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Electrocardiographic QT Interval Prolongation in Subjects With and Without Type 2 Diabetes – Risk Factors and Clinical Implications

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1. Introduction

Several studies have focused on the identification of patients at risk of sudden cardiac death, which is mostly due to depolarization and repolarization impairment. The measurement of QT interval indicates the total duration of ventricular myocardial depolarization and repolarization. Localized repolarization data can be obtained easily from the standard 12-lead electrocardiogram (ECG), a non-invasive method extensively used as a tool for cardiovascular risk assessment. [1,2] Non-uniform myocardial repolarization time may result from inhomogeneity, variation of action potential duration between the individual leads of the 12-lead ECG, or localized delay in activation due to slow conduction or altered conduction pathways. To ensure the recording of the earliest depolarization at the latest repolarization of the ventricular myocardium, the maximum QT interval should be measured from the beginning of the earliest QRS complex to the end of the latest T wave from all leads of a simultaneous 12-lead ECG. Nevertheless, the QT interval may reflect increased inhomogeneity of myocardial repolarization, resulting from delayed repolarization in some areas of the myocardium, and it can be caused by a uniform increase in action potential duration. A measure that can help differentiate between these two conditions is the QT dispersion. Using both the QT prolongation and the QT dispersion the individual lead variation and the interlead variation provide a measure of repolarization heterogeneity. [3]

The QT interval prolongation has been proposed as a marker of cardiovascular risk in the clinical setting and it has also been particularly associated with arrhythmias, sudden death and poor survival in apparently healthy subjects. [4,5] As for diabetic subjects, although some cross-sectional studies suggest that glycemic control, ischemic heart disease, and blood pressure, among other risk factors, are associated with the QT interval prolongation, its pathogenesis remains unclear. [6,8] Also, and increased mortality in newly diagnosed type 2 diabetes patients has been associated with QT interval prolongation. [9,10]

The aim of this study was to estimate the prevalence of QTc interval prolongation in diabetic and non-diabetic subjects, as well as to evaluate cross-sectionally and prospectively the associated risk factors of QTc interval prolongation and its clinical implications in subjects
2. Methods

The Mexico City Diabetes Study is a prospective, population-based investigation designed to describe the prevalence and incidence of diabetes and cardiovascular risk factors in low-income urban population from Mexico City. The detailed methodology has been reported elsewhere. [11] Briefly, the sample size included 2282 men and non-pregnant women aged 35 to 64 years who completed a baseline interview and physical examination in 1989-1990. Two follow-up visits were carried out in 1994-1996 (n=1773) and in 1998-2000 (n=1764). All evaluations included medical history, physical examination, ECG, and several laboratory tests. Current smoking was defined as at least one cigarette per day in the last year. Physical examination included an anthropometric evaluation with participants wearing lightweight clothing and no shoes. Height was measured using a stadiometer with subjects standing on the floor with the back against a wall; weight was measured using a clinical scale. Body mass index (BMI) was calculated as weight/height$^2$ in kg/m$^2$. Waist circumference (WC) was measured considering the umbilicus as the landmark. Systolic (SBP) and diastolic blood pressure (DBP) were measured 3 times in the right arm of seated subjects (after resting for at least 5 min) using a random zero sphygmomanometer (Hawksley, London). We used the average of the last 2 readings as the BP of the participants. Hypertension was defined as SBP$\geq$140 mmHg, DBP$\geq$90 mmHg, or treatment with antihypertensive drugs. In every visit, participants completed a 75-g oral glucose tolerance test. Diabetes was defined according to the World Health Organization criteria with a fasting glucose $\geq$7mmol/l (126 mg/dl), 2-hour glucose $\geq$11.1 mmol/l (200 mg/dl), or treatment with oral antidiabetic drugs. [12] Fasting and 2-hour plasma glucose and insulin as well as fasting serum lipids and all other biomarkers were measured using previously reported methods [13] at the research laboratory of the Division of Clinical Epidemiology at the Medicine Department of the University of Texas Health Science Center at San Antonio, USA. Insulin resistance was estimated by the homeostasis model (HOMA-IR) as follows: [fasting insulin (units/ml) X fasting glucose (mmol/l)]/22.5.

