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Prevalence of QT prolongation and associated LVEF changes in diabetic patients over a four-year retrospective time period

Zhongju Lu[a], Lloyd Lense[b], Mohit Sharma [a], Ankit Shah[a], Ying Luu[a], Lucien Cardinal[a], Joan Faro[a] and Alan Kaell [a]

[a]Department of Internal Medicine, John T. Mather Memorial Hospital, Port Jefferson, NY, USA; [b]Division of Cardiology, Stony Brook University Hospital, Stony Brook, NY, USA

ABSTRACT

Aim: To evaluate the prevalence and longitudinal changes of prolonged QTc in DM patients admitted to our community hospital, and to determine, if any, its correlation with changes of left ventricular ejection fraction (LVEF). **Methods**: A retrospective chart review of patients with Type 1 (T1DM) and Type 2 (T2DM) with at least two admissions during a four-year period was performed to identify QTc interval, and LVEF, as measured on transthoracic echocardiogram. Changes in QTc and LVEF between patient hospital admissions were compared. **Results**: A prolonged QTc interval was found in 66.7% (n = 24) of type 1 and 51.3% (n = 154) type 2 diabetic patients. The QTc interval is progressively increased in both type 1 and type 2 diabetes during follow-up, although it did not reach statistical significance. A total of 62% patients (23 out 37 patients) had a reduction of LVEF during follow-up. **Conclusion and Discussion**: High prevalence of QTc prolongation was confirmed in hospitalized patients with in both T1DM and T2DM. Significant reduction of LVEF correlated with QTc prolongation over a mean of 17.3 months in T2DM patients, and may have implications for interventions.

Abbreviations CHF: Congestive heart failure LVEF: Left ventricular ejection fraction

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KEYWORDS
Diabetes mellitus; prevalence; QTc; LVEF; heart failure; tyrosine kinase inhibitors

1. Introduction

Diabetes is a major health problem affecting almost 9.3% (29.1 million) of the U.S. population (National Diabetes Statistics Report, 2014) [1]. Such patients are at major risk for ventricular arrhythmias, complications of acute coronary syndrome, and sudden cardiac death [2]. The QT interval on the electrocardiogram reflects the total duration of ventricular myocardial depolarization and repolarization, and when corrected for heart rate (QTc) it is predictive of all-cause and cardiovascular mortality in apparently healthy people as well as in people with various conditions, including diabetes [2,3]. Measurement of QTc has been proposed as a simple and noninvasive method for the assessment of cardiovascular risk in the clinical setting [3–7]. QT prolongation has been found in various experimental diabetes animal models, which mimic type 1 and type 2 diabetes in human beings [8,9]. While investigating the QTc interval prolongation in both type 1 and type 2 diabetes, various studies have postulated such prolongation to be associated with long-term mortality from all-causes, cardiovascular, cardiac, and ischemic heart disease [10,11]. The prevalence of QTc interval prolongation reported in diabetes are variable [12,13]; the prevalence of QTc prolongation in type 2 diabetes is 30.1% among Chinese population obtained from a outpatient retrospective study [14] and 34.6% in a hospital-based cross sectional population study from European patients [15].

Congestive heart failure (CHF) is emerging as a major public health concern with high mortality. Overall, approximately 15–25% of patients with CHF have comorbidity with diabetes [16]. CHF is magnified in individuals with diabetes, in whom incidence rates are two to five times greater than those in the general population [16]. In a six-year retrospective cohort study incidence rates defined as 30.9 cases per 1000 person-years in diabetes vs. 12.4 cases per 1000 person-years in non-diabetes, with a median onset of CHF (measured from the initiation of cohort study) at 36 months in diabetic and at 48 months in nondiabetic patients. The incidence of CHF in the diabetic cohort was highest in those patients with history of ischemic heart disease, poorer glycemic control, and greater BMI [17]. DM is a predictor of mortality and morbidity in patients with heart failure [6,7]. An increased mortality has been seen in CHF patients with diabetes; patients with impaired LVEF (<50%), the risk of death for diabetics vs. non-diabetics was increased by 37% and 26%, respectively [18]. A meta-analysis from seven clinical trials and 10

CONTACT Zhongju Lu zhongjulu@gmail.com; Alan Kaell atkaell@gmail.com Department of Internal Medicine, John T. Mather Memorial Hospital, 75 North Country Road, Port Jefferson, NY 11777, USA

observational studies demonstrated a 28% higher aggregate mortality in diabetic with CHF compared with non-diabetic patients [19]. Interestingly, a significant reduction of LVEF and systolic dysfunction has been demonstrated in the heart of diabetic mice [8,20].

