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QT Dispersion & Insulin Resistance: Effective Markers to Assess Cardiovascular Risk in Type 2 Diabetes Mellitus

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Abstract **Original Research Article**

Background: Most recent trials revealed that insulin resistance could be an only risk factor for cardiovascular diseases in type 2 diabetics. Increased insulin resistance involved in a series of poorly investigated outcome, one of them is ventricular instability, manifested by increase in ventricular repolarization. Current study was undertaken to evaluate the QT Dispersion in type II diabetic subjects as it is cost effective and to assess its correlation with insulin resistance. ***Methods:*** 100 diabetics were screened for insulin resistance & QT dispersion & compared with 100 ages & sex matched non diabetics. HOMA -IR for insulin resistance & ECG derived indices QT interval QTi, Corrected QT interval QTc by Bazzet's formula & QT dispersion QTd were calculated by 12 lead ECG. Insulin resistance calculated from HOMA-IR was correlated with various parameters like abdominal circumference, HBA1c, QTi, QTc, & QTd. ***Results:*** QTd was significantly increased in diabetics than nondiabetics. HOMA -IR shows strong positive correlation with abdominal circumference, HBA1c, QT interval & QT dispersion. ***Conclusion:*** Raised insulin resistance is associated with increased sympathetic nerve activity which enhances myocardial cell membrane refractoriness and thus leads to prolongation of QT interval. We conclude that QTd as significant prognostic marker for early detection of cardiovascular mortality & can be used as screening tool to prompt further investigation.

Keywords: T2DM, QT dispersion, insulin resistance, cardiovascular risk markers, metabolic syndrome.

QT dispersion & insulin resistance: Effective markers to assess cardiovascular risk in type 2 diabetes mellitus.

Diabetes Mellitus (DM) is a complex, chronic metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1].

India has the highest number of type 2 DM individuals worldwide, with a prevalence of 11.6% in urban populations [2, 3]. Cardiovascular diseases (CVD) like myocardial infarction, ischemic stroke and peripheral arterial obstructive disease are the most prevalent cause of death in type 2 DM patients [4-6]. Asian Indians are known to be at a high risk for type 2 DM, CVD, and metabolic syndrome [7, 8].

Numerous epidemiological and clinical trials have shown that patients with type II diabetes mellitus are at increased risk of mortality from sudden cardiac death [9]. Elevated cardiovascular risk in this population persist even after other conventional cardiovascular risk factors (hypertension, dyslipidaemia, smoking , alcohol, physical inactivity) are eliminated or reduced suggesting that there are other incompletely understood mechanism which are increasing cardiovascular risk in such patients. The strong association between T2 DM and CVS diseases emphasizes the need for better understanding and pathophysiological mechanism responsible for this relationship. QT interval prolongation has been indicated predicator of mortality in T2 DM.

Further research is necessary to determine the association between QT prolongation and sudden cardiac death risk in patients of diabetes.

Most recent trials revealed the Insulin resistance could be an only risk factor for cardiovascular diseases. Insulin resistance appears to be associated with increased risk of type II diabetes and heart diseases. For this reason, it could be useful to identify the individuals who are insulin resistant. Insulin resistance is defined a diminished response to a given concentration of insulin [1]. Previous studies have shown that insulin resistance is associated with prolonged QT dispersion in type II diabetes mellitus. Although there is a general agreement that the QT

interval is affected by cardiac ischemia, the effect of hyperglycemia and insulin resistance but effect on QT measures is controversial. HOMA- IR (homeostatic model assessment of insulin resistance) is the widely used test to quantify insulin resistance and beta cell function. HOMA-IR is widely used as insulin resistant index in clinical and epidemiological studies [1]. Several studies suggest that assessing the QT interval could be a cost-effective way of stratifying such patients according to cardiovascular risk so that aggressive treatment could be directed appropriately to improve outcome [4]. It seems cardiovascular risk factors can be predicted by estimating the insulin resistance & QT dispersion in type II diabetic subjects. Therefore, current study was undertaken to evaluate the QT Dispersion in type II diabetic subjects as it is cost effective and to assess its correlation with insulin resistance.

METHODS

Study Design: cross sectional study consists of 100 type 2 diabetic patients including both male & female seen at diabetic clinic & medical outpatient department at Sassoon General Hospital, Pune. All subjects of age group between 18 to 50 years were evaluated for 12 lead ECG, insulin resistance & compared with healthy age & sex matched control (n=100).