A resting standard 12-lead ECG was taken with the subject in a supine position at each examination. A standard interpretation of ECGs at a reading center (Wake Forest University, EPICARE Center) was made using the Minnesota Code. [14] Heart rate (HR), QRS duration, R amplitude in AVL lead (R-AVL), S amplitude in V3 lead (SV3), left ventricular hypertrophy (LVH), QT interval, and myocardial infarction, among other variables, were coded. Left ventricular hypertrophy (LVH) was defined as (R-AVL) + (SV3) $\geq$2600$\mu$v in men and $\geq$2200$\mu$v in women. Myocardial infarction was defined according to the following codes: Q-QS pattern with 1.1-1.2, Q-QS and T wave pattern 1.2.8-1.3, and wave T pattern with 5.1-5.3. QT interval was measured from the electrocardiogram tracing in lead II and defined as the first deflection of the QRS complex and the end as the point of maximal change in the slope as the T wave merges with the baseline. QT corrected (QTc) was calculated according to Bazett’s formula as QT/square root of (R–R interval). The same measurement instruments were used throughout the study.

The Institutional Review Boards of both The University of Texas Health Science Center and the Centro de Estudios en Diabetes approved the study protocol. Each participant gave informed consent. For this analysis, we included 1661 subjects, 218 with and 1443 without type 2 diabetes who had not suffered from previous myocardial infarction corroborated on the ECG.
type 2 diabetes, without myocardial infarction at baseline corroborated by ECG, who were followed-up for a median of time of 4.26 and 3.32 years, respectively.

2.1 Statistical analysis
Comparisons of clinical and laboratory features were made according to diabetes status at baseline. Proportions and means (standard deviation [s.d.]) were compared by Pearson Chi\(^2\) and by T student, respectively, while medians (interquartile range [IQR]) were compared by Wilcoxon test. QTc interval was analyzed as continuous and dichotomous variable. Because of the normal distribution of the QTc interval, all analyses were carried out using the original units. QTc interval prolongation, using the Bazzett’s formula, was defined as an interval \(\geq 430\) msec in men and \(450\) msec in women. Partial Pearson correlation between QTc interval and some risk factors were estimated in diabetic and non-diabetic subjects, separately. To estimate the association between some cardiovascular risk factors and QTc interval prolongation in diabetic and non-diabetic subjects, both together and separately, multiple linear regression for cross-sectional analysis and generalized estimating equations regression models (GEE), with family normal identity link, for longitudinal analysis were carried out. Models were performed with the forward method considering the biological and statistical relevance. Results are given as regression \(\beta\) coefficients and 95% confidence interval (95%CI). P value equal or less than 0.05 was considered significant. All analyses were done with Stata/SE 9.0 (Stata statistical software: Release 9. College Station. Texas: Stata Corporation, 2005).

3. Results
Characteristics of the sample
A total of 1661 subjects (1443 non-diabetic and 218 diabetic subjects), aged 47.4±8.2 years at baseline were included. Table 1 shows comparisons of some QT interval risk factors between subjects with and without type 2 diabetes. Individuals with diabetes were older and had greater abdominal fat and upper-body fat accumulation, as well as higher BP levels, total cholesterol and fasting and 2-hour glucose levels compared with individuals without diabetes. The percentage of hypertension was higher for subjects with diabetes (27.1%) compared with non-diabetic subjects (13.0%); likewise, the proportion of individuals under antihypertensive medication was slightly greater in the diabetic group. Although the percentage of subjects who were under antihyperlipidemic medication was higher in subjects with diabetes compared with non-diabetic subjects, these differences were not significant. As for diabetic subjects, 136 (62.4%) were prevalent cases whereas 82 (37.6%) were incident cases, with a ratio 1:1.6. Mean of age at diagnosis of diabetes was 46.6 years (s.d. 8.0 years) and median of diabetes duration was 1.8 (IQR 25-75% 0-7.3).
Some characteristic on the ECG were compared between diabetic and non-diabetic subjects at baseline and during follow-up and are shown in table 2. The mean of heart rate, QRS duration, and R amplitude in AVL lead were significant higher in diabetic compared with non-diabetic subjects. Mean of QTc by the Bazzet’s formula was significantly higher (p<0.001) in diabetic (414.0 msec) than in non-diabetic (404.3 msec) individuals. The prevalence of longer QTc interval (≥430 msec in men and ≥450 msec in women) was greater in diabetic (10.1%) compared with non-diabetic subjects (4.0%). Prevalence was remarkably higher in both diabetic and non-diabetic men (16.3% vs. 4.5%, p<0.001) compared with
### Table 1. Characteristic of the study population by diabetes status

