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Medicine

CORRELATION BETWEEN QTC INTERVAL AND INSULIN RESISTANCE IN TYPE 2 DIABETES MELLITUS

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ABSTRACT **BACKGROUND:** World incidence of diabetes is 463 million in 2019 and rise to700 million 2045. Incidence of diabetes is 88 million in SEA in 2019 and rise to 153 million by 2045 IDF(2019) the present study was planned to assess the correlation between Insulin resistance and QTc interval in Type 2 Diabetes. **METHODS:**An observational hospital based cross-sectional study lasting one year from 1st November 2012 to 31st October 2013 was conducted in Post-Graduate Department of Medicine AcharyaShriChander Hospital Sidhra, Jammu. The study was approved by the Institutional Ethics Committee, Jammu University. All patients were subjected to thorough history,examination and necessary investigations. QTc interval was assessed using Bazzet's formula and insulin resistance was estimated at the baseline by Homeostasis Model Assessment (HOMA) described by Matthews et al. **RESULTS:** In this present observational cross-sectional study, a total of 82 patients were screened, out of which 61 patients met the inclusion criteria and hence, were the subjects. Among them 11 patients were enrolled from indoors while 50 patients were from outdoors. Out of 61 subjects, males and females were almost equally represented with a slight preponderance of female subjects. There were 29 (47.5%) male subjects and 32 (52.5%) female subjects. Their age ranged from 33-68 years. Mean age was 54.393 (±9.204) years. One fourth of the patients (15/61 i.e. 24.6%) were observed to have prolonged QTc interval while three-fourths 46 (75.4%) had QTc interval within the normal range. The mean QTc Interval of study cohort was 0.416 (±0.040)**CONCLUSION:-**In this study the frequency of prolonged QTc interval among Type 2 DM patients was considerably high (24.6%). These findings support that patients with Type 2 DM who have prolonged QTc interval have a high risk of major cardiovascular complications and it could be utilized as a rapid, objective and cost-effective screening method to identify patients at high risk for cardiovascular events.

KEYWORDS : Diabetes, QTC Interval, HOMA, Insulin Resistance, Metabolic Syndrome

INTRODUCTION

Diabetes is a global health problem,World incidence of diabetes is 463 million in 2019 and rise to700 million 2045. Incidence of diabetes is 88 million in SEA in 2019 and rise to 153million by 2045 IDF(2019)[1]. As a contributor to mortality, Diabetes mellitus is the 5th leading cause of death in the world due to both micro and macro-vascular and acute (Hypoglycemia/ketosis/HHS) complications. The principal cause of mortality and morbidity in diabetes is cardiovascular disease which occurs most commonly as Coronary heart disease (CHD) followed by Cerebro-vascular and Peripheral vascular disease (PVD). Compared with non-diabetic individuals, patients with diabetes have a two to fourfold increased risk for development and dying of CHD (Preis SR *et al* 2009)[2]and DM per se confers as much additional risk as having had a previous Myocardial Infarction. More than 90% of all diabetic patients having coronary heart disease are type 2 diabetics. DM is associated with an increased risk for MI and across the spectrum of acute coronary syndrome (ACS) events, it may affect more than one in three patients (Fang J *et al* 2000)[3] and these patients have worse CVD outcomes after ACS events (Wiviott SD *et al* 2008)[4].

INSULIN RESISTANCE: The impaired biologic response to either exogenously administered or endogenously secreted insulin is termed as Insulin Resistance. It is manifested by decreased insulin stimulated glucose transport and metabolism in adipocytes and skeletal muscle along with impaired suppression of hepatic glucose output (John B. Buse *et al* 2011)[5]. Prospective studies have shown that insulin resistance predicts the onset and is present many years before the onset of DM. Insulin sensitivity is influenced by a number of factors i.e. age, weight, ethnicity, body fat (especially abdominal), physical activity and medications. Insulin resistance is associated with the progression to IGT and Type 2 DM, although diabetes is rarely seen in insulin-resistant persons without some degree of beta-cell dysfunction. Insulin resistance is associated with increase in several factors involved in clotting and fibrinolysis e.g. fibrinogen, factor VII and PAI-1. PAI-1 has been extensively studied and there is a clear relationship between elevated PAI-1 levels and risk of coronary artery disease. Elevated plasminogen activator inhibitors (especially PAI-1) and Fibrinogen in individuals with increased Insulin Resistance and Type 2 DM, enhance the coagulation process, impair fibrinolysis and thus favour thrombosis. Hence, Insulin Resistance is a strong predictor of cardiovascular disease and the risk conferred is independent of other classic risk factors (eg. Smoking) and other related variables (eg. BMI). Thus, measurement of Insulin Resistance assumes significance while evaluating these patients.

