STUDY OF QTC INTERVAL IN TYPE-2 DIABETES MELLITUS PATIENT

H. M. Vaghela*, M. V. Shanishchara* , H. B. Mehta, C. J. Shah***.**

*Tutor, **Professor and Head, *** Associate professor, Physiology Department, Govt. Medical College, Bhavnagar.

Abstracts: **Background & Objectives:** To study the prevalence of Corrected QT interval in type 2 diabetic patients and their relationship with clinical and metabolic variables. **Methods:** This work was done on 110 patients with type 2 DM (56 females; 54 males) in the age range of >30 years, with various duration of disease. All the 110 patients analysed by taking Standard 12- leaded electrocardiograms After calculating QT interval, we found out QTc by usin -Bazett 1920 QTc = QT/ √ RR interval. **Results:** QTc was prolonged (64%) in both male &female patient. In female RR is decreased while , QTc, QTcMin duration is found to be increased. Patients with increased QTc duration having lower age(p=0.0457), & higher pulse rate(p<0.0001).There is no significant difference in QTc between groups according to various duration of diabetes. This study shows 39.96%. Percent of the variance in QTc explained by this model. The P value is 0.0330, considered significant. Age(years) (p=0.0048), &FBS(p=0.0182), contribute significantly in QTc. **Conclusion:** This study, looked into various aspects of T2DM and its correlation with QTc. and cardiovascular dysfunction.

Key Words: Type 2 Diabetes, QT Interval, QTc Interval, RR Interval, cardiovascular dysfunction.

Author for correspondence: Dr. H. M. Vaghela , Department of Physiology, Government Medical College, Bhavnagar, E- mail: v.hardev@yahoo.in

Introduction:

Recent estimates indicate there were 171 million people in the world with diabetes in the year 2000 and this is projected to increase to 366 million by 2030[1].

India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the “diabetes capital of the world”. According to the recent projections of World Health Organization (WHO), India already leads the world with the largest number of diabetic subjects (nearly 40 million) and it is predicted that this number would reach almost 80 million by the year 2030[2]. The International Diabetes Federation (IDF) estimates the number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025 unless urgent preventive steps are taken. India & china contribute to 75% of total diabetic patient load of world. Diabetes is an iceberg disease. India faces a grave health care burden due to the high prevalence of type- 2diabetes

Diabetes is a condition primarily defined by the level of hyperglycemias giving rise to risk of micro vascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced life expectancy, significant morbidity due to specific diabetes related micro vascular complications, increased risk of macro vascular complications (ischemic heart disease, stroke and peripheral vascular disease), and diminished quality of life[3]

Cardiac autonomic neuropathy (CAN) is a serious and common complication of diabetes. It is associated with a variety of adverse outcomes including cardiovascular death [4,5.] The QT interval reflects the duration of the ventricular myocardial depolarization and repolarization. Prolongation of the corrected QT interval (QTc) has been demonstrated to be a specific indicator of CAN in most studies [6-8.]

The prevalence of hypertension is almost two folds higher in patients with type 2 DM than in non diabetic subjects [9] In type 2 DM, arterial hypertension is diagnosed at the beginning of the metabolic disorders being closely related to the presence of obesity, hyperinslunaemia and dyslipidaemia but not due to kidney disorders [10]

Arterial hypertension may be complicated by left ventricular hypertrophy due to pressure overload and patients with left ventricular hypertrophy are at increased risk for major cardiovascular complications, including chronic heart failure (CHF) and serious atrial or ventricular arrhythmias[11]

The hypertrophied myocardium is a fertile ground for the development and propagation of arrhythmias

This study looked into the QT interval and its relevance in Type 2 Diabetes Mellitus. to evaluate; QT abnormalities in predict cardiac death in several medical conditions including diabetes. QT interval is

affected by cardiac ischemia and autonomic neuropathy but the influence of hyperglycemia is uncertain[12] QT interval analysis is superior to ABPI and RR interval analysis in identifying diabetic patients who are at high risk of a cardiac death.[13]