Diagnosis of DM was done according to American Diabetes Association [1].

a) Symptoms of diabetes like polyuria, polydipsia, weight loss, slow healing of ulcers + Random sugar ≥ 200mg/dl. b) Fasting plasma glucose ≥ 126mg/dl after an overnight fasting & postprandial Plasma glucose ≥ 200mg/dl) c). HBA1c ≥ 6.5.

Exclusion criteria include Known arrhythmia, myocardial infarction, unstable angina, stroke, alcoholics., smokers, Patients taking Beta blockers, Calcium channel blockers, Antipsychotics. Electrolyte imbalance, Postmenopausal women, Subjects taking oral contraceptives, Chronic Obstructive Pulmonary Disease. Endocrinal disorder like hypothyroidism, PCOS, Acromegaly, Cushing Syndrome.

DATA COLLECTION

All subjects underwent thorough clinical examination, detailed history, lifestyle and diet was taken. All subjects were evaluated for age, height, weight, BMI, waist circumference, waist to hip ratio & vital parameters like blood pressure, heart rate.

Measurement of ECG derived indices

Participants were instructed not to consume tea or caffeine or exercise 12 hours prior to testing. Resting 12 lead ECG was taken in a room with comfortable temperature (22 to 25^0C) speed of 25mm/sec with gain of 10 mm/ mV.

Heart rate, Uncorrected QT interval (QTi), Corrected QT interval (QTc), QT dispersion (QTd) was calculated from 12 lead ECG.

QT interval QTi was calculated as beginning of Q wave to the end of T wave i.e. reaching of T wave to isoelectric line. Corrected QT interval (QTc) was calculated by Bezett's formula QTc = QT/ √RR.

QT dispersion (QTd) was calculated as difference between shortest & longest QT interval recorded from 12 lead ECG, at least three consecutive cycles were measured for each lead and then averaged.

Biochemical parameters: Blood samples Fasting (8 to 10 hrs after last dinner) and Post prandial (after 2 hrs of food) was collected in a vacutainer by venepuncture with all aseptic precautions and the blood samples were stored at 2 – 8 degree Celsius.

The various tests were performed like fasting and post prandial Blood glucose, HBA1c & Fasting serum insulin. Blood sugar was done by GOD POD method using Pathozyme kit. HBA1c was measured by using Seimen autoanalyzer using HBA1c kit. Serum insulin was done in biochemistry department by Electrochemiluminescence method using Cobas (Roche) kit. Normal fasting insulin < 25 microliter / ml & 2 hrs after glucose administration 16- 166 microliter / ml was considered [1].

Insulin resistance was measured by HOMA – IR (Homeostatic Model Assessment of Insulin Resistance) by using a formula = Fasting glucose (mg /dl) × Fasting insulin (µl /ml) / 405 for estimation of insulin sensitivity. It is the way to reveal the dynamic between your baseline (fasting) blood sugar and the responsive hormone insulin.

Healthy range – 1.0 (0.5 – 1.4), Less than 1 – Insulin sensitive, Above 1.9 – Early insulin resistance, Above 2.9 - Significant insulin resistance.

RESULTS

Table-1: Showing characteristics of T2DM & control group

Parameters	T2DM (n=100) Mean ± SD	Control (n=100) Mean ± SD	P value
Age (yrs)	41.28 ± 7.8	39.04 ± 6.9	> 0.05
BMI (kg/m2)	27.42 ± 5.53	26.2 ± 3.35	> 0.05
Abdominalcircumference (AC) cm	93.5 ± 4.2	63.6 ± 4.4	≤0.0001
Waist to Hip Ratio (WHR)	0.96 ± 0.06	0.84 ± 0.03	≤ 0.0001
SYSTOLIC BP (mm Hg)	132.5 ± 20.6	119.3 ± 7.8	< 0.0001
DIASTOLIC BP (mm Hg)	84.3 ± 14.2	75.4 ± 4.5	< 0.0001
HEART RATE (beats / min)	79.3 ± 10.3	73.15 ± 3.13	< 0.0001