HOMA (QUICKI)- The **HOMA index** is widely used as a **gold standard'** To target interventions earlier in order to predict and prevent the cardiac morbidity and mortality in diabetics, there is a need for a simple screening test for early detection of these high risk patients at a time when overt cardiac disease is absent. Besides its already known effects on the metabolic state, increased insulin resistance may be involved in a series of poorly investigated outcomes, one of them is ventricular instability which is manifested by increase in repolarization time which can be assessed by calculating the corrected QTc interval. Also, hyperglycemia induces ventricular instability manifested by increase in QTc interval (Pickham *et al* 2014)[6].The prevalence of a prolonged QTc interval is higher (26%) in people with Type 2 DM than in non-diabetic subjects (Veglio *et al* 1999)[7]particularly in the presence of autonomic neuropathy (Sivieri *et al* 1993)[8]. However, even patients with a recent diagnosis of diabetes and without overt cardiac complications have been observed to have an increased QTc as compared with non-diabetic subjects (Cardoso *et al* 2001)[9]. Prolonged QTc is an observed independent marker for CHD risk in Type 2 DM (Veglio *et al* 2002)[10]and has been demonstrated to be a highly significant predictor of cardiac death (Sawicki *et al* 1996)[11], even in newly diagnosed Type 2 DM. Many authors discuss the involvement not only of the hyperglycemic state in the QTc prolongation but also the involvement of the hyperinsulinic state, which is mainly caused by insulin resistance (Dekker *et al* 1996)[12]. In insulin-resistant individuals, compensatory hyperinsulinemia may act unopposed on membrane polarization, thereby leading to persistent QTc lengthening. The detailed mechanism of induction of QTc prolongation by insulin is unknown; however, several factors have been suggested. With regard to the mechanism of insulin-induced hyperpolarization, the finding that QTc and serum potassium levels are reciprocally related suggests that stimulation of cellular potassium uptake is the common mechanism for both insulin-induced hyperpolarization and insulin-induced hypokalemia. In both excitable and non-excitable cells insulin acts directly on the cell membrane to shift extracellular potassium into the cytoplasm, thereby hyperpolarizing the membrane. Hyperpolarization prolongs the repolarization phase either by increasing the temporal dispersion of action potential recovery or through early after depolarization, which leads to prolongation of QT interval. Hypokalemia could mediate adrenergic activation and sympathetic overactivity would also lead to prolongation of QTc interval (Gastaldelli *et al* 2000)[13]. Thus, Insulin resistance has been proposed as an independent determinant of QTc interval. There is a possibility of the usefulness of QTc interval as an indirect indicator of insulin resistance syndrome and because of its

simplicity, low-cost, non-invasiveness, acceptability and feasibility it might emerge as the most cost effective tool for assessing IR. Hence, the present study was planned to assess the correlation between Insulin resistance and QTc interval in Type 2 Diabetics of Jammu, as no such study has been reported from this region so far.

AIMS AND OBJECTIVE

1) To assess frequency of QTc prolongation in Type 2 Diabetes Mellitus patients attending Department of Medicine ASCOMS.
2) To study the relationship between QTc prolongation and Insulin Resistance as evaluated by HOMA-IR in these subjects

MATERIAL AND METHODS

An observational hospital based cross-sectional study lasting one year from 1st November 2012 to 31st October 2013 was conducted in Post-Graduate Department of Medicine AcharyaShriChander Hospital Sidhra, Jammu. All Type 2 Diabetes Mellitus patients attending indoor or outdoor wings of Department of Medicine, not on insulin therapy or on any drug prolonging QTc interval and without any previous history of Cardiovascular/ Renal/ Liver disease were the subjects. The study was approved by the Institutional Ethics and Board of Studies Committee of University of Jammu.

