# QTc INTERVAL AND INSULIN RESISTANCE IN TYPE 2 DIABETES MELLITUS

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**Abstract**

**Introduction:** Patients with type 2 diabetes mellitus (DM) are at increased risk of dying from cardiovascular diseases. Elevated cardiovascular risk in this population persists even after other conventional cardiovascular risk factors are eliminated or reduced, suggesting that there are other, incompletely understood, mechanisms which are increasing cardiovascular risk in such patients. Ventricular instability, such as that observed in QT abnormalities, may be an important additional mechanism. QT prolongation has been shown to predict cardiac death in type 2 DM.

The aims of our study were to evaluate the prevalence of QTc prolongation in patients with type 2 DM and to assess the relationship between insulin resistance, evaluated by HOMA-IR and QTc. We also investigated the relationship between QTc and the duration of DM, HbA1c, plasma lipids, systolic blood pressure (SBP), diastolic blood pressure (DBP) and body mass index (BMI).

**Materials and method:** We enrolled 104 patients with type 2 DM. For each subject, 100 consecutive heart beats were recorded on the resting ECG tracing. QTc was calculated according to Bazett's formula.

**Results and discussion:** In patients with type 2 DM, the prevalence of a prolonged QTc interval was 34.6%. We found a significant increase, with 64 ms (p= 0.004) in QTc interval for the insulin resistant cohort (mean QTc= 419 ms; n= 92) compared to the sample with normal HOMA IR (mean QTc= 355; n=12).

**Conclusion:** Insulin resistance, estimated by HOMA-IR, was strongly correlated with prolonged QTc. Prolonged QTc identifies type 2 DM patients with an elevated risk of cardiovascular events.

**Keywords:** Diabetes Mellitus, Insulin Resistance, QTc, HOMA-IR

## Introduction

Epidemiological studies have demonstrated that diabetics display a cardiovascular risk which is twice that of the sex- and age-matched non-diabetic population (Vinik, 2001; Langer, 1991). Patients with type 2 diabetes mellitus (DM) are at increased risk of dying from cardiovascular diseases. Excess cardiovascular risk in this population persists even after normalization for other conventional cardiovascular risk factors (hypertension, dyslipidemia, physical inactivity, smoking), suggesting that there are other incompletely understood mechanisms which increase cardiovascular risk in diabetic patients. Ventricular instability, as manifested in QT abnormalities, may be an important additional mechanism (Kumar, 2004). The QT interval on an electrocardiogram represents the time needed for ventricular repolarization. Increased length of this interval, known as corrected QT (QTc) prolongation, can be a precursor of torsade de pointes, a potentially life-threatening ventricular dysrhythmia (Pickham, 2013) and ventricular fibrillation (Jackman, 1988). Prolongation of QTc increases morbidity and mortality and QTc has been found to be longer in patients with DM than in healthy controls.

QT prolongation has been shown to predict cardiac death in type 2 DM. Although there is general agreement that the QT interval is affected by cardiac ischemia, the effect of hyperglycemia on QT measures is controversial. 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 (Kumar, 2004).

The aims of our study were to evaluate the prevalence of QTc prolongation in patients with type 2 DM and to assess the relationship between QTc and insulin resistance, evaluated by HOMA-IR. We also evaluated the relationship between QTc and the duration of DM, HbA1c, plasma lipids, systolic blood pressure (SBP), diastolic blood pressure (DBP), and body mass index (BMI).

## Main Text

## Materials And Method

*Study population:* We conducted a hospital-based study lasting one year – January to December 2012 – at the Diabetes and Nutrition Department of the Timisoara Emergency Clinical Country Hospital.