Table-2: Showing biochemical parameters in T2DM & control group

Indicators	T2DM(n=100) Mean ± SD	Control(n=100) Mean ± SD	P value
Fasting Blood Sugar (mg/dl)	193.04 ± 58.03	107.2 ± 23.6	< 0.05
Postprandial Blood Sugar (mg/ dl)	254.6 ± 79.0	126.2 ± 44.0	< 0.05
HBA1c (%)	8.68 ± 1.3	5.3 ± 0.71	< 0.05
Fasting Serum Insulin	6.77 ± 2.68	8.5 ± 3.9	< 0.05
HOMA - IR	3.24 ± 1.5	2.2 ± 1.3	< 0.05

Table-3: Showing ECG derived indices QTi , QTc & QTd in T2DM & control group

ECG indices	T2 DM (n =100) Mean ± SD	T2 DM(n =100) Mean ± SD	P value
QT INTERVAL (ms)	303.9 ± 7.5	316.8 ± 35.4	<0.05
CORRECTED QT INTERVAL (ms)	441.1 ± 38.5	380.3 ± 35.5	< 0.0001
QT DISPERSION (QTd) (ms)	79.60 ± 15.44	37.28 ± 5.62	< 0.0001

Table-4: Shows Pearson correlation coefficient of HOMA -IR with various parameters in T2DM

Parameters	T2DM	P value
Age (yrs)	-0.011	>0.05
BMI (kg/m2)	0.0308	>0.05
Waist circumference (cm)	0.0527	<0.001
Waist to hip ratio	0.0483	>0.05
HBA1c	0.2557	<0.05
QT interval QTi (ms)	0.0198	<0.05
Corrected QT interval QTc (ms)	0.0492	<0.001
QT dispersion QTd (ms)	0.0692	<0.001

STATISTICAL ANALYSIS

The data obtained was tabulated in Microsoft excel sheet. Mean and standard deviation was calculated for diabetic and control group. Statistics was done by software Graph Pad Prism version 5.1. Appropriate statistical test was applied. Unpaired t test was applied for ECG parameters and cardiometabolic parameters were compared between diagnosed diabetics (n= 100) and control (n=100). Correlation was done by

Pearson Correlation coefficient (r) between HOMA – IR with ECG indices and Biochemical parameters.

DISCUSSION

Diabetes mellitus is associated with a marked increase in risk of sudden cardiac deaths [10] QT interval prolongation has been indicated as an independent predicator of mortality and has been associated with a suspected increase in risk of sudden cardiac deaths in diabetic patients [11]. We did not find significant change in BMI but there is significant change in adiposity markers like WHR and Abdominal circumference. BMI represents generalized obesity and adiposity markers represent visceral obesity. It appears that it is the visceral obesity responsible for deranged glucose metabolism than generalized obesity. In T2 DM visceral obesity is the most important cause for development of Insulin resistance leading to hyperglycemia.

Stokic E *et al.* [12] have shown that intraabdominal fat is associated with a number of metabolic complications. Montague *et al*. [13] showed that visceral obesity is an important predictor of increased cardiovascular metabolic complications and mortality.

We observed a statistically significant increase in vital parameters in T2 DM as compared to healthy control. Psallas *et al*. [14] have shown that T2 DM shared broad cardiometabolic disorders including obesity, insulin resistance, β-cell dysfunction, inflammation, oxidative stress, vascular dysfunction, sodium retention, sympathetic excitation, renin-angiotensin-aldosterone system activation, and kidney damage, which has been widely proposed in the initiation of hypertension.

Table 3 shows comparison of QT interval, Corrected QT interval and QT dispersion between two groups. We found QT interval is decrease in T2 DM patients as compared to control group. Increase in resting heart rate affect QT interval but after correction with heart rate by Bazett's formula [15]. Corrected QT interval (QTc) is more and statistically significant in T2 DM patients as compared to control group. It indicates QT interval is heart rate dependent variable.

There is significantly increase in QT dispersion (QTd) in T2 DM patients as compared to control group. Previous studies showed [14, 16] prolonged QTd in diabetics compared to non-diabetics & QTd is affected by hyperglycemia. It depends on duration of hyperglycemia, longer the duration of hyperglycemia, more prolonged the QT dispersion.

Neki *et al*. [17] studied cardiac autonomic function in T2 DM and found that QTc was prolonged in T2 DM and has linear positive correlation with the degree of Cardiac Autonomic Neuropathy (CAN).