Materials and Method*:*

This study has been carried out in medicine (OPD) of Sir T Hospital and Cardiovascular Lab in Department of Physiology at Government Medical College Bhavnagar after obtaining prior approval of IRB (Institutional Review Board) Bhavnagar and informed consent from the participants. The study population was consisted of 110 type-2 Diabetics patient (diagnosed by physician) Attending medicine OPD and applying following criteria

Inclusion Criteria:

1. 110 known type-2 Diabetics patient, 2. Age :> 30 year and <65 year. 3. Sex : either sex 4. Those who can give written informed consent

Exclusion Criteria:

1. The subjects having H/O CHD/IHD, Renal failure, cv stroke 2. Those having pace maker, hypothyroidism, and electrolyte imbalance 3.Those who not give informed consent 4. Patients with left bundle branch block, hypertrophic obstructive Cardio myopathy or taking drugs affecting QT interval e.g. amiodarone, quinidine or procainamide

Methods of the study:

Clinical study: Thorough history taking including Name, age, sex, duration of diabetes and Complete physical examination including height, weight, BMI Pulse rate Blood Pressure, Routine investigations: Fasting and post prandial blood sugar level.

Specific investigations: Standard 12- leaded electrocardiograms: Standard supine 12-lead electrocardiograms (ECG) are recorded. RR and QT intervals are measured in lead II in the resting ECG. The QT interval was taken from the beginning of the QRS complex to the end of the down slope of the T wave (crossing of the isoelectric line). The QT interval is corrected for the previous cardiac cycle length (QT c) was calculated according to the Bazzet's formula , the QT c for each subject will taken. The RR intervals were also measured for the same. QT c > 440 ms (0.44s) is universally considered as prolonged.

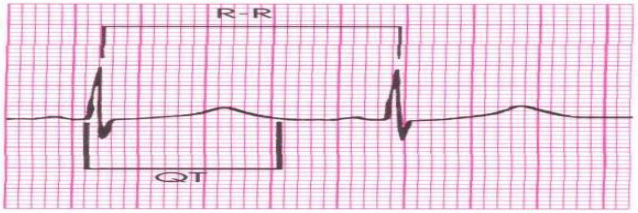

Figure-1: ECG showing QT and RR Interval.

Formula for calculating Corrected QT :

Corrected QT interval (QT c) - Bazett 1920

$$QT\,c = QT/\sqrt{RR\ \text{interval}}$$

Benefits: The greatest advantage of using the QT interval as a screening test is that it does not require patient compliance, is non-invasive, easily obtained and cost effective

Observations and Results:

The present study of QTc is done on 110 type 2 Diabetes patients(54 male&56 female)having various age(30 years to 65 years)done during March 2013 to February 2014.We have found prolonged QTc(64%) in both male &female patient as follows;

Table -1: Total case distribution of Normal &prolonged QTc .

	QTc	
	≤ 440 ms	> 440 ms
Male(54)	28(52%)	26(48%)
Female(56)	11(20%)	45(80%)
Total (110)	39(36%)	71(64%)

Table-2: Comparison of the physical parameters of the patients- Males and Females included in the study group

Parameter	Male(54) (Mean±SD)	Female(56) (Mean±SD)	Total(110) (Mean±SD)
Age(year)	56.79±8.32	52.16±9.27	54.44±9.09
BMI(Kg/m2)	24.30±3.79	25.43±3.88	24.88±3.86
Pulse/min	81.66±9.49	86±8.58	83.87±9.26
SBP(mmHg)	133.77±15.17	134.46±12.16	134.13±13.6
DBP(mmHg)	81.81±7.53	82.96±0.03	82.4±6.8
DM-Duration (year)	5.12±4.51	4.81±5.27	4.96±4.90
FBS(mg/dl)	175±60.78	186.05±58.35	180.92±59.5
PP_2BS(mg/dl)	230.85±76.27	248.3±85.24	239.74±81.

			0

The physical parameters of the patients- Males and Females included in the study group are shown in the following Table . The mean ± SD of the age of the patients in years, Body mass index (BMI) in kg/m^2, pulse rate in beats/min and systolic & diastolic blood pressure in mm Hg ,duration of diabetes in years ,fasting and post prandial blood sugar in mg/dl are depicted for males and females.

