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Prevalence and Risk Factors of Prolonged QTc Interval among Egyptian Type 2 Diabetes Patients

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Abstract

Objectives: *The aim of this study was to evaluate the prevalence and the risk factors of prolonged QTc interval among Egyptian patients with type 2 diabetes.*

Patients and methods: *We enrolled in this cross-sectional study from June 2011 to December 2015, a total of 220 patients (108 male & 112 female) with mean age 50.42± 7.453years diagnosed with type 2 DM.*

Results: *In this study, we found (33.6%) 74 T2 DM patients with QTc>440 ms had statistically significant longer diabetes duration and, diastolic BP, Total cholesterol. LDL-C and UACR with 146 type 2 DM patients with ≤ 440QTc ms (P value ≤ 0.05). Also statistically significant higher incidence of insulin therapy, retinopathy and nephropathy has been founded in 74 T2 DM patients with QTc>440 Ms.*

By Pearson correlation, we found QTc interval significantly correlated with diabetes duration, Diastolic BP, TC , LDL-C and UACR., also by using multiple regression analysis we found LDL-c, diabetic duration and UACR were statistically significant predictors of QTc interval.

In logistic regression analysis for identification of risk factors for QTC interval prolongation, only LDL-c and UACR were statistically significant (P value<0.05) predictors of QTc interval.

Conclusion: *Prolonged QTc prevalence among type 2 diabetic Egyptian patients was 33.6%. Although QTc prolongation was associated with longer diabetes duration, diastolic BP, total cholesterol, LDL-C, albumin urinary excretion, insulin therapy and retinopathy, only statistically significant predictors of QTc interval main risk factor for QTc prolongation were LDL-c and UACR.*

Keyword: *QTc; Bazett's formula; Type 2 DM; Egyptian*

Introduction

Diabetes is a major health problem affecting and associated with significant morbidity and mortality [1]. Type 2 diabetes accounts for 90–95% of all diagnosed cases of diabetes [2].

Despite the overall increased risk of adverse outcomes associated with type 2 diabetes, the risk is not uniform in all affected individuals [3]. Excess risk of mortality in persons with type 2 diabetes cannot be fully explained by CVD or known CVD risk factors [4].

The QT interval on ECG measures the total time for ventricular depolarization and repolarization, and prolonged QT interval corrected for heart rate (QTc) may be a trigger for ventricular arrhythmia and, consequently, sudden death [5]. Moreover, it is predictive of all-cause and cardiovascular mortality in both healthy population [5] and patients with diabetes [6].

Thus, QTc prolongation could be utilized as a rapid objective method to target patients with high risk of cardiovascular events. In spite of the reported prevalence of QTC prolongation as high as 26% in patients with T2 DM [7], No studies about the problem in Egypt up to our knowledge.

The aim of this study was to evaluate the prevalence and the risk factors of prolonged QTc interval among Egyptian patients with type 2 diabetes.

Subjects and Methods

In this cross-sectional study from June 2011 to December 2015, a total of 220 patients (108 male & 112 female) with age ranged 27–64 years (mean age 50.42± 7.453years). diagnosed with type 2 DM that was conducted at endocrinology and diabetes unit, Mansoura University in Egypt.

Informed consent obtained from all patients, Inclusion criteria were patients with type 2 diabetes were free of clinically apparent macrovascular and heart disease, age between with age ranged between 18 and 65 in both sex.

