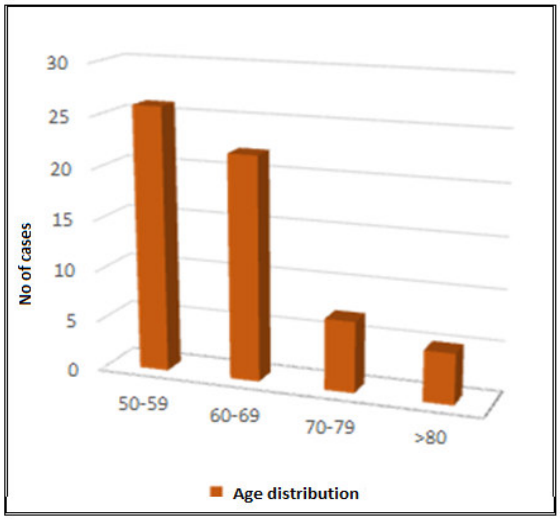


Table 2
Sex distribution

Sex	No. of cases	Percentage
Male	35	58.66
Female	25	41.33
Total	**60**	**100**

A male preponderance is seen in the patients

Graph 2
Sex distribution

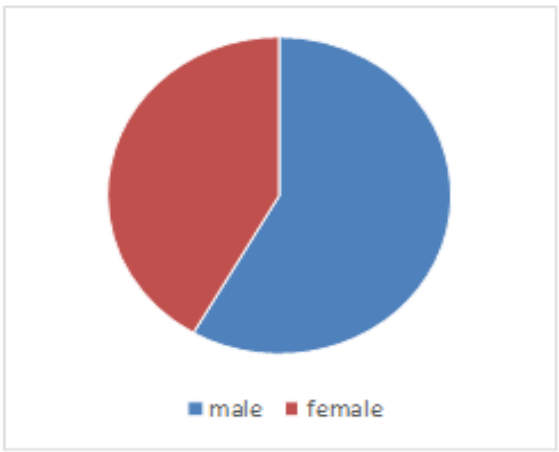


Table 3
Association of qtc prolongation With microalbuminuria

	CAN (QTc Prolongation >440 m sec)		Total
	Present	Absent	
Microalbuminuria	21(67.76%)	10(32.24%)	31(100%)
Normoalbuminuria	7(24.13%)	22(75.86%)	29(100%)
Total	**28(46.67%)**	**32(53.33%)**	**60(100%)**

Out of 60 cases, 28 cases (46.67%) have QTc prolongation. Out of 31 cases of microalbuminuria. 21 cases had QTc prolongation (67.76%). Out of 29 cases of normoalbuminuria 7 had QTc prolongation (24.13%). This value (67.76% Vs 24.13%, P<0.001, HS) is statistically significant.

Graph 3
Qtc prolongation

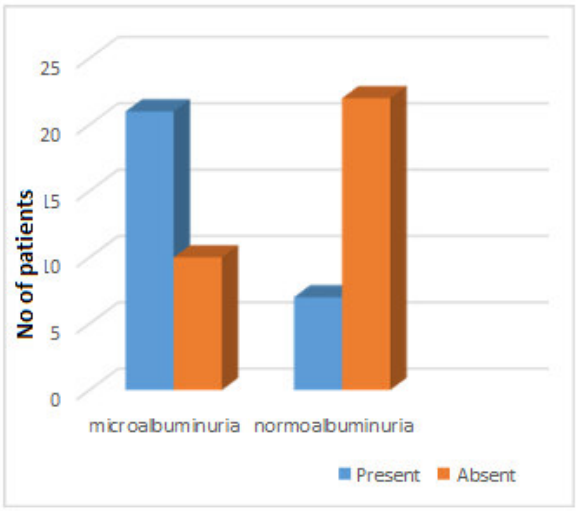


Table 4
Incidence of qtc prolongation with Duration of type 2 diabetes

Duration of diabetes (in years)	CAN (QTc Prolongation >440 m sec)		Total
	Present	Absent	
5-10	10(35.72%)	18(64.28%)	28(100%)
10-15	14(53.85%)	12(46.15%)	26(100%)
15-20	4(66.67%)	2(33.33%)	6(100%)
Total	**28(46.67%)**	**32(53.33%)**	**60(100%)**

As the duration of diabetes increases, incidence of CAN (QTc prolongation) increases. In 5-10 years it is 35.72%, 10-15 years it is 53.85% and in 15-20 years it is 66.67%