The Mean ±SD of the outcome parameter interval of QT ,RR, QTc, QTc max,QTc min of male ,female (comparison)& total patients are as follows:

Table-3: The Mean ±SD of the outcome parameter interval of QT ,RR, QTc, QTc max,QTc min of male ,female (comparison)& total patients

Parameter	Male(54) (Mean±SD)	Female(56) (Mean±SD)	P-value	Total(110) (Mean±SD)
QT (ms)	0.378±0.028	0.383±0.02	0.3175	0.381±0.026
RR (ms)	0.741±0.09	0.702±0.085	0.0273	0.721±0.09
QTc (ms)	0.441±0.03	0.459±0.026	0.0020	0.450±0.03
QTc max (ms)	0.459±0.03	0.469±0.026	0.0954	0.465±0.03
QTcmin (ms)	0.385±0.03	0.402±0.03	0.0057	0.394±0.032
The P value is < 0.05 considered as significant				

The physical parameter comparison of QTc duration of normal(≤ 440 ms) and Prolonged(> 440 ms) interval.

Table-4: comparison of QTc duration of normal(≤ 440 ms) and Prolonged(> 440 ms) interval.

Physical Parameter	QTc (ms)		
	≤ 440 ms	> 440 ms	P- value
Age(year)	56.41±8.09	53.35±9.47	0.0457
BMI(Kg/m2)	24.56±3.62	25.06±4.01	0.2586
Pulse/min	79.28±9.13	86.39±8.37	<0.0001
SBP(mmHg)	133.28±11.95	134.59±14.57	0.3164
DBP(mmHg)	82.46±7.25	82.37±6.6	0.4722
DM-Duration (year)	4.91±5.32	4.99±4.69	0.4665
FBS(mg/dl)	179.23±64.37	181.84±57.13	0.4134
PP_2BS(mg/dl)	236.54±89.62	241.49±79.6	0.3803
The P value is < 0.05 considered as significant			

This table shows significant difference in Age (year) & Pulse rate/min between normal & prolonged QTc interval

According to duration of diabetes (Group A=<5 year, B=5-10 year& C=>10 years) effect on QTc

Table-5: This table shows no significant difference in QTc &QTcD between groups according to duration of diabetes.

Group	A	B	C
QTc	0.451±0.03	0.451±0.024	0.445±0.03

Comparison	Group	P value
QTc	A v/s B	P>0.05
	A v/s C	P>0.05
	B v/s C	P>0.05

Multiple regression analysis of QTc showing combined variance effect & correlation of each physical parameter on it:

Table-6: Multiple regression analysis of QTc .

Variable	α/β	P value	Significant	correlation coefficient (r)
constant (α)	0.4115	< 0.0001	Yes	
Age (β)	- 0.001300	0.0048	Yes	-0.2996
BMI(β)	+ 0.0002775	0.7772	No	0.0903
Pulse(β)	+ 0.0004304	0.4025	No	0.3059
SBP(β)	+ 0.0004981	0.1773	No	0.1534
DBP(β)	+ 0.0001982	0.8089	No	0.0625
DM-Duration (β)	+ 0.002738	0.0604	No	0.0871
FBS(β)	- 0.0003056	0.0182	Yes	-0.1287
PP_2BS(β)	+ 0.0001164	0.1413	No	0.0757

This table shows Age(years)&FBS contribute significantly in QTc

Discussion :

The prevalence of T2DM is increasing in all populations, worldwide. It is a major risk factor for death and numerous nonfatal complications. With increasing prevalence of diabetes the complications are also set to rise. Diabetic autonomic neuropathy is one of major complications of long standing diabetes. There is general agreement that the presence of cardiac

autonomic dysfunction increases the duration of the QT interval. So this study was undertaken to look into the QTc its relevance in Type 2 Diabetes Mellitus.

The present study was carried out on 110 diabetic patient (56 females; 54 males) in the age range of >30 years, of having various duration of disease.

Prevalence of prolonged QTc : The present study shows mean QTc duration of 0.450±0.03 ms. QTc > 440 ms (0.44s) is universally considered as prolonged, although there are small gender based differences.

The prevalence of QTc prolongation has been reported to be as high as 26% in type 2 diabetes,[14]while In this study we find QTc prolongation in 64% of cases.