|                        | Non-diabetic subjects | Diabetic subjects | p value |
|------------------------|-----------------------|-------------------|---------|
|                        | n=1443                | n=218             |         |
| Age (years)            | 46.6 (8.0)            | 52.5 (7.7)        | <0.001  |
| Age at diabetes diagnosis (years) | -                     | 47.8 (8.3)        | -       |
| Women (no., %)         | 848 (58.8)            | 138 (63.3)        | 0.204   |
| Current smoking (no., %) | 487 (33.8)            | 65 (30.0)         | 0.269   |
| BMI (kg/m²)            | 28.0 (4.3)            | 29.1 (4.8)        | 0.001   |
| Waist circumference (cm) |                       |                   |         |
| Men                    |                        |                   |         |
| Women                  | 93.6 (9.1)            | 98.8 (11.7)       | <0.001  |
| Hypertension (no., %)  | 188 (13.0)            | 61 (28.0)         | <0.001  |
| SBP (mmHg)             | 115.6 (16.1)          | 122.9 (18.6)      | <0.001  |
| DBP (mmHg)             | 72.5 (10.3)           | 75.4 (9.6)        | <0.001  |
| Total cholesterol (mmol/L)* |          |                   | <0.001  |
| Men                    | 0.7 (0.6-0.9)         | 0.8 (0.7-0.9)     | 0.319   |
| Women                  | 0.9 (0.7-1.0)         | 0.9 (0.7-1.0)     | 0.334   |
| Triglycerides (mmol/L)* | 1.9 (1.4-2.8)         | 2.5 (1.8-3.6)     | <0.001  |
| Fasting glucose (mmol/L)* | 4.7 (4.2-5.1)         | 8.9 (6.6-13.5)    | <0.001  |
| 2-hour glucose (mmol/L)* | 5.7 (4.6-6.8)         | 14.1 (11.6-18.8)  | <0.001  |
| Antihypertensive medication (no., %)† | 67 (35.6) | 27 (44.3) | 0.227 |
| Antihyperlipidemic medication (no., %) | 4 (0.3) | 1 (0.5) | 0.638 |
| Diabetes cases         |                       |                   |         |
| Prevalent              | 136 (62.4)            | -                 |         |
| Incident               | 82 (37.6)             | -                 |         |
| Hypoglycemic medication (no., %) | 143 (65.9) | - |         |
| Diabetes duration (years)* | 1.8 (0-7.3) | - |         |
| Duration of follow-up (years)* | 3.32 (3.15-3.74) | 4.26 (4.00-4.44) | 0.0001  |

*Median (IQR 25-75).
†Only subjects with hypertension.

Missing values in non-diabetic subjects: WC, 26; HDL-C, 2; 2-hour glucose, 1; antihyperlipidemic medication, 37.

Missing values in diabetic subjects: current smoking, 1; WC, 3; triglycerides, 2; 2-hour glucose, 122; antihyperlipidemic medication, 9.

Table 1. Characteristic of the study population by diabetes status

Women (6.5% vs. 3.7%, p>0.05). Similar differences were observed on the QTc interval as continuous and dichotomous variable during the follow-up. In addition, after stratifying by hypertension, prevalence of longer QTc interval was significantly higher in both diabetic (13.3%) and non-diabetic subjects (5.2%) with hypertension compared with diabetic (8.9%) and non-diabetic subjects (3.8%) without hypertension. When stratification was made by BMI<25 and BMI≥25, prevalence remained significantly higher in diabetic compared with non-diabetic subjects with normal weight (14% vs. 1.8%, respectively) and with overweight/obesity (9.1% vs. 4.7%, respectively).
Table 2. QTc interval segment and other electrocardiographic parameters in subjects with and without type 2 diabetes