Graph 4
Incidence of qtc prolongation with duration of 2 diabetes

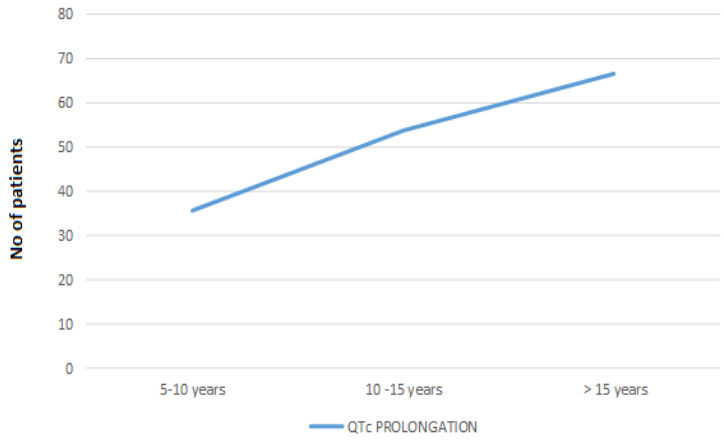
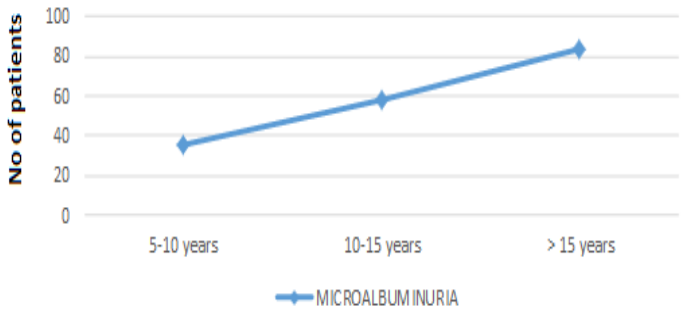


Table 5
incidence of microalbuminuria
With duration of type 2 diabetes

Duration of diabetes (in years)	Microalbuminuria	Normoalbuminuria	Total
5-10	10(35.72%)	18(64.28%)	28(100%)
10-15	15 (57.69%)	11 (42.31%)	26 (100%)
>15	5 (83.33%)	1 (16.67%)	6 (100%)
Total	**30**	**30**	**60**

Mean duration of diabetes with microalbuminuria comes to 11.18 years. As duration of diabetes increases there is increased incidence of microalbuminuria. In 5-10 years it is 40.65%, 10-15 years it is 54.54% and in more than 15 years it is 83.33%.

Graph 5
Incidence of microalbuminuria with duration of type 2 diabetes



DISCUSSION

In a study conducted in South India, the prevalence of Cardiac autonomic dysfunction among non-insulin-dependent type 2 diabetes mellitus was assessed by blood pressure responses and heart rate responses. 336 patients were studied. In 35.7% of patients (n=120) CAN was detected. With the increase in age and duration of diabetes, an increase in prevalence of CAN was noted. In 0-5 years of diabetes duration group, 28.2% of Patients and in 16 -20 years of diabetes duration group, 56.2% of patients had CAN respectively.[4] In another study conducted in Rajasthan, 50 diabetic patients, were evaluated for CAN. Out of them 19 (38 %) were found to have evidence of cardiac autonomic neuropathy. Out of these 19 patients, 15 had QTc prolongation which correlated with the severity of cardiac autonomic neuropathy.The study suggests that in diabetes QTc prolongation can be taken as a direct evidence of cardiac autonomic neuropathy.5 A similar study was conducted in USA in asymptomatic type 2 diabetics with no clinical evidence of coronary disease, comparing QTc prolongation and QTc dispersion where 43 patients with microalbuminuria were matched with 43 normoalbuminuric patients. In microalbuminuric patients, QTc max was greater, while Qt dispersion showed no significant difference in both the groups. The study showed that 1) QTc max and/or QTcd were not associated to albumin excretion rate but more strongly to factors associated with microalbuminuria such as blood pressure 2) QTc prolongation and microalbuminuria are interlinked. QTc prolongation may contribute to the increased mortality observed in microalbuminuric type 2 diabetes.6

Epidemiology

Diabetes is one of the most common chronic non – communicable disease in India with every fifth diabetic in the world being Indian.[7] One of the most common and chronic complications of type 1 and type 2 diabetes is Diabetic neuropathy, especially CAN. This is one of the reasons for high morbidity and mortality of diabetic patients.