Inclusion Criteria:

Patients fulfilling the criteria for the diagnosis of Type 2 DM according to American Diabetes Association (ADA) guidelines or those on Oral Anti-diabetic medications.
Duration of illness (arbitrary) 0 to 10 years from time of diagnosis.

Exclusion Criteria:

All the patients on Insulin therapy.
Critically ill patients.
H/O Cardiovascular Disease
Patients with H/O Renal / Hepatic disease
Patients on drugs prolonging QTc interval.
Conditions associated with prolonged QTc interval.

Evaluation of Patients: All subjects were explained the purpose of the study in the local language and a written informed consent was obtained as per proforma enclosed. All patients were subjected to thorough history especially regarding the following: Diabetes, Hypertension, Smoking, Heart disease, Renal disease, Liver disease using standard questionnaire and Past drug history.

Anthropometric Measurements: Height, Weight and Waist circumference (W.C.),BMI were recorded according to the standard technique.

Blood Pressure: Blood pressure was measured with a standard mercury sphygmomanometer on the left arm and after at least 10 min of rest. Mean values were determined from two independent measurements.
Hypertension was defined as:
Systolic Blood Pressure ≥140mmHg, Diastolic Blood Pressure ≥90mmHg (Joint National Committee 7, 2003)[14]
Patients on treatment with Anti-hypertensive drugs.
The details of history and examination were recorded as per attached proforma.

Investigations Done:

Fasting Blood sugar
Lipid profile- (S. Cholesterol, S. Triglycerides, HDL cholesterol, LDL cholesterol)
Blood Urea
S. Creatinine
S. Potassium
S. Calcium
HbA1c levels
Fasting serum Insulin levels using Electro-chemiluminescence Immunoassay (ECLIA) on Roche elecsys module immunoassay analyzer.
Standard 12- Lead Electrocardiography (ECG) was performed in all of these subjects.

Measurement of Insulin Resistance: In each subject, the degree of insulin resistance was estimated at the baseline by Homeostasis Model Assessment (HOMA) as described by Matthews *et al*. Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) was calculated using the following formula:
HOMA-IR = (Fasting Insulin x Fasting Glucose)/ 405
(Glucose in mg/dl, Insulin in μU/ml).

The reference intervals for HOMA-IR for Indian population have not been yet established. In the present study, HOMA-IR ≥2.5 was taken as the cut off for assessment of insulin resistance as proposed by (Matthews *et al* 1985)[15] and also adopted by other authors (Kuwana B *et al* 2002)[16]; (Chizumi Yamada *et al* 2011)[17].

Measurement of QTc Interval:

Standard 12-lead electrocardiography (ECG) was performed in all patients. The ECG from each patient was printed at a gain of 10 mm/mV and a paper speed of 25mm/s. RR and QT intervals were measured on the resting ECG tracing of the patients: Five consecutive beats were evaluated on lead V5. The QT interval was taken from the beginning of the QRS complex to the end of the downslope of the T wave (crossing of the isoelectric line). If a U-wave was present, it was defined as duration between starting point of QRS complex and lowest point of curve between T-wave and U-wave. The QT interval corrected for the previous cardiac cycle length (QTc) was calculated according to the Bazett's formula:
$QTc = QT/\sqrt{(RR)}$.The QTc for each subject was taken as the mean value of the five calculated intervals. QTc greater than 0.44 sec was considered abnormally prolonged.

Statistical Analysis:

Descriptive data have been summarized as Mean (±SD) for all continuous variables (e.g. QTc Prolongation etc.) while categorical variables (e.g. sex etc.) have been presented as n (%) i.e. number of subjects and percentage. Baseline characteristics of study samples are described with mean, standard deviation, standard error, median, minimum and maximum. Univariate relationship was assessed as Odds Ratio (OR) along with 95% Confidence Interval (C.I.) and statistical significance of parameters was evaluated using Chi Square/Fisher Exact test, as applicable. Wherever required, two sample t-test was applied to check statistical significance of mean difference between the groups. Multivariate methods were employed to see the independent or joint effect of other variables affecting QTc interval by adopting stepwise logistic regression model. A *p*-value less than 0.05 was considered as statistically significant and all statistical tests were two sided. All statistical analysis was performed using SPSS Statistics for Windows, Version 17.0. andEpi-Info Version 6.0. for windows.