The participants were selected from patients hospitalized in the Diabetes and Nutrition Department of the Timisoara Emergency Clinical Country Hospital. The study enrolled 104 patients with type 2 DM, whose ages ranged from 26 to 76 years. The diagnosis and classification of their diabetes were based on guidelines of the EASD: symptoms of diabetes: polydipsia, polyuria, unexplained weight loss; plus a random plasma glucose >200 mg/dL (11.1 mmol/L) or fasting plasma glucose > 126 mg/dL (7.0 mmol/L) after an overnight fast (at least 8 hours) or two-hour plasma glucose> 200mg/dL (11.1 mmol/L) during a standard 75g oral glucose tolerance test; any of these criteria establishes the diagnosis but needs to be confirmed some days later. We excluded those with known arrhythmia, unstable angina, myocardial infarction, or cerebrovascular disease, and those who were taking any autonomic drug such as a β-blocker, β- agonist, or calcium channel blocker. The study protocol was approved by the ethics committee of the Timisoara Emergency Clinical Country Hospital, and the participants signed to show their informed consent at the time of recruitment.

Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Blood pressure was measured twice (5 minutes apart) on both right and left arms after the participants had been sitting and calm for at least 10 minutes. The highest blood pressure of two sides was considered as the participant`s blood pressure.

Patients' baseline characteristics are presented in Table 1.

***Table 1.*** *Baseline characteristics of the studied group*

| | **Entire group** | **Men** | **Women** | **p (men vs. women)** |
|---|---|---|---|---|
| **Number** | 104 | 56 (53.5%) | 48 (46.2%) | n/a |
| **Median age** | 52.5 ± 11.1 | 51.3 ± 10.1 | 53.8 ± 12.1 | 0.251 |
| **Median diabetes duration** | 6.2 ± 6 | 5.7 ± 6.2 | 6.75 ± 5.8 | 0.378 |
| **HbA1c (%)** | 10.02 ± 2.46 | 10.05 ± 2.26 | 9.97 ± 2.7 | 0.083 |
| **HOMA-IR** | 4.36 ± 2.47 | 4.53 ± 2.3 | 4.17 ± 2.67 | 0.459 |
| **BMI (kg/m$^2$)** | 30.6 ± 6.4 | 29.91 ± 4.84 | 31.53 ± 7.84 | 0.201 |
| **SBP (mmHg)** | 133.8 ± 19.4 | 135.9 ± 20.52 | 131.2 ± 18 | 0.21 |
| **DBP (mmHg)** | 82.7 ± 12.5 | 85.0 ± 12.49 | 80.1 ± 12.13 | 0.045 |
| **Triglycerides (mg/dL)** | 233.3 ± 147.5 | 259.1 ± 145.1 | 203.29 ± 146.16 | 0.054 |
| **Total cholesterol (mg/dL)** | 213.6 ± 57.6 | 215.16 ± 63.61 | 211.83 ± 50.21 | 0.77 |
| **HDLc (mg/dL)** | 37.9 ± 11.4 | 35.18 ± 8.13 | 41.08 ± 13.75 | 0.008 |

*Values are expressed as means ± standard deviations. P was assessed using an unpaired t-student test.*

The homeostasis model assessment (HOMA) index was calculated as the product of the peptide C (pmol/l) level and the fasting plasma glucose level (mmol/L) divided by 2800, plus 1.5.

*QTc:* The evaluation of QTc was performed in a quiet and temperature-controlled room, participants having been advised to abstain from caffeinated food and beverages on the day of their assessments. Repeated assessments were performed at precisely the same time of day after 48 hours. After 15 minutes of supine rest with a regular and calm breathing pattern, 100 consecutive heart beats were recorded on the ECG tracing. QT and RR intervals were measured with a rule for 5 consecutive beats on the V5 lead on the resting ECG tracing. QTc was calculated according to Bazett's formula. Any QTc > 0.44s was considered abnormally prolonged.

*Statistical methods:* Statistical analysis was performed using IBM SPSS v. 15 and Graph Pad Prism v.5. In order to assess the significance of differences, an unpaired t-student test for parametrical variables and the Mann-Whitney test for non-parametrical data were used (means), together with Fisher's exact test for proportions. To assess the interdependence between variables, univariate and multivariate regression models were developed. To obtain the analysis B coefficient, β exponent and Pearson's correlation coefficient were used, their significance being calculated using a t-distribution test.