Multiple studies in animal models have shown that when in response to stimulation with insulin, Tyrosine kinase (TK) can be activated, which causes subsequent activation of Phosphatidylinositol (PI) 3-kinases signaling (PI3K) [21,22]. Diabetes is associated with a reduction in TK-PI3K signaling, which regulates the APD of individual myocytes and thus the QT interval by altering multiple ion currents in canine heart [22]. Significant evidence suggesting that low insulin/PI3K signaling is the cause of the cardiac repolarization defect and QT prolongation in the diabetic mice [9]. Diabetic patients might have a decreased TK/PI3K signaling in the heart due to insulin insufficiency or resistance, which causes multiple cardiac ion current/channels abnormalities and a subsequent QT prolongation. Similarly, the reduction of LVEF in diabetes may be also due to a decreased PI3K signaling in the heart since a reduced Ca^{2+} entry through the L-type calcium channel (LTCC), which might contribute to the negative effect of diabetes on cardiac contractility has been identified in type 1 and type 2 diabetic mice [20,23].

However, there is less information from the inpatient community hospital concerning the possibility of associated change of QTc prolongation and LVEF change in diabetes. Our study is a preliminary retrospective cohort exploration with two aims. First, we wanted to ascertain whether diabetes is associated with higher prevalence of QT prolongation. Secondly, we wanted to investigate whether any development change of LVEF is associated with QTc prolongation in diabetes.

2. Methods

2.1. Study population

We conducted a retrospective study based on data obtained from patients admitted to John T. Mather Memorial (JTMM) hospital in Port Jefferson, NY 11,777. The proposal was approved by both the Institutional Review Board (IRB) at JTTM and at the IRB in the school of medicine at State University of New York at Stony Brook (SUNY SB SOM) as the general medical education internal medicine (GME IM) program at Mather is sponsored by SUNY SB. All study subjects were identified as patients with type 1 or type 2 DM on the electronic medical record with a discharge diagnosis code denoting DM. Case screening and data collection including QTc measurement in EKG was performed by trained physician. A diagnosis of diabetes was based on the World Health Organization (WHO) diagnostic criteria for diabetes [fasting plasma glucose ≥7.0 mmol/L, or 2 h plasma glucose ≥11.1 mmol/L, or glycated hemoglobin (HbA1c) ≥6.5%] and treatment for diabetes, including the use of oral hypoglycemic agents or subcutaneous insulin injection. We reviewed the chart of patients who were admitted with DM over a four-year period (from 1 January 2009 to 31 December 2012). The flow diagram of the study population is shown in Figure 1. Patients were selected for Data Extraction in a de-identified Health Insurance Portability and Accountability Act (HIPAA) compliant fashion, as approved by both IRBs, according to the inclusion criteria and exclusion criteria. A total of 24 out of 62 patients with type 1 DM and 155 out of 181 patients with type 2 DM were included in our study. Fifteen patients with type I DM and 26 patients with type 2 DM were excluded due to history of CABG, permanent pacemaker (PPM), myocardial infarction (MI), QRS>120 ms or BMI>40. Four patients with type 1 DM were excluded due to history of pancreas transplantation. Nineteen patients with type I DM had neither EKG nor TTE documented and thus they were excluded from the study. Among 24 patients with type 1 DM, only 16 patients have documented EKG and TTE on the first and second visit. Among 155 patients with type 2 DM, 70 patients had TTE and EKG on the first visit and 37 patients had TTE and EKG on the second visit.

2.2. Inclusion criteria

We identified by historical chart review a series of 448 patients with DM type 1 or type 2 who were admitted to JTMM Hospital between January 1st, 2009 and December 31st, 2012.

The inclusion criteria are patients admitted to JTMM hospital, and actively treated for diabetes. The diagnosis of diabetes is based on the World Health Organization (WHO) diagnostic criteria for diabetes [fasting plasma glucose ≥7.0 mmol/L, or 2 h plasma glucose ≥11.1 mmol/L, or glycated hemoglobin (HbA1c) ≥6.5%] and treatment for diabetes, including the use of oral hypoglycemic agents or subcutaneous insulin injection.