| Parameter                        | Non-diabetic subjects | Diabetic subjects | p value |
|---------------------------------|-----------------------|-------------------|---------|
| At baseline                     |                       |                   |         |
| Heart rate (bpm)                | 65.2 (9.2)            | 70.9 (12.0)       | <0.001  |
| QRS duration (msec)             | 90.9 (10.4)           | 88.9 (10.7)       | 0.007   |
| R amplitude in AVL lead         | 294.4 (239.8)         | 346.8 (270.5)     | 0.003   |
| S amplitude in V3 lead          | 879.9 (523.3)         | 917.2 (545.1)     | 0.330   |
| LVH, no (%)                     | 33 (2.3)              | 6 (2.8)           | 0.672   |
| QTc interval (msec)             | 390.0 (25.4)          | 384.3 (28.5)      | 0.002   |
| QTc interval by the Bazzett’s formula (msec) | 404.3 (22.5) | 414.5 (23.8) | <0.001 |
| QTc interval by the Bazzett’s formula ≥430 in men and ≥450 in women (no., %) | 58 (4.0) | 22 (10.1) | <0.001 |
| At the end of follow-up         |                       |                   |         |
| Heart rate (bpm)                | 62.8 (9.5)            | 66.6 (9.4)        | <0.0001 |
| QRS duration (msec)             | 89.9 (10.9)           | 88.0 (15.2)       | 0.027   |
| R amplitude in AVL lead         | 338.5 (224.5)         | 369.0 (233.4)     | 0.063   |
| S amplitude in V3 lead          | 815 (434.7)           | 880.3 (503.5)     | 0.045   |
| LVH, no (%)                     | 20 (1.4)              | 6 (2.8)           | 0.130   |
| QTc interval by the Bazzett’s formula (msec) | 406.7 (22.3) | 416.1 (21.6) | <0.001 |
| QTc interval by the Bazzett’s formula ≥430 in men and ≥450 in women (no., %) | 77 (5.3) | 20 (9.2) | 0.024 |

Missing values in non-diabetic subjects: S amplitude in V3 lead 1.
Bazzett’s formula: QT/square root of (R–R interval).

Table 2. QTc interval segment and other electrocardiographic parameters in subjects with and without type 2 diabetes

Figure 1 shows the relation between QTc interval and BMI in subjects with and without type 2 diabetes according to age. The values of QTc interval were slightly greater in subjects with greater BMI in both diabetic and non-diabetic individuals, regardless of age group. A similar trend was observed when BMI was substituted for WC. (Data not shown)

As for fasting glucose in diabetic subjects, a slight increment in the QTc interval was observed in subjects with higher levels of fasting glucose, particularly in subjects with levels between 12 mmol/l and 20 mmol/l. (Figure 2) For non-diabetic subjects, a modest increment in the QTc interval was observed when 2-hour glucose (≥ 6 mmol/l) and HOMA-IR (≥ 10 units) increased (Figure 3).
Fig. 1. Comparison between QTc interval level and BMI at baseline in subjects with and without type 2 diabetes stratifying by age <50 (upper panel) years and ≥50 years (bottom panel).

In diabetic subjects, partial Pearson correlations with QTc interval were statistically significant for age (rho=0.15, p=0.024), BMI (rho=0.19, p=0.006), and WC (rho=0.20, p=0.003). No significant correlation with diabetes duration was observed. In non-diabetic subjects, correlations with QTc interval were significant for age (rho=0.16, p<0.0001), SPB (rho=0.10, p=0.0002), DBP (rho=0.07, p=0.008), BMI (rho=0.23, p<0.0001), and WC (rho=0.21, p<0.0001). During follow-up, the correlation of QTc interval with BMI and WC remained significant (p<0.001) in both diabetic (BMI, rho=0.24 and WC, rho=0.25) and non-diabetic individuals (BMI, rho =0.23 and WC, rho=0.26).
Electrocardiographic QT Interval Prolongation in Subjects With and Without Type 2 Diabetes – Risk Factors and Clinical Implications

Fig. 2. Comparison between QTc interval level and fasting glucose level at baseline in subjects with type 2 diabetes.