There are several explanations have been put forward to explain prolonged QT dispersion in T2 DM & its relation with insulin resistance.

- Type 2 DM is associated with cardiac autonomic neuropathy (CAN) is a result of glucose metabolism and may lead to disorders of sympathovagal balance and increased cardiac sympathetic activity.
- The duration and dispersion of the QT interval reflect various subclinical disturbances such as Left Ventricular Hypertrophy, Ischemia, and Myocardial fibrosis. The severity of these lesions is positively associated with increase in QTd.
- Other mechanisms are increased oxidative stress, increased free radical production, dysfunction of nitric oxide production and endothelial dysfunction can alter cardiac repolarization.
- As insulin resistance develops, your body fights back by producing more insulin. Over months and years, the beta cells in your pancreas that are working so hard to make insulin get worn out and can no longer keep pace with the demand for more and more insulin. Then years after insulin resistance silently began, your blood sugar may begin to rise and you may develop T2DM. Insulin level starts falling as you developed frank diabetes. That fmay be reason current study shows increase in HOMA-IR & fall in insulin levels in T2DM patients.
- Insulin resistance affects the membrane of cardiac myocyte and electrophysiology of myocytes which leads to prolongation of repolarization phase and thus there is QT interval prolongation. Raised insulin level is associated with increased sympathetic nerve activity which enhances myocardial cell membrane refractoriness and thus leads to prolongation of QT interval. QT interval prolongation represents an independent risk factor for development of tachyarrhythmias and sudden cardiac death.

HOMA-IR represents the actual accepted indicator for assessing the insulin resistance. Increased insulin resistance involved in a series of poorly investigated outcome, one of them is ventricular instability, manifested by increase in ventricular repolarization.

Table 4 shows strong positive correlation of HOMA-IR with visceral obesity. It is the main predictive factor of cardiometabolic risk factors and associated with Insulin resistance in T2 DM.

HBA1c, Glycated hemoglobin indicates as a reflection of glycaemia, is an important indicator of glycemic control for the previous 3 months. Positive correlation of HOMA -IR with HBA1c in T2DM indicates decreased insulin sensitivity in T2 DM [18].

We found positive correlation of HOMA-IR with QT interval and QT dispersion in T2 DM demonstrate that presence of Insulin resistance causes increase in QT dispersion. Duration of QT interval on surface ECG is a global measure of time the heart takes to depolarize and repolarize. Prolonged QT interval is associated with life threatening rhythm disturbances and sudden cardiac deaths [19].

QT dispersion calculated from QT interval is an important marker gives an idea about cardiac action potential. Prolonged QT dispersion indicates inhomogeneous ventricular repolarization [20].

Therefore, in present study we tried to assess cardiovascular risk factors like insulin resistance, prolonged QT dispersion in T2DM. We emphasize the need to assess these risk factors routinely in T2 DM to decrease cardiovascular mortality. Assessment of the QT interval could be a cost-effective way of stratifying such patients according to cardiovascular risk so that aggressive treatment could be directed appropriately to improve outcome.

Regular exercise should be promoted to increase energy expenditure and achieve weight loss and increase insulin sensitivity. Instruction of physical activity needs to be gradual and graded.

CONCLUSIONS

- Insulin resistance, estimated by HOMA – IR was tightly correlated with visceral obesity & prolonged QT dispersion, considered as a marker for early assessment and prevention of cardiovascular complications in T2DM.
- QT dispersion is a noninvasive and cost-effective marker of arrhythmogenicity, so analysis of routine ECG is an important, non-invasive, inexpensive bedside diagnostic tool to detect early arrythmias in T2 DM.
- The important impact of prolonged QT dispersion & insulin resistance on cardiovascular complications requires undivided attention throughout the course of disease.
- Lifestyle changes that focus specifically on diet and physical activity are the best way to prevent cardiovascular complications in T2DM.

LIMITATIONS

- Manual measurement of QT interval without support of any technology that could ensure a more precise measurement should have taken into account.
- We did not use the gold standard in assessment of insulin sensitivity i.e glucose clamp method.
- We need to see for further research on the link between insulin resistance and sudden cardiac death which require long term follow up study in evaluating the risk of malignant cardiac arrhythmia.

Presentation at a meeting

Ethical committee BJMC PUNE, Approved by Maharashtra University of health sciences Nashik.

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