Physical parameters: This study shows mean age is lower in female patients(52.16±9.27 year) compared to (56.79±8.32year) in male patients and(54.44±9.09year) in total patients. The mean BMI is found higher (24.88±3.86kg/m^2) in total patients. The mean pulse rate is found higher in female patients (86±8.58/min) compared to(81.66±9.49/min) in male patients and(83.87±9.26/min) in total patients.

Male v/s female patients: In prolonged QTc, the most common risk is female sex [15].After puberty, women have a longer baseline QT interval it has been shown that androgens increase IKs and IKr channels and thereby reduce AP duration[16,17]. This study shows significant difference in RR(p=0.0273), QTc,(p=0.0020) QTcMin(p=0.0057) duration between male& female patients. In female patient due to increased heart rate RR is decreased while , QTc, QTcMin duration is found to be increased.

Normal v/s prolonged QTc : QT interval prolongation is an independent predictor of mortality in patients with diabetes and is associated with CAN [5]. The pathogenesis of QT prolongation is multifac-torial, and its correlates include female gender, nephropathy, coronary heart disease, glycemic control, systolic blood pressure, physical activity, and body mass index. In the recent ACCORD trial, assessment of CAN included heart rate (reflecting overall autonomic function and cardio respiratory fitness), measures of heart rate variability, and the QT interval (reflecting mainly sympathetic function) computed from 10-s resting electrocardiograms[18]. Patients with increased QTc duration had higher age and blood pressure values, whereas no differences in BMI and diabetes duration were found[,14,9]

In this study we found Patients with increased QTc duration having lower age(p=0.0457), & higher pulse rate(p<0.0001), might be due to decreased pulse rate (bradycardia) in old age &CAN can be detected in younger diabetic.

Duration of diabetes: QTc is abnormal at the time of initial diagnosis of non-insulin dependent diabetes and does not progressively worsen, but instead remain abnormal in patients[19]

This study shows no significant difference in QTc between groups according to various duration of diabetes.

Multivariable model of QTc : In multivariate models, QTc interval prolongation was consistently predicted by sex, BMI, and fasting glucose in diabetic subjects.[20] On a multivariate regression model, having as outcome the length of the QTc interval. The results reveal the significant involvement of HOMA-IR, age and HbA1c on the QTc interval, whereas diabetes duration and BMI were not significant when correlated with the length of the QTc interval[21] This study shows 39.96%. percent of the variance in QTc explained by the model. The P value is 0.0330, considered significant. Age(years) (p=0.0048), & FBS(p=0.0182), contribute significantly in QTc. Present study shows negative correlation with age and FBS whereas positive correlation with BMI. pulserate, BP ,duration of DM & PPBS.

Conclusion:

In present study prolonged QTc(64%)) in both male &female patient The QTc duration and age,BMI,Pulse rate were significantly correlated (0.19, P < 0.001). In female patient due to increased heart rate RR is decreased while , QTc, QTcMin duration is found to be increasedPatients with increased QTc duration having lower age(p=0.0457), & higher puse rate(p<0.0001)This study shows no significant difference in QTc between groups according to various duration of diabetes.This study shows 39.96%. percent of the variance in QTc explained by the model. The P value is 0.0330, considered significant. Age(years)

(p=0.0048), &FBS(p=0.0182), contribute significantly in QTc

This study, therefore, looked into various aspects of T2DM and its correlation with QTc Correlation was seen between QTc and cardiovascular autonomic neuropathy. The QTc is a simple, quick and cost effective bedside test to find out autonomic involvement in T2DM ,which could lead to detailed tests being carried out.

Patients with this QT abnormality could be targeted for more detailed cardiac investigations including a treadmill test, echocardiogram and angiography. If other structural or functional cardiac abnormalities are identified, specific therapeutic efforts, e.g. aggressive lowering of blood pressure etc. may be undertaken in an attempt to alter the outcome favorably.

However, it remains to be seen if more aggressive control of Hyperglycemia in this subgroup will help in improving QT abnormalities (i.e. ventricular instability) and, therefore, cardiac outcome. More long-term interventional studies are needed to shed light on this issue.