Cross-sectional analysis

In the whole sample, QTc interval prolongation was significantly associated with age, sex, BMI, and diabetes. For each unit of change on age (year), the QTc interval increased 0.36 msec (95%CI 0.23; 0.49). For each unit of increment on BMI, the QTc interval increased 0.75 msec (95%CI 0.51; 1.00). Women had a greater QTc interval mean than men (difference of 13.36 msec (95%CI 11.36; 15.76). Regarding diabetes, the difference on the QTc interval between diabetic and non-diabetic subjects was 6.33 msec (95%CI 3.24; 9.43). Models stratified by diabetes status were also performed. In diabetic subjects, risk factors significantly associated with QTc interval were sex and BMI, whereas age had a borderline significance. For each unit of increment on BMI, the QTc interval increased 0.72 msec (95%CI 0.07; 1.37). Women had a greater QTc interval than men (difference of 15.93 msec, 95%CI 9.50; 22.35). In non-diabetic subjects, risk factors significantly associated with QTc interval were age (beta=0.35, 95%CI 0.21; 0.50), sex (beta=13.69, 95%CI 11.27; 16.10), BMI (beta=0.62, 95%CI 0.33; 0.91), hypertension (beta=4.18, 95%CI 0.14; 8.22), and HOMA-IR (beta=0.43, 95%CI 0.08; 0.78) (Table 3).

Longitudinal analysis

When the whole sample was considered, the progression of QTc interval prolongation was significantly associated with age, sex, BMI, hypertension, and diabetes. The QTc interval prolongation increased with age (beta= 0.33, 95%CI 0.24; 0.42) and BMI (beta= 0.73, 95%CI 0.56; 0.90). Women had a greater QTc interval prolongation than men (difference of 11.84 msec, 95%CI 10.09; 13.59), as did diabetic compared with non-diabetic subjects (difference of 6.58 msec, 95%CI 4.02; 9.13). In a model restricted to diabetic subjects, the QTc interval was predicted by sex (beta= 11.18, 95%CI 6.27; 16.10), BMI (beta= 0.84, 95%CI 0.38; 1.30), and fasting glucose (beta= 0.42, 95%CI 0.11; 0.74). In non-diabetic subjects, predictors of QTc
Fig. 3. Comparison between QTc interval level and fasting glucose, 2-hour glucose and HOMA-IR levels at baseline in subjects without type 2 diabetes.
Electrocardiographic QT Interval Prolongation in Subjects With and Without Type 2 Diabetes – Risk Factors and Clinical Implications

Table 3. Risk factors associated with the QT interval prolongation in subjects with and without type 2 diabetes. Cross-sectional analysis

|                          | Non-diabetic subjects | Diabetic subjects | Whole sample |
|--------------------------|-----------------------|-------------------|--------------|
|                          | N=1368                | N=218             | N=1661       |
| Age (years)              | 0.35                  | 0.37              | 0.36         |
|                          | (0.21;0.50)           | (-0.04;0.79)      | (0.23;0.49)  |
|                          | <0.001                | <0.077            | <0.0001      |
| Women                    | 13.69                 | 15.93             | 13.56        |
|                          | (11.27;16.10)         | (9.50;22.35)      | (11.36;15.76) |
|                          | <0.001                | <0.001            | <0.0001      |
| BMI (kg/m²)              | 0.62                  | 0.72              | 0.75         |
|                          | (0.33;0.91)           | (0.07;1.37)       | (0.51;1.00)  |
|                          | <0.001                | <0.001            | <0.0001      |
| Hypertension             | 4.18                  | 0.93              | 3.11         |
|                          | (0.14;8.22)           | (-0.02;7.88)      | (-0.47;6.69) |
|                          | 0.043                 | 0.792             | 0.088        |
| HDL-C (mmol/L)           | -2.50                 | -5.56             | -2.69        |
|                          | (-7.68;2.68)          | (-18.67;7.54)     | (-7.33;1.94) |
|                          | 0.344                 | 0.404             | 0.255        |
| Fasting glucose (mmol/L) | 0.44                  | 0.209             |             |
|                          | (-0.25;1.13)          |                   |             |
| HOMA-IR                  | 0.43                  | 0.016             |             |
|                          | (0.08;0.78)           |                   |             |
| Diabetes                 | -                     | -                 | 6.33         |
|                          | -                     | -                 | (3.24-9.43)  |
|                          | <0.0001               |                   |             |
| Diabetes duration (years)| -                     | 0.28              | -           |
|                          | -                     | (-0.29;0.85)      | -           |
|                          | 0.331                 |                   |             |
| Antihypertensive         | -2.26                 | -1.21             |             |
| medication               | (-8.68;4.17)          | (-6.64;4.23)      |             |
|                          | 0.491                 |                   |             |
|                          | (-0.29;0.85)          |                   |             |
|                          | -1.21                 |                   |             |
|                          | (-6.64;4.23)          |                   |             |
|                          | 0.664                 |                   |             |
| Hypoglycemic medication  | -                     | -4.45             |             |
|                          | -                     | (-11.91;3.00)     |             |
|                          | 0.240                 |                   |             |
|                          | (-0.80;0.032)         |                   |             |