**Results**

Normal HOMA-IR was found in 12 patients, while 92 had HOMA-IR values over 2.4. In the entire group, the prevalence of a prolonged QTc interval was 34.6 % (24.24% to 47.9%; 95% CI). The prevalence was not significantly different in men (30.4%) and in women (39.6%), p=0. 41 (Fisher's exact test).

The insulin resistant cohort (mean QTc=419. 8 ms) had an increased mean corrected QT interval with 64.3 ms compared to the normal HOMA-IR cohort (mean QTc=355. 5 ms), the differences being statistically significant (p=0. 004; unpaired t-student test). The percentage of patients presenting prolonged QTc were 39.1% in the insulin resistant group while none of the patients with normal HOMA-IR had a QTc interval over 440ms.

The corrected QT interval is strongly positive and statistically significant correlated with HOMA-IR values (Pearson r=0.62; p< 0.001 t-distribution test), meaning that the QTc interval increases once with HOMA-IR (Figure 1).

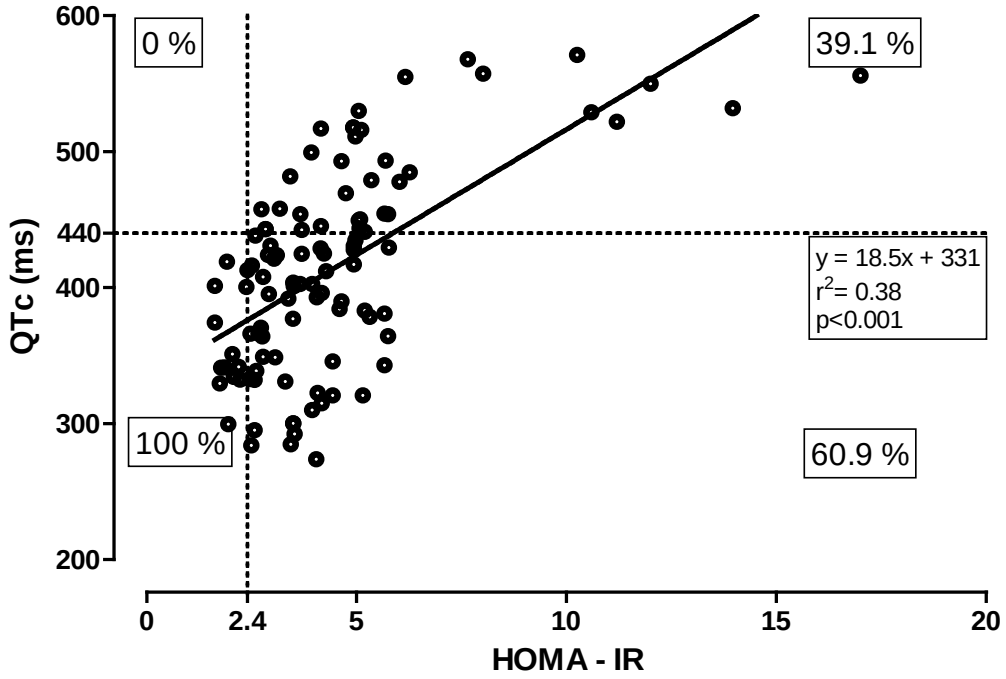


***Figure 1.*** *The correlation between HOMA-IR and QTc*

In order to assess the influence of individual factors (HOMA-IR, HbA1c, age, diabetes duration and BMI), we fitted these 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 (Table 2).