2.3. Exclusion criteria

We excluded patients with (1) less than 20 years of age, or older than 90; (2) Morbidly obese as defined by BMI> 40; (3) Evidence of hypertensive cardiomyopathy as defined by LVH on ECG/transthoracic echocardiogram; (4) Prior myocardial infarction; (5) a previous history of open-heart surgery or status post pancreas transplantation; (6) significant valvular

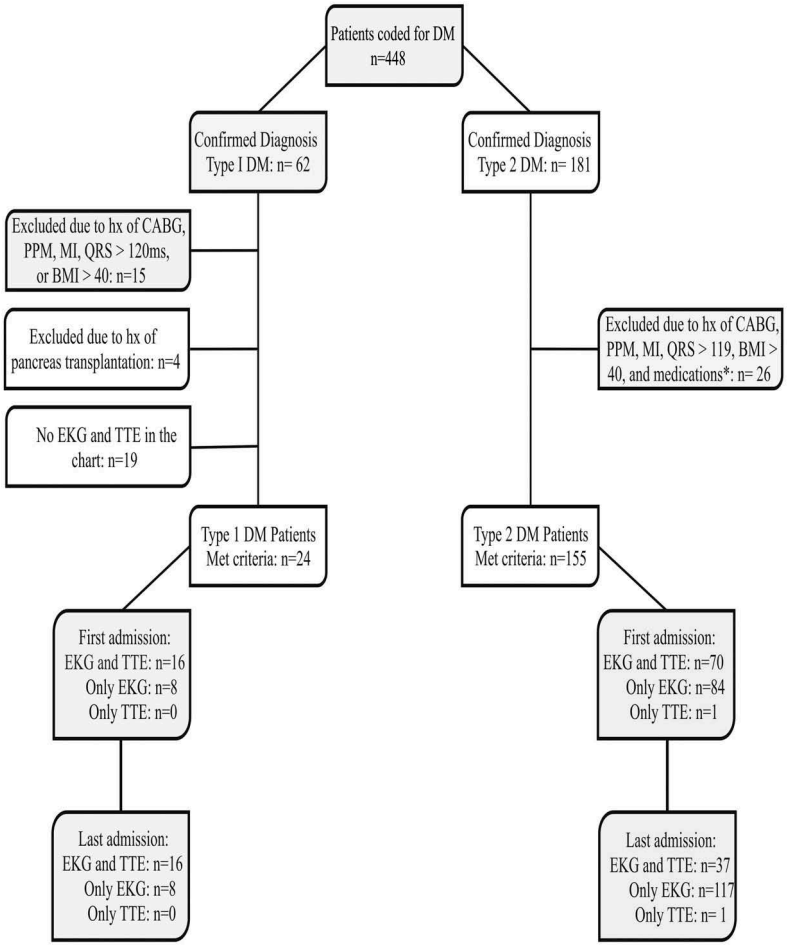

Figure 1. Enrollment of patients in the study.

heart disease; (7) EKG with QRS>120 ms or computer diagnosis of atrial or ventricular pacing, 2nd or 3rd degree AV block, Wolff-Parkinson-White pattern or artifact. (8) on medication(s) that are known to prolong QT intervals (for more information see website www.qtdrugs.org); (9) electrolytes abnormalities that are known to prolonged QT intervals. (10) Patients who had neither EKG nor TTE were excluded from the study.

2.4. Measurement of QTc interval from the 12-lead ECG

A standard 12-lead ECG tracing at 25 mm/s paper speed and 10 mm/mV amplitude was used. The QT interval was measured from the beginning of the earliest onset of the QRS complex to the end of the T wave. The end of the T wave was defined as the return of the descending limb to the TP baseline when not followed by a U wave or if distinct from the following U wave. QT intervals and the preceding RR intervals were measured on the resting ECG tracing in lead II. QTc was calculated according to Bazett's formula (QTc = QT/(RR)1/2 if HR is between 60 and 100 beat/min) or Fredericia formula (QTc = QT/(RR)1/3 if HR < 60 or >100 beat/min). The QTc interval >0.45 s in men and QTc interval >0.47 s in women were considered abnormally prolonged [24–26].