Table 3. Risk factors associated with the QT interval prolongation in subjects with and without type 2 diabetes. The QT interval prolongation were age (beta=0.34, 95%CI 0.25; 0.44), sex (beta=12.23, 95%CI 10.29; 14.18), BMI (beta=0.64, 95%CI 0.44; 0.83), hypertension (beta=3.72, 95%CI 1.57; 5.87), HOMA-IR (beta=0.45, 95%CI 0.16; 0.75) (Table 4). Antihypertensive therapy had a negative effect in QTc prolongation. In a multivariate model with diabetes duration equal or greater than 1 year, the increment of QT interval prolongation remained similar for fasting glucose (beta=0.38, 95%CI 0.06; 0.70, p=0.021), whereas a significant increment with diabetes duration was observed (beta=0.42, 95%CI 0.04; 0.80, p=0.032). (Data not shown)

4. Discussion

The methods used in the Mexico City Diabetes Study meet the accepted international criteria in terms of study protocol, diagnostic algorithms, and particularly electrocardiographic interpretations. [11] The ECGs were interpreted without disclosure of clinical or laboratory data, in a reference center recognized as a gold standard for this procedure. A rigorous quality control procedure was followed along the study. In this population, there is a high prevalence of cardiovascular risk factors, namely overweight,
Table 4. Risk factors associated with the QT interval prolongation in subjects with and without type 2 diabetes. Longitudinal analysis

|                     | Non-diabetic subjects N=1368 | Diabetic subjects N=216 | Whole sample N=1661 |
|---------------------|-----------------------------|------------------------|---------------------|
|                     | Beta (95%CI) P              | Beta (95%CI) P         | Beta (95%CI) P      |
| Age (years)         | 0.34 (0.25; 0.44) <0.0001   | 0.22 (-0.8; 0.53) 0.151 (0.24; 0.42) <0.0001 |
| Women               | 12.23 (10.29; 14.18) <0.0001 | 11.18 (6.27; 16.10) <0.0001 | 11.84 (10.09; 13.59) <0.0001 |
| BMI (kg/m²)         | 0.64 (0.44; 0.83) 0.0001    | 0.84 (0.38; 1.30) <0.0001 | 0.73 (0.56; 0.90) <0.0001 |
| Hypertension        | 3.72 (1.57; 5.87) 0.001     | 1.67 (-1.80; 5.14) 0.345 (0.74; 4.52) 0.006 |
| Fasting glucose (mmol/L) | - - 0.42 (0.11; 0.74) 0.009 - - |
| HOMA-IR             | 0.45 (0.16; 0.75) 0.002     | - - - - |
| Diabetes            | - - - - 6.58 (4.02; 9.13) <0.0001 |
| Diabetes duration (years) | - - 0.24 (-0.12; 0.61) 0.191 - - |
| Antihypertensive medication | -3.57 (-6.50; -0.64) 0.017 - - -1.27 (-3.78; 1.24) |
| Hypoglycemic medication | - - -3.00 (-8.41; 2.41) 0.277 - - |

Models were run by using generalized estimating equations with family normal and identity link.

In the present study, prevalence of QTc interval prolongation was higher in diabetic that in non-diabetic subjects without previous myocardial infarction detected by ECG, independently of age and sex. As expected, subjects with diabetes had 6 times the risk of developing QTc interval prolongation compared with non-diabetic subjects. In multivariate models, QTc interval prolongation was consistently predicted by sex, BMI, and fasting glucose in diabetic subjects. In non-diabetic subjects, age, sex, BMI, hypertension, HOMA-IR, and antihypertensive medication predicted QTc interval prolongation. In both groups, results were largely unchanged when WC was used in place of BMI, or when 2-hour glucose was included instead of fasting and HOMA-IR in diabetic and non-diabetic subjects, respectively.