OBSERVATIONS

In this present observational cross-sectional study, a total of 82 patients were screened, out of which 61 patients met the inclusion criteria and hence, were the subjects. Among them 11 patients were enrolled from indoors while 50 patients were from outdoors. Out of 61 subjects, males and females were almost equally represented with a slight preponderance of female subjects. There were 29 (47.5%) male subjects and 32 (52.5%) female subjects. Their age ranged from 33-68 years. Mean age was 54.393 (±9.204) years.

RESULTS

TABLE 1: Frequency of QTc Prolongation among Type 2 DM Patients.

Qtc Interval	Number of Patients (n=61)	%age
Normal (<0.44s)	46	75.4%
Prolonged (≥0.44s)	15	24.6%

One fourth of the patients (15/61 i.e. 24.6%) were observed to have prolonged QTc interval while three-fourths 46 (75.4%) had QTc interval within the normal range. The mean QTc Interval of study cohort was 0.416 (±0.040)s.

TABLE 2: Gender distribution in relation to QTc Interval in Type 2 DM

SEX	Qtc Normal n (%)	QTc-Prolonged n (%)	TOTAL	Crude OR (95%) CI
Female	22 (68.75)	10 (31.25)	32	2.18 (0.56-8.82)
Male	24 (82.76)	5 (17.24)	29	
TOTAL	46	15	61	
Chi Square 1.61; p value=0.20				

10 (31.25%) out of 32 females patients, had prolonged QTc interval. 5

(17.24%) out of 29 males, had prolonged QTc interval. Though the observed value were higher in females, the results were statistically insignificant (*p value*=0.20).

TABLE 3: Baseline Charecteristics of Study Sample

Variable	Mean	SD	Standard Error	Median	Min.	Max.
Age (Years)	54.393	9.204	1.178	56.000	33	68
DM Duration (Years)	3.590	1.961	0.251	3.000	1.000	8.000
SBP(mmHg)	130.033	16.679	2.136	130.000	100.000	170.000
DBP(mmHg)	81.508	9.568	1.225	80.000	60.000	100.000
BMI(Kg/m²)	26.236	3.155	0.404	25.700	21.800	34.600
W.C. (cm)	87.884	8.043	1.030	87.000	75.000	105.000
FBS (mg/dl)	169.902	63.670	8.152	146.000	72.000	322.000
HbA1c (%)	7.930	1.238	0.159	7.800	5.700	12.000
Cholesterol (mg/dl)	172.295	51.746	6.625	172.000	64.000	320.000
TGL	159.049	52.693	6.747	141.000	72.000	292.000
LDL (mg/dl)	105.066	40.900	5.237	89.000	47.000	225.000
HDL (mg/dl)	45.065	6.289	0.812	45.000	22.000	57.000
Non-HDL (mg/dl)	126.688	53.938	6.963	125.500	13.000	278.000
S. Insulin (µU/ml)	8.302	4.851	0.626	7.210	2.610	23.940
HOMA-IR	3.311	2.038	0.263	2.420	0.960	8.740
QTc Interval (sec)	0.416	0.040	0.005	0.410	0.320	0.500

TABLE 4: Relation between Fasting Blood Sugar and QTc interval.

FBS	QTc Normal n (%)	QTc-Prolonged n (%)	TOTAL	Crude OR (95%) CI
≤130 mg/dl	20 (80.00)	5 (20.00)	25	1.54 (0.39-6.22)
>130 mg/dl	26 (72.22)	10 (27.78)	36	
TOTAL	46	15	61	
Chi square 0.48, p value= 0.45				

5 (20%) out of 25 patients with FBS ≤130mg/dl, had prolonged QTc interval. 10 (27.78%) out of 36 patients with FBS >130mg/dl, had prolonged QTc interval. These results observed were statistically insignificant (*p value*=0.45).

TABLE 5: Relation of HbA1c to QTc Interval.