Cardiac autonomic neuropathy

Cardiac autonomic neuropathy(CAN),a common form of autonomic dysfunction found in diabetic patients causes abnormalities in central and peripheral vascular dynamics and in heart rate. Parasympathetic dysfunction will result in a high resting heart rate due to unopposed increased sympathetic outflow. Persons with a combined sympathetic/ parasympathetic/ dysfunction will haves lower heart rates and those with severe autonomic dysfunction, will have fixed heart rate.The earliest indicator of CAN is reduction in variability of heart rate. Clinical manifestations of CAN include orthostatic hypotension (OH), asymptomatic ischemia, exercise intolerance, intra operative cardiovascular lability, painless myocardial infarction (MI)and increased risk of mortality.[19]

Risk factors

Age, obesity, hyperinsulinemia, duration of Dm, hypertension, retinopathy, and smoking,HbA1c, SBP, age retinopathy, albuminuria, PNP, hyper triglyceridemia, dyslipidemia, gender (female), and duration of Dm.[20]

Clinical manifestations of cardiac autonomic neuropathy

Resting tachycardia
Resting heart rates of 90 to 100 bpm with occasional increase up to 130 bpm can occur.[8]

Exercise intolerance
CAN causes exercise intolerance, reduced response in heart rate and blood pressure (BP), and blunts cardiac output changes in response to exercise.[9]

Intraoperative and perioperative cardiovascular instability
Perioperative Cardiovascular morbidity and mortality are increased 2 -3 fold in patients with diabetes. [10]

Orthostatic hypotension
Orthostatic hypotension is defined as a fall in BP (i.e., >30 mm hg systolic or >10 mm Hg diastolic BP) in response to a postural change from supine to standing.[11]

Can and sudden death
QTc prolongation can also predispose to life endangering arrhythmias and sudden death. Results from the EURODIAB Insulin -Dependent Diabetes Mellitus (IDDM) complications study showed that male patients with impaired HRV (CAN) had a higher corrected QTc prolongation than males without CAN.[12]

Table 1
Diagnostic assessment of cardiovascular autonomic function[13]

PARASYMPATHETIC	SYMPATHETIC
Resting heart rate	Resting heart rate
Beat-to-beat variation with deep breathing (E:I ratio)	Spectral analysis of heart rate variation, very low frequency power(VLFP; 0.003-0.04Hz)
30:15 Heart rate ratio with standing	Orthostatic blood pressure
Valsalva ratio	Hand grip blood pressure
Spectral analysis of heart rate variation, high-frequency power (HFP; 0.15 - 0.40Hz)	Cold pressor response, Sympathetic skin galvanic response (cholinergic), Sudorometry (cholinergic), Cutaneous blood flow (peptidergic).
Sympathetic/parasympathetic balance =VLFP/HFP.	

Qt interval
The QT interval is measured from the beginning of the QRS complex to the end of the T-wave in the lead with the longest interval and without a prominent U wave. It corresponds to the duration of ventricular action potential.[14]The duration of the QT interval decreases as heart rate increases, as does the duration of normal ventricular action potential duration. Normal QTc is 440msec.[14] The modification of Bazett's formula by Hodges and co –workers[15], as follows, corrects more completely for high and low heart rates QTc = QT+ 0.00175 (ventricular rate –60).An association exists between diabetic CAN and a prolonged QTc interval on ECG which may predispose to life threatening ventricular arrhythmias. It has been proposed that the combination of prolongation of QTc interval and a relatively heightened sympathetic tone might increase the likelihood of arrhythmias leading to sudden death.[16]

Diabetic nephropathy
Normal Albumin excretion ranges from 1.5-20 µg/min which is called as Normoalbuminuria.[17] Microalbuminuria is the hyper excretion of albumin between 20 - 200µg/min (30 -300mg/day) [18]. Reagent sticks for urinary protein can't identify microalbuminuria as they generally become positive only when proteinuria is more than 550mg/day which is called Macroproteinuria. Increased AER was observed in newly diagnosed youngsters with IDDM by Mongenstron[19] and later by Parving et al. (Table2)

Table 2
Definition of microalbuminuria and clinical nephropathy[20]

Term	Urinary albumin level
Normoalbuminuria	<20 µg/l
Microalbuminuria (Incipient nephropathy)	20-200 µg/min
Microalbuminuria (Clinical nephropathy/ overt nephropathy)	>200 µg/min