2.5. Echocardiography

The LVEF and diastolic function were evaluated by transthoracic echocardiograms and obtained directly by reading from the chart.

2.6. Statistical analysis

Continuous baseline variables were summarized as mean ± standard error of mean (Mean ± SEM) stratified by subjects with QTc ≤450 ms and QTc >450 ms in type 1 and type 2 diabetic patients, as QTc >450 has been chosen as cut off for upper limits of normal in women and for QT prolongation in men [26]. We used the Student t test (paired or non-paired) to test for differences between independent continuous variables and the X^2 test to test for

differences between categorical variables. Data were collected, mean or median and 95% confidence intervals (CIs) were determined. A probability value $P < 0.05$ was considered statistically significant. All statistical analyses were performed using OriginPro 8 software (Northampton, USA).

3. Results

Baseline characteristics of the study population on the first visit stratified by diabetic status are presented in Table 1. The patients in our study consists of 13% (24/179) type 1 diabetes. The mean QTc are 457.8 ± 5.9 ms (n = 24) for the type 1 and 450.9 ± 3.2 ms (n = 154) for the type 2 diabetes. The average LVEF are 63.2 ± 2.2% for type 1 and 60.4 ± 1.4% for type 2 diabetes. The LV diastolic function was abnormal in 8.3% (n = 24) type 1 and 74.7% (n = 154) type 2 diabetes. The mean age was 47.5 ± 3.5 (n = 24) years for type 1 and 76.2 ± 0.9 (n = 155) for type 2 diabetic patients. The study included 50% female patients with type 1 and 49.7% female patients with type 2 diabetes. BMI was 27.1 ± 0.7 for type 1 and 28.7 ± 0.5 for type 2 diabetes. HbA1c was 9.3 ± 0.6% for type 1 and 6.7 ± 0.5 % for type 2 diabetes; all type 1 diabetic patients received insulin treatment and only 33.3% patient with type 2 DM received insulin treatment. Of the study population, 37.5% type 1 DM and 43.2% type 2 DM were smokers; 56.7% type 1 and 87.7% type 2 DM had hypertension. Hyperlipidemia was present in 31.3 % type 1 and 47.7% type 2 diabetic patients, respectively.

3.1. Prevalence of QTc interval prolongation in diabetes and its risk factors

A prolonged QTc interval was found in 66.7% (n = 24) of type 1 and 51.3% (n = 154) type 2 diabetic patients. There are multiple studies that have been done with a mean QTc interval of around 400 ms in the non-diabetic patient [12,13]. To identify the potential risk factors responsible for the prolongation of QTc interval, we subgroup patients with QTc ≤450 ms or QT >450 ms and stratify risk factors. We have not identified any other significant predictive factors associated with QTc interval prolongation except for a significant hyperlipidemia in Type 1 diabetes (P = 0.01, T-test) (Table 1).

3.2. Developmental change of QTc interval prolongation and LVEF reduction

The QTc interval is progressively increased in both type 1 and type 2 diabetes during follow-up, although it did not reach statistical significance (Figure 2, upper panel). The QTc interval increased from 457.8 ± 5.9 ms for first visit to 464.2 ± 6.5 ms in the second (last) visit in all type 1 diabetes. The corresponding QTc are 423.5 + 5.9 ms at first visit to 437.5 ± 5.4 ms at second visit in the group of QT ≤450 ms and 475.4 ± 4.0 ms at first visit to 481.2 ± 6.4 ms at second visit in the group of QT>450 ms. Similarly, the increase of QTc in all type 2 diabetes from 450.9 ± 3.2 ms for the first visit to 453.8 ± 3.8 ms at the last visit is not statistically significant (P = 0.57, t-test). The corresponding QTc are 422.1 ± 3.6 ms at first visit to 433.0 ± 3.8 ms at second visit in the group of QT ≤450 ms and 478.3 ± 2.6 ms at first visit to 470.3 ± 3.6 ms at second visit in the group of QT >450 ms. The overall mean LVEF (Mean LVEF>60%) was not impaired in both types of diabetes at the first visit. There is a trend that LVEF was reduced in the follow-up visit in both types of diabetes (Figure 2, middle panel). The median follow-up time between the first and last admission during the time frame that data was extracted 20.5 months (95% CI 14.7, 28.1) for type 1 DM and 17.3 months (95% CI 14.4, 20.2) In type 1 DM, the average LVEF in overall patients is 63.2 ± 2.2% for the first visit and 61.8 ± 2.0% for the second or the last visit. This change of LVEF is not statistically different (P = 0.63, unpaired t-test). The corresponding LVEF are 64.3 ± 4.2% at first visit to 62.3 ± 3.2 at second visit in the group of QT ≤450 ms and 62.6 ± 2.6% at first visit to 61.9 ± 2.5 % at second visit in the group of QT >450 ms. In contrast, for type 2 diabetes the average LVEF are 60.4 ± 1.4%