Several studies have demonstrated that the prevalence of prolonged QTc interval is higher in subjects with type 2 diabetes (26%) than in subjects without. [18-21] Also, the QTc interval...
Electrocardiographic QT Interval Prolongation in Subjects With and Without Type 2 Diabetes – Risk Factors and Clinical Implications

prolongation has been associated with a high risk of ischemic heart disease, ventricular fibrillation, and sudden death (range 2 to 5) in several studies, even in subjects with short duration of diabetes. [10] In our study, we observed a significantly higher proportion of prolonged QTc interval in diabetic compared with non-diabetic subjects (10.1% vs. 4.0%). After adjustment for other risk factors, the mean difference on the QTc interval between diabetic and non-diabetic subjects was 6.33 msec. It has been suggested that this difference relates to the sympathetic activity present in diabetes, which reduces both the ability to regulate heart rate and the heart rate variability. [19,20]

As for diabetes duration, it has been reported as a risk factor for chronic complications, including QTc interval prolongation, the latter being related to neuropathy in subjects with diabetes. [19] In our study, neither at baseline nor at follow-up duration of diabetes was significantly associated with QTc interval, which could be explained, in part, by the high proportion of new cases at baseline (37.6%). When the analysis was restricted to subjects with diabetes duration equal or greater than 1 year, QTc interval prolongation was predicted by duration, independently of other risk factors, despite the short median duration of the disease in subjects with previous diagnosis of diabetes (median 5.4 years, IQR 2.1-10.6).

We found a significant prospective association between fasting plasma glucose and prolonged QTc interval in diabetic subjects, even after adjustment for other risk factors. Some studies have reported an association between fasting glucose and QTc interval, particularly in individuals in the normal high level or with impaired fasting glucose, after adjustment for diabetes duration, among other risk factors. [21-22] However, other studies have not found any significant association. [23] As for non-diabetic subjects, we noted an independent association between HOMA-IR and QT-interval prolongation. These results showed an important degree of insulin resistance, maybe related to overweight and obesity in this population, and both predicted QTc interval prolongation. No association was observed with fasting plasma glucose in this group. By contrast, previous studies have reported an association between plasma glucose and QT interval in healthy subjects [24], even after hyperglycemic clamp insulin release, which suggests that the effect of glucose on the QTc interval is not mediated by insulin.

The association of higher BMI with the prolongation of the QTc interval observed in the non-diabetic group is not clearly seen in the diabetic group, probably because of the effect of weight loss as a result of poor metabolic control. It is particularly interesting the finding that HOMA-IR index has a significant association with the prolongation of the QTc duration in both the cross-sectional and the prospective analyses. The pathophysiologic implications direct our attention to the cellular effects of insulin resistance in the electrophysiology that mediates the depolarization and repolarization of the myocardium. Somewhat surprisingly, we could not show a demonstrable effect of therapy for diabetes or hypertension in the QTc duration.

Some of the limitations with the QT interval evaluation relate to the lack of accuracy and reproducibility of the measurements, since there is no standard method for analysis and lead selection. The definition for the end of the QT interval is unclear as well, and may represent a changing T wave morphology that could provide a measure of altered disparity of repolarization. [25,26] Nevertheless, its application as a non-invasive and cost-effective screening tool is invaluable for cardiovascular risk stratification of population. On the other hand, because of the lack of QT interval dispersion measurement in this study, we were not able to determine the type of variation on repolarization.
5. Conclusion

In this study, in addition to specific cardiovascular risk factors associated with the QTc interval prolongation in diabetic and non-diabetic subjects, general excess of body weight measured by BMI was a significant risk factor for both groups. Our findings clearly show the deleterious effects of the identified cardiovascular risk factors on the QTc interval, particularly those related to insulin resistance. In diabetic subjects, the lack of metabolic control (measured by fasting glucose level) predicted strongly the QTc prolongation, whereas in non-diabetic subjects the presence of insulin resistance (HOMA-IR) predicted it. Given the cardiovascular clinical implications of QTc interval in subjects with and without diabetes, further interventional researches are needed to confirm whether the metabolic control in diabetic subjects and the decrease of insulin resistance in non-diabetic subjects together with weight reduction can prevent QTc interval prolongation.

6. Acknowledgments

The authors would like to thank the residents of the neighborhoods that participated in the study. The Research Grant RO1HL 24799 of the National Heart Lung and Blood Institute, Bethesda, MD, USA, supported this work. Funding from The Consejo Nacional de Ciencia y Tecnologia, CONACYT, Grants 2092/M9303, F677-M9407, 3502-M9607 helped in some parts of the study. The Fundacion Mexicana para la Salud provided administrative support.

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