References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care. 2004; 27:1047-53
2. Alberti KG, Zimmet P, Shaw J. IDF Epidemiology Task 4. Force Consensus Group: The metabolic syndrome—a new worldwide definition. Lancet 2005; 366: 1059-62
3. 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 Nov 1;78(9):10579
4. Vinik, R. E. Maser, B. D. Mitchell, and R. Freeman,"Diabetic autonomic neuropathy," Diabetes Care, vol. 26, no.5, pp. 1553–1579, 2003.
5. R. E. Maser, B. D. Mitchell, A. I. Vinik, and R. Freeman, "The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes a meta-analysis,"Diabetes Care, vol. 26, no. 6, pp. 1895–1901, 2003.
6. M. Veglio, M. Borra, L. K. Stevens, J. H. Fuller, and P. C. Perin, "The relation between QTc interval prolongation and diabetic complications. The EURODIAB IDDM Complication Study Group," Diabetologia, vol. 42, no. 1, pp. 68–75, 1999.
7. E. A. Whitsel, E. J. Boyko, and D. S. Siscovick, "Reassessing the role of QT(c) in the diagnosis of autonomic failure among patients with diabetes: a meta-analysis," Diabetes Care, vol. 23,no. 2, pp. 241–247, 2000.
8. N. Tentolouris, N. Katsilambros, G. Papazachos et al., "Corrected QT interval in relation to the severity of diabetic autonomic neuropathy," European Journal of Clinical Investigation,vol. 27, no. 12, pp. 1049–1054, 1997.
9. Fagan TC and Deedwania PC (1998): The cardiovascular dysmetabolic syndrome. Am. J. Med. 105 (Suppl. IA) S77:S85.
10. Jesus R. Giraudo, (1999): Diabetes and cardiology institute of endocrinology Diabetes and Nutrition, Cardoba-Arginitin
11. Aryl. Gold Berger (1999): A trial and Ventircular enlergement, In clinical electrocardiography, 6th ed. P. 64-66.
12. Rajeev Kumar, Miles Fisher and Peter W MacfarlaneBritish Journal of Diabetes & Vascular Disease 2004 4: 146
13. Heart. 2005 January; 91(1): 44–50. doi: 10.1136/hrt.2003.017632 B S Rana,1 P O Lim,1 A A O Naas,1 S A Ogston,2 R W Newton,3 R T Jung,3 A D Morris,3 and A D Struthers1
14. Veglio M, Bruno G, Borra M et al. Prevalence of increased QT interval duration and dispersion in type 2 diabetic patients and its relationship with coronary heart disease: a population-based cohort. J Inter Med 2002;25:317-24.
15. Makkar, R., Fromm, B., Steinman, R., Meissner, M. and Lehmann, M. (1993) Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs. JAMA 270: 2590–2597
16. Arya, A. (2005) Gender-related differences

in ventricular repolarization: beyond gonadal steroids. J Cardiovasc Electrophysiol 16: 525–527.
17. Pham, T. and Rosen, M. (2002) Sex, hormones, and repolarization. Cardiovasc Res 53: 740–751
18. R. Pop-Busui, G. W. Evans, H. C. Gerstein et al., "Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial," Diabetes Care, vol. 33, no. 7, pp. 1578– 1584, 2010.
19. B. S. Rana, P. O. Lim, A. A. O. Naas et al., "QT interval abnormalities are often present at diagnosis in diabetes and are better predictors of cardiac death than ankle brachial pressure index and autonomic function tests," Heart, vol. 91, no. 1, pp. 44–50, 2005.
20. Electrocardiographic QT Interval Prolongation in Subjects With and Without Type 2 Diabetes – Risk Factors and Clinical Implications Jimenez-Corona Aida, Jimenez-Corona Maria Eugenia and Gonzalez-Villalpando Clicerio.
21. European Scientific Journal April 2013 edition vol.9, No.12 ISSN: 1857 – 7881 (Print) e - ISSN 1857- 7431 70 QTc INTERVAL AND INSULIN RESISTANCE IN TYPE 2 DIABETES MELLITUS Romulus Timar Simona Popescu Mihaela Simu Laura Diaconu Bogdan Timar

Disclosure: No conflicts of interest, financial, or otherwise are declared by authors