Table 1. Baseline characteristics of patient with type 1and type 2 DM on first admission in JTMM Hospital.

	Type 1 DM			Type 2 DM		
Variables	QTc ≤450 ms (n = 8)	QTc >450 ms (n = 16)	P value	QTc ≤450 ms (n = 75)	QTc >450 ms (n = 79)	P value
QTc (ms)	423.5 ± 4.9	475.4 ± 4.0	<0.001	422. 1 ± 3.6	478.3 ± 2.6	<0.001
LVEF, % (n)	64.3 ± 4.2 (n = 7)	62.6 ± 2.6 (n = 12)	0.72	61.3 ± 1.6 (n = 55)	56 ± 3.0 (n = 15)	0.2
Diastolic Dysf. (%)	0	12.5	0.29	73.3	75.9	0.70
Age (years)	43.3 ± 6.0	49.6 ± 4.3	0.41	76.9 ± 1.1	75.6 ± 1.3	0.44
Male (%)	62.5	43.8	0.39	48.0	51.9	0.63
BMI (kg/m^2)	27.3 ± 0.9	27.0 ± 1.0	0.86	28.8 ± 0.7	28.6 ± 0.6	0.80
Smoking Hx (%)	37.5	37.5	1	44.0	41.8	0.78
Hypertension (%)	50	62.5	0.56	92.0	83.5	0.11
Dyslipidemia (%)	0	50	0.01	48.0	46.8	0.88
HbA1c, %(n)	9.0 ± 1.0(n = 6)	9.4 ± 0.8(n = 13)	0.77	6.6 ± 0.2(n = 31)	6.8 ± 0.3(n = 23)	0.47
Insulin Tx (%)	100	100	1	38.7	29.1	0.21