HbA1c	QTc Normal n (%)	QTc-Prolonged n (%)	TOTAL	Crude OR (95%) CI
<7%	8 (88.89)	1 (11.11)	9	2.95 (0.32-68.52)
≥7%	38 (73.08)	14 (26.92)	52	
TOTAL	46	15	61	
Fisher exact p value=0.43				

9 patients had HbA1c Levels <7%, out of which 1 (11.11%) had prolonged QTc Interval.Among patients with HbA1c ≥7%, QTc interval was prolonged in 14 (26.92%) patients. The results observed were statistically insignificant (*p value*=0.43).

TABLE 6: Risk Factor-Hypertension in relation to QTc Interval.

Hypertension	QTc Normal n (%)	QTc-Prolonged n (%)	TOTAL	Crude OR (95%) CI
Normotesive	38 (90.48)	4 (9.52)	42	13.06 (2.81-66.84)
Hypertensive	8 (42.11)	11 (57.89)	19	
TOTAL	46	15	61	
Chi square 16.51; p value<0.0001				

Among hypertensive subjects, 11 (57.89%) had QTc interval prolongation, while 8 (42.11%) had normal QTc interval. The results were observed to be statistically highly significant (*p value*<0.0001).

TABLE 7: Relation between Insulin Resistance by HOMA-IR and QTc Interval.

HOMA-IR	QTc Normal n (%)	QTc Prolonged n (%)	TOTAL	Crude OR (95%) CI
<2.5	33 (91.67)	3 (8.33)	36	10.15 (2.13-54.96)
≥2.5	13 (52.00)	12 (48.00)	25	
TOTAL	46	15	61	
Chi square 12.52; p value=0.0004				

3 (8.33%) out of 36 patients had HOMA-IR <2.5 and prolonged QTc Interval. Among 25 patients with HOMA-IR ≥2.5, 12 (48%) had prolonged QTc interval. The results observed were statistically highly significant (*pvalue*=0.0004).

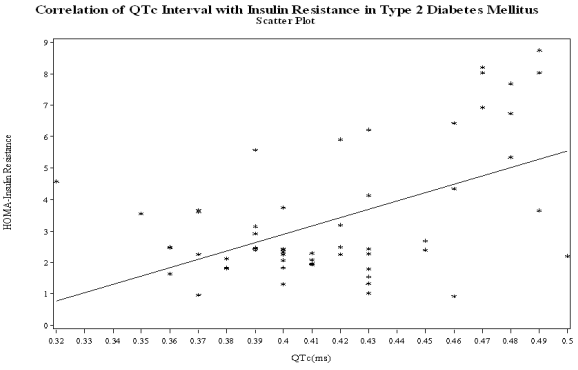

FIGURE 1-

TABLE 8: QTc Interval difference between Normal HOMA-IR and Abnormal HOMA-IR.

HOMA-IR	Qtc Interval (sec)				
	Mean	Standard Deviation	Standard Error	Minimum	Maximum
<2.5	0.4044	±0.0293	0.00489	0.3600	0.5000
≥2.5	0.4316	±0.0487	0.00974	0.3200	0.4900
p value=0.0175					

The mean QTc Interval among subjects normal HOMA-IR (<2.5) was 0.4044(±0.0293)s and ranged from 0.36-0.50s. Among the Insulin resistant subjects (≥2.5) mean QTc Interval was higher i.e. 0.4316 (±0.0487)s and ranged from 0.32-0.49s. The insulin resistant cohort had an increased mean corrected QT interval with 0.0272s compared to the normal HOMA-IR cohort the differences being statistically significant (*p value*=0.0175).