Exclusion criteria were medications that may affect QT interval (i.e. antiarrhythmic drugs, β–blocker, α–blocker, diltiazem, antibiotics, antipsychotic agents or antihistamines), clinical signs of cardiovascular disease, History of CAD, abnormal ECG (AF, atrial flutter or QRS interval > 120 ms), advanced renal dysfunction, malignant disease, type 1 DM and hepatic decompensation,

Clinical evaluation were performed of all the patients with respect to age, sex ,body weight, height, waist circumference, BP, diabetes duration, type of therapy according insulin use and presence of diabetic complications including retinopathy(by fundus examination) and nephropathy. Laboratory evaluation included HbA1c, creatinine, lipids (total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides), and urine albuminto-creatinine ratio (UACR)

QTc was estimated according to Bazett's formula, where interval was measured in relation to the previous QRS complex $QTc = QT/ (RR)^{1/2}$. [8]

Statistical Analysis

All data were analyzed using the SPSS statistical version 22.0. An independent t test was used for comparison of continuous variables. Categorical data were analyzed by the Pearson Chi-square. A multivariate analyses model (stepwise backward method) was used to examine the relationship between QTc and other parameter. P values less than 0.05 were considered significant.

Result

A total two hundred and twenty (108 males & 112 females) type 2 diabetic patients enrolled in this study from June 2011 to December 2015. 220 patients (108 male & 112 female) with age ranged 27–64 years (mean age 50.42± 7.453years), diagnosed with type 2 DM. Details of patient characteristics were presented in Table 1.

In this study, when we classified patients with prolonged QTc according Bazzet formula >440 Ms, we found 74 T2 DM patients with QTc>440 ms had statistically significant longer diabetes duration, diastolic BP, total cholesterol. LDL-C and albumin urinary excretion (142.16±14.07

years, 88.95±9.95 mmHg, 261.69±58.07 mg/dl , 167.76±62.39 and 292.96±240.71 mg/gm. respectively) in comparison with 146 type 2 DM patients with ≤ 440QTc ms (9.61±4.43years, 85.75±10.09 mmHg, 241.32±33.47mg/dl, 145.78±38.18 and 126.66±173.96 mg/gm. respectively) and (p value ≤ 0.05). Also statistically significant higher incidence of insulin therapy, retinopathy and nephropathy has been founded in 74 T2 DM patients with QTc>440 Ms. But as regard age, sex ,Hba1c ,BMI, height, weight or waist circumference non statistically significant was found in DM patients with QTc>440 versus those with QTc<440 as described in table 2.

In this study by using Pearson correlation we found QTc interval significantly correlated with diabetes duration, Diastolic BP, Total cholesterol , LDL-C and UACR (r = 0.303, 0.151, 0.257, 0.236 and 0.292 respectively P value< 0.05). Also by using multiple regression analysis we found LDL-c, diabetic duration and UACR were statistically significant predictors of QTc interval (we exclude total cholesterol from regression analysis due to strong correlation with LDLc) but after controlling effect of UACR diabetic duration not significantly predict QTc interval (Table 3).

In logistic regression analysis for identification of risk factors for QTC interval prolongation, only LDL-c and UACR were statistically significant (P value<0.05) predictors of QTc interval (Table 4).

Table 1: Patients' characteristics

	Mean (n = 220)	Standard deviation
Age (year)	50.42	7.453
Diabetic duration(year)	10.63	4.362
Sex (male/female)	108/112	
Insulin therapy	88 (40%)	
Body weight (kg)	83.97	14.014
Height (m)	1.6610	.07686
BMI (Kg/m^2)	30.5405	5.39001
Waist circumference(cm)	114.34	19.134
Systolic BP (mmHg)	140.14	13.740
Diastolic BP (mmHg)	86.80	10.128
QTc (ms)	415.8953	51.29711
Heart rate /min	74.4364	8.66687
Total cholesterol mg/dl	248.17	44.263
LDL-C mg/dl	153.18	48.697
HDL-C mg/dl	45.71	7.791
Triglycerides mg/dl	246.40	91.285
UACR mg/gm	182.60	213.430
Retinopathy	81 (36.8 %)	
Nephropathy	51 (23.3%)	
Hba_1c %	7.8095	1.62872

Table 2: Comparison of clinical and laboratory characteristics of type 2 DM patients with QTc ≤ 440 ms versus type 2 DM patients with QTc >440 ms.