***Table 2.*** *Multivariate regression results.*

| Predictor | B (95% CI) | Exp (β) | p |
|---|---|---|---|
| **HOMA-IR** | 1.76 (1.3 to 2.2) | 0.58 | < 0.001 |
| **Age** | 0.125 (0.02 to 0.25) | 0.158 | 0.048 |
| **Diabetes duration** | 0.028 (-0.18 to 0.23) | 0.023 | 0.786 |
| **HbA1c** | 0.37 (0.23 to 0.61) | 0.146 | 0.041 |
| **BMI** | 0.119 (-0.068 to 0.307) | 0.014 | 0.208 |

## Discussion

Cardiac autonomic neuropathy is a well-recognized complication of diabetes and is believed to be responsible for an increased risk of sudden death. Prolonged QTc is an independent marker for CHD risk in type 2 diabetes (Veglio, 2002) and has been demonstrated to be a highly significant predictor of cardiac death (Sawicki, 1996), even in newly diagnosed type 2 diabetes. The prevalence of a prolonged QTc interval is higher in people with type 2 diabetes than in non-diabetic subjects (Veglio, 2002; Veglio, 1999) in particular in the presence of autonomic neuropathy (Sivieri, 1993). The prevalence of QT prolongation has been reported to be as high as 26% in type 2 diabetes (Veglio, 2002). However, even patients with a recent diagnosis of diabetes and without overt cardiac

complications have been observed to have an increased QTc compared to non-diabetic subjects (Cardoso, 2001). The QT interval is affected by CHD and autonomic neuropathy and it is possible that these new diabetic patients with prolonged QT interval may have had undiagnosed neuropathy or CHD.

It is already known that hyperglycemia induces ventricular instability manifested by increases of the QTc interval (Pickham, 2013). Many studies discuss the involvement not only of the hypoglycemic state in the QTc prolongation but also the involvement of the hyperinsulinic state, which is mainly caused by insulin resistance (Dekker, 1996). Hyperinsulinemia and insulin resistance have been implicated as key factors in the etiology of coronary heart disease (DeFronzo, 1991). They provide a basis for the clustering of several risk factors. Genetic predisposition, lack of physical activity, and positive energy balance, followed by increased body weight, result in high insulin levels. Hyperinsulinemia notably increases the triglyceride level and lowers HDL cholesterol. QTC prolongation and its sequelae may be an additional feature of this cluster (Dekker, 1996).

Animal studies have shown that glucose-insulin infusion reduces and improves the associated conduction delay (Bekheit, 1993). Altered ion exchange activities may be induced by reduced myocardial glucose uptake resulting from impaired insulin binding (Almira, 1986). Hyperinsulinemia and disturbed glucose uptake may contribute to a longer QTc (Dekker, 1996).

HOMA-IR represents the actual accepted indicator for assessing the insulin-resistance, the key component of the Metabolic Syndrome. 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 being ventricular instability, manifested by increases in repolarization which can be assessed by calculating the corrected QTc interval.

Our results demonstrate that the presence of insulin resistance causes an increase in the mean QTc interval, which is statistically significant. Not only is this mean increased, but being in the insulin-resistant cohort causes a major increase in the probability of having a corrected QT interval over the cutoff value of 440 ms which the international guidelines consider to be the maximum safe value. These results are sustained by the tight positive correlation between the HOMA-IR levels and QTc intervals encountered, QTc being a recognized predictor of serious cardiac rhythm events, potentially life threatening, such as torsade de pointes (Pickham, 2013) and ventricular fibrillation (Jackman, 1988), which indirectly involve insulin resistance in this chain of occurrences.

The multivariate regression model indicates that insulin resistance is involved in prolonging the QTc interval both in association with other predictors (in our case age and HbA1c) and also independently, 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.

**Conclusions**

Insulin resistance, estimated by HOMA-IR, was closely correlated with prolonged QTc. No association between QTc and gender has been observed in type 2 DM. Prolonged QTc identifies type 2 DM patients as having an elevated risk of cardiovascular events. No association between QT abnormalities and gender has been observed in type 2 diabetes. Diabetic patients with more pronounced QT abnormalities tend to have higher age and blood pressure and they tend to have cardiovascular complications.

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