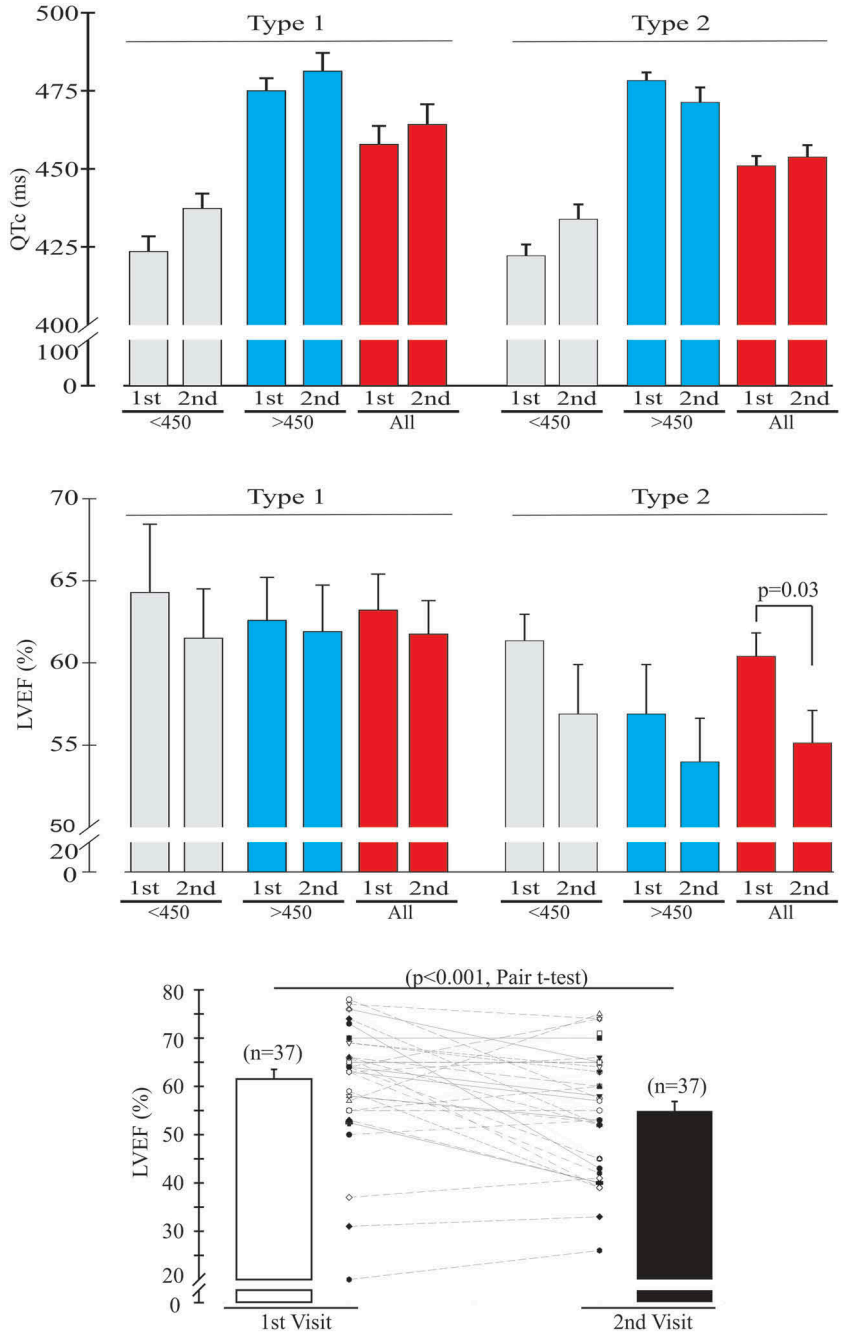

Figure 2. Developmental change of QTc and LVEF in diabetes.
Upper panel: Developmental change of QTc in diabetes (left panel: type 1 DM, right panel: type 2 DM)Middle panel: Developmental change of LVEF in diabetes. (Left panel: type 1 DM, right panel: type 2 DM). Note a significant reduction of VEF in the last visit compared to that in the first visit (P < 0.05, unpaired t-test)Bottom panel: Comparison of LVEF in type 2 DM in the first and second visit. The reduction of LVEF is very significant different during the follow-up (P < 0.001, paired T-test).

(n = 70) for the first visit and 55.1 ± 2.0% (n = 37) for the second visit and this change is significantly different (P = 0.03, unpaired t-test). The corresponding LVEF are 61.3 ± 1.6% at first visit to 57.2 ± 2.4 at second visit in the group of QT ≤450 ms and 56.9 ± 3.0% at first visit to 54.2 ± 2.8 % at second visit in the group of QT >450. We further compare back-to-back 37 type 2 DM patients during the follow-up (in the bottom panel of Figure 2). We found that 11% patients (4/37) at first visit and 30% patients (11/37) at last visit had impaired LVEF (<50%). In summary, 62% patients (23 out 37 patients) had a reduction of LVEF during follow-up. LVEF reduced from 62.4 ± 1.9 % (n = 37) at first visit to 55.5 ± 2.0 % (n = 37) at second visit, which is very significantly different (p < 0.001, paired T-Test).

4. Discussion

This study confirmed a high prevalence of QTc prolongation in diabetes. We also demonstrated a progressive prolongation of QTc interval in type 1 and type 2 diabetes over a short period of follow-up. The LVEF reduction is seen and reached statistical

significance in type 2 diabetes. Our finding is consistent with previous reports of reduced LVEF in diabetic patients regardless of the extent of coronary artery disease [27,28]. Our study observed in a subset of patient with DM (type 2 only) that demonstrated a concomitant developmental change in QTc and LVEF with an inverse relationship. As both QTc prolongation and LVEF are important independent predictors of survival in diabetes, this finding may have important epidemiological impact for the DM population. Although this change is small within a short period of follow-up, it is worthy of further investigation for the subset found to increase QTc over time.