Table3
Stages of Diabetic Nephropathy Typical Findings[21]

STAGE	GLOMERULAR FILTRATION	ALBUMIN URIA	BLOOD PRESSURE	TIME OF COURSE YEARS AFTER DIAGNOSIS
Renal hyper function	Elevated	Absent	Normal	At diagnosis
Clinical latency	High normal	Absent	Normal	At diagnosis
Microalbuminuria (incipient nephropathy)	Within the normal range	20-200µg/min (30-300µg/day)	Rising within or above Normal range	5-15
Macro albuminuria or persisting proteinuria (clinically manifesting nephropathy)	Decreasing	>200µg/min (>300mg/day)	Increased	10-15
End stage renal failure	Diminished	Massive	Increased	15-30

Estimation of microalbuminuria by micral test

In our study we used Micral test for estimation of microalbuminuria. Micral test[22] (Boehringer Mannheim, West Germany) is an immunochemical dip stick method of estimation of microalbuminuria. It has shown to have 89 % sensitivity and 99% specificity when compared to radioimmunoassay in a study by M.Vishwanathen and et al.

microalbuminuria is graded as

Mild (20-50mg/L) - +

Moderate (50-100mg/L) - ++

Severe (100-300mg/L) - +++

CAN is a frequent and life threatening complication of type 2 DM. Failure to recognize this leads to high mortality and morbidity. Studies[6, 8] have shown that prolonged QTc is an indicator of cardiac autonomic neuropathy. This is a simple, quick and non-invasive test for CAN. Many studies[23] have also proven that diabetic nephropathy can be predicted by microalbuminuria. In our study we are finding the association between CAN (ECG QTc prolongation) with nephropathy (microalbuminuria) in type 2 Diabetes Mellitus. In our study the proportion the proportion of microalbuminuric patients with QTc max (>440 msec) is (67.76% Vs 24.13% p<0.0001 HS) which is highly significant.

STUDIES	QTc PROLONGATION IN MICROALBUMINURIA	QTc PROLONGATION IN NORMOALBUMINURIA	P-VALUE
Rutter et al[6]	67%	38%	0.01(S)
Present study	67.76%	24.13%	<0.0001 (HS)

In our study, there is an increase in incidence of QTc prolongation (cardiac autonomic dysfunction) as the duration of diabetes increases. In 5 -10 years it is 35.72%, 10 -15 years 53.85%, and >15 years it is 66.67%. Because, with the increase in the duration of diabetes mellitus, it causes more autonomic dysfunction and more damage to nerve fibers. In our study sex ratio (M: F) in QTc prolongation (CAN) is 1.15:1 Our study's age of onset of CAN correlates well with other similar studies. In our study mean age of onset of cardiac autonomic neuropathy is 62.14 years In our study, as the duration of diabetes increased, the incidence of microalbuminuria increased i.e., in 5 -10 years it is 35.72%, 10-15 years it is 57.69% and >15 years it is 83.33% and mean duration of diabetics in microalbuminuria patients is 11.82 years.In our study, out of 20 cases of peripheral neuropathy, 16 cases had QTc interval prolongation (CAN) accounting to 80%, which is significant and out of 19 cases of retinopathy, 14 cases had QTc prolongation (CAN) which accounts to 73.68%. In our study, prevalence of microalbuminuria in retinopathy is 68.72% and neuropathy is 65% both of which are significant .

CONCLUSION

There is a significant association between Prolongation of QTc interval and Microalbuminuria in these patients as evidenced by (67.76% Vs 24.13%, P<0.0001) more number of cases with microalbuminuria having prolonged QTc interval. Microalbuminuria per se is not a causative factor for QTc prolongation but they both are associated with each other. QTc prolongation is an indicator of cardiac autonomic neuropathy which can lead to life threatening ventricular arrhythmias and sudden cardiac death.So, all diabetic patients having microalbuminuria should be screened with ECG to look for QTc interval prolongation (cardiac autonomic neuropathy) as it can be prevented by exercise, anti - hypertensive medications and beta blockade. The incidence of both cardiac autonomic neuropathy (QTc prolongation) and microalbuminuria increases with the duration of diabetes. Patients having either CAN or microalbuminuria should also be screened for other micro vascular complications like retinopathy and neuropathy as they are frequently associated with these conditions.

CONFLICT OF INTEREST

Conflict of interest declared none.

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