TABLE 9: Patient characteristics with respect to QTc Interval

Parameter	QTc Interval Normal (n=46)			QTc Interval Prolonged (n=15)		
	Mean	Standard Deviation	Standard Error Mean	Mean	Standard Deviation	Standard Error
Age	53.478	9.533	1.405	57.2	7.729	1.995
Duration of DM	3.108	1.538	0.226	5.066	2.404	0.620
SBP	126.5	14.251	2.101	140.8	19.358	4.998
DBP	79.304	7.811	1.151	88.266	11.460	2.959
BMI	25.478	2.809	0.414	28.556	3.105	0.801
W.C	86.160	7.283	1.073	93.166	8.189	2.114
FBS	169.326	65.973	9.727	171.7	58.13	15.009
HbA1c	7.832	1.231	0.181	8.226	1.255	0.324
Cholesterol	171.7	55.547	8.19	174.2	39.404	10.174
TGL	150.5	49.840	7.348	185.1	54.296	14.019
LDL	98.456	42.772	6.306	125.3	26.556	6.856
HDL	43.195	6.344	0.935	44.20	5.440	1.404
Non-HDL	128.311	56.760	8.461	130	42.372	11.324
HOMA-IR	2.600	1.163	0.173	5.491	2.591	0.692

TABLE 10: MULTIVARIATE ANALYSIS.

Name of Variables	Regression Coefficient (β)	Standard Error	Statistical Significance	Adjusted OR (95% CI)

HOMA-IR	-0.933	0.367	0.011	0.393 (0.191-0.808)
AGE	-0.31	0.064	0.623	0.969 (0.856-1.098)
HYPERTENSION	-2.966	1.199	0.013	0.052 (0.005-0.540)
TGLs	0.000	0.012	0.991	1.000 (0.978-1.023)
LDL	-0.013	0.018	0.455	0.987 (0.953-1.022)
BMI LEVELS	-0.803	1.322	0.544	2.232 (0.167-9.796)
CONSTANT	13.226	7.216	0.067	-

A multivariate regression model analysis was done, having the length of the QTc interval as outcome. The results reveal the significant involvement of HOMA-IR and Hypertension on the QTc interval, whereas Age, Triglyceride, LDL Cholesterol and BMI were not significant when correlated with the length of the QTc interval.

DISCUSSION

Prediction of risk of cardiovascular morbidity and mortality in Type 2 DM remains a great challenge. Surface electrocardiography is a simple, easily available, cost-effective tool, which has been used to pick up many of these asymptomatic patients. Prolonged QT interval has been proposed as a marker of cardiovascular risk in the clinical setting, as it has been particularly associated with arrhythmias, sudden death and poor survival (Schouten EG *et al* 1991)[18]. Further, an increased mortality in newly diagnosed Type 2 DM patients has also been associated with QT prolongation (Naas AAO et al 1998)[19], (Zeegler D *et al* 2008)[20]. It further assumes significance because it is a non-invasive, cheap and easily available investigation and hence, forms a cost-effective tool, more so in developing nations. Although, some cross-sectional studies suggest that poor glycemic control, IHD and hypertension are among the risk factors associated with prolongation of QT interval in diabetics, yet its pathogenesis remains unclear (Salles GF *et al* 2003)[21], (Kumar R et al 2004)[22]. It is also reported to be associated with increased mortality in several diseases including IHD, Cardiac Failure and Diabetes (Ewing DJ *et al* 1991)[23], (Barr CS *et al* 1994)[24]. HOMA-IR represents the accepted indicator for assessing IR, which is the key component of Metabolic Syndrome. It has become a widely used clinical and epidemiological tool for determining IR and when used appropriately, can yield valuable data. Though it has already been investigated for its known effects on metabolic states, ventricular instability remains one of its poorly investigated outcomes. Corrected QTc Interval, which measures the ventricular excitation and repolarization time, has been reported to increase with the serum insulin levels which induces hyperpolarization of myocardial cells and elongates the repolarization period. The profound usefulness of QTc as an indirect indicator of insulin resistance syndrome arises because of not only its simplicity, low-cost and non-invasiveness but also as a recognized predictor of serious cardiac rhythm events, often potentially life threatening eg. torsade de pointes and ventricular fibrillation (Romulus Timar *et al* 2013)[25].Cut-off for the measurement of HOMA-IR as a measure of IR has been a point of debate and varies in study populations in different geographic areas belonging to different ethnicity. It has ranged from 1.73-4.325 in different study populations(Bonora *et al* 1998)[26], (Yeni-Komshian *et al* 2000)[27], (Ascaso *et al* 2001)[28], (Buccini *et al* 2008)[29],(Bruno *et al* 2009)[31], (Esteghamati *et al* 2010)[31], (Hydrie *et al* 2012)[32], (Romulus Timar *et al* 2013)[25]. The reference intervals for HOMA-IR for Indian population have not been yet established. In the present study, HOMA-IR ≥2.5 was taken as the cut off for assessment of insulin resistance as proposed by (Matthews *et al* 1985) and also adopted by other authors (Kuwana *et al* 2002)[16]; (Dickerson *et al* 2009)[33]; (Chizumi Yamada *et al* 2011)[17]. 40.09% (25/61) patients had a HOMA-IR of ≥2.5 and nearly half of them had prolonged QTc (48%; 12/25). Thus, the chances of having prolonged QTc interval was 6 times more in the group with HOMA IR ≥2.5 as compared to that of <2.5. The mean HOMA-IR of patients with normal QTc was 2.600 (±1.163) as compared to 5.491 (±2.591) in the group with prolonged QTc. The mean corrected QT interval in the insulin resistant group was 0.4316 (±0.0487)s which was 0.0272s longer than the normal HOMA-IR cohort (0.4044±0.0293s). The difference was statistically significant (p=0.0175). The multivariate regression model indicates that insulin resistance adversely affects the QTc duration not only in association with Hypertension but also independently. Thereby, suggesting that improving the insulin resistance could have an important role in normalizing the QTc Interval and so reducing the risk of coronary heart disease and sudden death.**Limitations of the study**: Despite the best efforts under the possible circumstances and in the allotted time period, I could identify certain limitations in the present study:-