	QTc ≤440 ms (n=146)	QTc> 440 ms (n=74)	P value
Age (year)	50.12±7.72	51.03±7.72	0.393
Sex (male/female)	76/70	32/42	0.217
BMI (Kg/m^2)	30.72±5.29	30.17±5.59	0. 13
Height (m)	1.66±0.076	1.65±0.077	0.308
Body weight (kg)	84.89±14.01	82.15±13.93	0.171
Waist circumference(cm)	114.8±19.04	113.42±19.4	0.614
Hba_1c %	7.93±1.67	7.56±1.51	0.115
Diabetic duration(year)	9.61±4.43	12.64±3.43	<0.001
Insulin therapy	47 (32.1%)	41 (55.4%)	0.001
Systolic BP (mmHg)	139.11±13.51	142.16±14.07	0.120
Diastolic BP (mmHg)	85.75±10.09	88.95±9.95	0.032
Total cholesterol mg/dl	241.32±33.47	261.69±58.07	0.001
LDL-C mg/dl	145.78±38.18	167.76±62.39	0.001
HDL-C mg/dl	45.82±8.25	45.51±6.81	0.787
Triglycerides mg/dl	248.63±88.75	241.99±96.5	0.611
Retinopathy	34 (23.2%)	47 (63.5%)	< 0.001
Nephropathy	18 (12.3%)	33 (44.5%)	< 0.001
UACR mg/gm	126.66±173.96	292.96±240.71	< 0.001

Table 3: simple correlation and multiple regression analysis between heart-rate corrected QT interval with other statistically significant correlated independent factor.

	R	P value	B	β	pvalue
Diabetic duration	0.303	<0.001	2.094	307.614	.029
Diastolic BP	0.151	0.013	.497	307.614	.120
Total cholesterol	0.257	0.001	Strong correlation with LDL-c So excluded		
LDL-C	0.236	0.001	.230	.066	.001
UACR	0.292	<0.001	.041	.019	.033

Table 4: logistic regression analysis (Forward Stepwise method) for risk factors of QTC interval prolongation.

	B	S.E.	Wald	Sig.	OR	95% C.I.for OR	
						Lower	Upper
UACR	.004	.001	25.893	<.001	1.004	1.002	1.005
LDLC	.010	.003	9.968	.002	1.010	1.004	1.017
Constant	-3.050	.577	27.903	.000	.047		

Discussion

QTc interval represents an index of electrical stability and predictive of all-cause and cardiovascular mortality in both healthy population and patients with diabetes. Thus QTc prolongation is important to target patients with high risk of cardiovascular events. The major finding of our study is that degree of albuminuria and LDL were significant predictors and risk factors for QTc prolongation.

In this study we found prolonged QTc prevalence among type 2 diabetic Egyptian patients was 33.6% (74 from 220 T2DM patients). The prevalence of QT prolongation has been reported to be as high 26% in T2 DM in Italy [9] and 30 % in China [10]. But in T1DM still controversy few

studies reported QTc interval prolongation in Type 1 diabetes [5,11]. While recent study no significant difference in QTc between the TIDM patient and other population [12].

Several risk factors affected QTc interval prolongation among Type 2DM patients in this study. Prolonged QTc interval associated with longer duration of diabetes, diabetic microvascular complications such diabetic nephropathy and diabetic retinopathy, diastolic BP, total cholesterol, LDL-C, albumin urinary excretion and insulin therapy.

Our data showed prolonged QTc interval associated with albuminuria. Degree of albuminuria and LDL were significant predictors of QTc and risk factors for QTc prolongation. The relationship between QTc interval and albuminuria has been reported in type 2 diabetes [10] [13]. Although mechanisms that might explain this association between QTc and albuminuria are unclear, there are some studies hypothesized to be caused by endothelial dysfunction, oxidative stress and chronic inflammation through vascular nitric oxide (NO) reduction [14]. Other studies postulated atherosclerosis accelerated by albuminuria may increase ventricular load by rapid return of blood from the periphery toward the heart which promote myocardial and electrophysiological remodeling, leading to prolongation of the QT interval[15]. Micro albuminuria is a renal marker of generalized vascular endothelial damage and early atherosclerosis[16]. Another explanation by suggested the relationship between high prevalence of diabetic cardiovascular autonomic neuropathy (CAN) in diabetic nephropathy with QT prolongation as earlier studies have suggested that QTc duration is specific and easier methods for determination of CAN [17]