4.1. QTc prolongation in diabetes

QTc prolongation is an independent predictive marker for mortality caused by cardiovascular disease in diabetes [3,29]. Retrospective studies have shown that the prevalence of QTc prolongation has been reported to be around 25%–30% in diabetes. The EURODIAB Prospective Complication Study has shown an 18.7% cumulative incidence of QTc prolongation in a seven-year follow-up period in type 1 diabetes [13]. The possible reasons for a relative higher prevalence of QTc prolongation (over 50% in both type 1 and type 2 diabetes) in our study are multifactorial. Several risk factors of prolonged QTc interval among patients with diabetes have been cited in the literature, including age [30], gender [31], components of insulin resistance syndrome such as BMI [32], hypertension [30,33], insulin concentration [34], hyperglycemia [35], diabetic microvascular complications such as diabetic retinopathy, neuropathy and microalbuminuria, and preexisting coronary heart disease [32,36]. The exclusion of patients with pancreatic transplantation, uncontrolled glucose with elevated HbA1c (HbA1c 9.3 in type 1 DM), high percentage of HTN, and included patients with older age may be the confounding factors contributing to a high prevalence of QTc prolongation in our population study. Although there are inconsistencies among studies regarding all the various risk factors, hypertension was identified by most studies as an independent risk factor. In accordance with previous studies, a high HbA1C and the presence of hyperlipidemia in our analysis, led to a significant higher rate of prolonged QTc interval [14].

4.2. LVEF in diabetic patients

Multiple studies have shown that impaired LVEF may be an independent risk factor for increased mortality and sudden cardiac death in diabetes [37–39]. A preserved LVEF (mean LVEF >60%) was found on the baseline in all diabetic patients in our study. A developmental change in LV systolic function was demonstrated, after serial LVEF measurement in type 2 DM patients, despite remaining in the normal range. In our study a small but significant reduction of LVEF within a short period (<2 years) of follow-up was seen in 62% of type 2 diabetes. Recently, abnormal left ventricular longitudinal strain pattern detected on TTE has been identified even in asymptomatic patients with type 2 DM and preserved LVEF [40].

4.3. Limitations of the study

The study has several limitations. First, due to its retrospective study design, we could not determine temporal or causal relationships between risk factors and QTc prolongation. Second, compared with population-based studies, our study, limited to a single community hospital setting, has potential for a selection bias, thus this limits the strength of the study. It is possible that those DM patients with recognized significant prolonged QTc and/or LVEF <40% self select or are physician directed to the tertiary hospital, which is located three miles away. Our descriptive analysis enables us to focus on the population entering our community hospital. Third, our data did not allow us to specifically adjust for the use of beta blockers which is known to affect LVEF, although reduced LVEF has been reported regardless of coronary artery disease (CAD) in diabetes [41]. There is always some technical limitation since we cannot rule out the intrinsic slight inaccuracies of the methods for measuring LVEF by TTE and the routine physiological variations in LVEF. Finally, the small numbers of type 1 diabetic patients and the short period time of follow-up limited the power to analyze the changes of QTc and LVEF in diabetes that may be likely to occur over a longer time frame.

4.4. Clinical implications

The high prevalence of QTc prolongation and LVEF reduction in diabetes in our study may alert for or secure a more frequent monitoring with EKG and TTE in hospital setting given their known prediction role for all-cause and cardiovascular mortality.

It is noteworthy that tyrosine kinase inhibitors have recently entered clinical use as anticancer medications [42,43]. Given reduced tyrosine kinase signaling in diabetes and many risk factors including heart disease and electrolytes disorder in cancer patient, use of other medications that prolong the QT interval that might make them especially vulnerable to long QT syndrome or LVEF reduction induced by tyrosine kinase inhibitors. This is a particular concern in treating cancer patients with a comorbidity of diabetes who have a reduced/impaired tyrosine kinase-PI3K signaling.

5. Conclusions

We observed in the community hospital setting in type 1 and type 2 DM who require admission for DM management a high prevalence of QTc interval prolongation. There was an observed serial decrease in LVEF in 62% of type 2 DM patients in this cohort. The significance of this change in LVEF over a relatively short period of time may have clinical and diagnostic implications. The relationship of changes in LVEF and changes in QTc, especially in type 2 DM patients, merit further exploration into electromechanical properties of the diabetic patient.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Mohit Sharma http://orcid.org/0000-0003-3819-5475
Alan Kaell http://orcid.org/0000-0001-8473-4551

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