1) Compared with population-based studies, this study has a potential for a selection bias as patients from only one centre (one medical college) were included in the study.
2) In the current study, only QT interval was measured. QT dispersion also has been suggested to have a predictive role in cardiovascular mortality in Type 2 diabetes by some authors. Hence, measuring QT dispersion could have also added another dimension to the present study.
3) Due to its cross-sectional design spread over a limited period of one year, the temporal or causal relationship between risk factors and prolongation of QTc interval cannot be determined. A longer prospective randomized controlled study would have been a better option.
4) Current study is confined to the North-Indian subjects of Jammu region. Further multicentric studies including a diverse ethnic and geographic cohort are need of the hour.
5) The sample size of this study was small. A larger sample size with a longer follow up would better examine the association between prolonged QTc and prevalence of clinical vascular events.
6) Microalbuminuria also has been considered as a strong predictor of premature cardiovascular death in Type 2 DM. Though it would have added to the cost, its assessment could have further added to the virtues of this study.
7) Assessment of Left Ventricular Mass on Echocardiography could have also improved the cardiovascular evaluation

SUMMARY AND CONCLUSION This hospital based, cross-sectional study40% of subjects had Insulin resistance (HOMA-IR ≥2.5), half of which had prolonged QTc interval. The mean QTc interval of the insulin resistant group was 0.4316 (±0.0487)s which was significantly longer by 0.0272s than the group with normal HOMA-IR. On the other hand, patients with prolonged QTc interval had measurable insulin resistance 2.1 times higher as compared to those with normal QTc interval.However, on Multivariate Linear Regression analysis, insulin resistance was implicated in prolonging the QTc duration both in association with hypertension and also independently, suggesting that improving the insulin resistance could have an important role in normalizing QTc interval and hence reducing risk of coronary heart disease and sudden death. To conclude, the current study has observed the frequency of prolonged QTc interval among Type 2 Diabetes Mellitus patients to be considerably high (24.6%) and that the prolongation of QTc interval is closely as well as independently associated with not only Insulin Resistance (HOMA-IR ≥2.5) but also with Hypertension. These findings support that patients with Type 2 Diabetes Mellitus who have prolonged QTc interval also have a high risk of major cardiovascular complications and it could be utilized as a rapid, objective and cost-effective screening method to identify patients at high risk for cardiovascular events. Interventions like Lifestyle Modifications which not only improve the insulin sensitivity but also other common co-morbidities like Obesity and Hypertension can go a long way to improve the ultimate outcome and reduce their mortality risk. However, larger, population based, randomized controlled prospective studies are needed to validate the usefulness of QTc interval as an indicator of insulin resistance to identify patients with major cardiovascular risk factors and at risk of sudden death.

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