Also in this study prolonged QTc interval associated with higher incidence of diabetic retinopathy which in concordance with other studies in T2DM [18] while contrasted another studies [10]. but in regression analysis retinopathy was non-significant risk factor of QTc interval prolongation.

In this study insulin therapy was found to be associated with longer QTc interval. Previous study reported a significant increase of QTc in type 2 diabetes patients despite the improvement of glycemic control with insulin therapy [18]. In addition another study of correlate insulin levels with QTc interval in non diabetic subjects [19]. These results may explain a relative increase in mortality with intensive glucose lowering therapy in the ACCORD study [20]. The detailed mechanism of induction of QTc prolongation by insulin is unclear; however, several factors have been suggested. In addition, other authors suggested insulin-induced hypokalemia [21] and shortening of RR interval associated with hyper insulinemia [22].

Prolonged QTc interval associated with longer duration of diabetes in this study explained by strong correlation between degree of albuminuria and duration of diabetes and after controlling effect of UACR, diabetic duration not significantly predict QTc interval.

In the current study, neither BMI, height, weight or waist circumference affected QTc interval which was similar to Takebayashi et al 2012 results [18]. It has been reported that QTc interval prolongation is associated with high BMI in general population [23] , and with height and waist circumference but not BMI in type 2 diabetes [10]

Diabetic control not affect QTc interval, in this study prolonged QTc interval was not associated with significant difference in Hba1c levels which similar with Hashimoto et al 2015 results [13]. But other study in T1DM [12] and in T2DM [10] reported higher Hba1c in patient with prolonged QTc interval. This controversy may explained by different patients selection and single-site study studies limitation which included our and other studies.

We found prolonged QTc interval not associated with age in concordance with other studies s had been conducted on type 1 DM [11], type 2 DM patients [10] and non diabetic [23].

As regard lipid profile in this study we found prolonged QTc interval associated with higher total cholesterol and LDLc levels. Similar results were reported previously in T2DM [10] and T1DM [12]. In this study QT interval were not affected by triglyceride and HDL levels. The effect of LDLc on QTC interval may explained by coronary atherosclerosis and sub clinical CHD, as cardiac ischemia may prolong the QTc interval by increasing the repolarization time [24] in diabetic patients, this procedure underestimates the prevalence of the disease compared with exercise ECG [25].

The study has some limitations. First, single-site study. Second, relatively small sample. Thus, larger multicenter study is needed to better assess. Third, in the current study, we only measured the QT interval. We did not analysis other QT parameters such as QT dispersion. fourthly retrospective cross-sectional design; prospective studies will confirm the role of type 2 diabetes in pathogenesis of prolongation of QTc interval.

In conclusion, prolonged QTc prevalence among type 2 diabetic Egyptian patients was 33.6% and only statistically significant predictors of QTc interval main risk factor for QTc prolongation were LDL-c and UACR. These results will spot attention of physician, cardiologist and endocrinologists to early identification type 2 diabetic patients with risk of electrical stability and cardiovascular mortality early management.

Conclusion

Prolonged QTc prevalence among type 2 diabetic Egyptian patients was 33.6%. Although QTc prolongation was associated with longer diabetes duration, diastolic BP, total cholesterol, LDL-C, albumin urinary excretion, insulin therapy and retinopathy, only statistically significant predictors of QTc interval main risk factor for QTc prolongation were LDL-c and UACR

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures performed in this study were in accordance with ethical standards of our institutional in accordance with ethical standard of Declaration of Helsinki 1964. Informed consent was obtained from all individual participants included in this study.

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