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EFFECT OF EMPAGLIFLOZIN ON HR VARIABILITY AND QT DISPERSION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS T2DM

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ABSTRACT

Background: Individuals with type 2 Diabetes Mellitus(T2DM) are at high risk for development of cardiovascular complications. Treatment with empagliflozin may affect on impaired heart rate variability and impaired ventricular repolarization heterogeneity which associated with the risk of sudden cardiac death(SCD). **Objective**: the present study aims to assess the effects of empagliflozin on QT dispersion(QTd) and HR variability (HRV) in patients with T2DM. **Materials and Methods** This is prospective study conducted in the department of cardiology in Tishreen University Hospital-Lattakia - Syria from September 2019 to September 2020. Patients with T2DM who aged 42 to 80 with indication for treatment with empagliflozin were enrolled in the study. QT dispersion, HR variability were recordered before starting empagliflozin and at the end of follow up. **Results:** A total of 40 patients were included, Median age was 52.5 years, 22 (55%) were male, hypertension was detected in 28(70%) of the patients. Empagliflozin reduced glycemia (186.10±54.9 vs125.72±33.3. p:0.0001), systolic blood pressure SBP(132.3±12.7vs 124.9±9.8, p:0.001),QTd (62.22±21.4 vs52.15±22.6, p:0.003), and increased SDNN(89.15±22.2 vs96.40±21.2,p:0.03) in the study participants. Spearman's correlation analysis revealed positive correlation between changes in SBP and QTd(Spearman's =0.6, P=0.0001) and negative correlation with SDNN(Spearman's =-0.3, P=0.02). Reduction in glycemia was correlated with increased in QTd(Spearman's = -0.2, P=0.07) and decreased in SDNN(Spearman's = 0.1, P=0.3). **Conclusion:** Empagliflozin alters ventricular repolarization indices and impaired HRV, and this could be the mechanism by which empagliflozin reduced cardiovascular events.

KEYWORDS: Type 2 Diabetes Mellitus, empagliflozin**,** HR variability, QT dispersion.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder in which prevalence has been increasing steadily all over the world, and these patients are predisposed to serious cardiovascular complications.[1] Intensive glycemic control reduced incidence of microvascular disease but had limited effects on cardiovascular events including SCD.[2]

Empagliflozin, a Sodium-glucose co –transporter 2(SGLT2)inhibitor represents a new milestone in treatment of T2DM.It has pleiotropic effects beyond its glucose control effect through different mechanisms.[3] EMPA-REG OUTCOME trial is the first of the positive cardiovascular outcome trials of empagliflozin in patients with T2DM.[4]

Among the suggested mechanisms mediating the beneficial effects of empagliflozin on cardiovascular mortality is reversing ventricular repolarization heterogeneity,[5] and also through the effects on cardiac sympathetic and parasympathetic activity.[6] The current study was designed to investigate effects of empagliflozin on ventricular repolarization indices and heart rate variability HRV.

Study design and data collection

We prospectively studied patients with T2DM aged 42 to 80 years who presented to the department of endocrinology in Tishreen University Hospital –Lattakia-Syria from September 2019 to September 2020. Patients with one of the following: evidence of presence atrial fibrillation, chronic renal failure stage IV and V, treatment with antiarrhythmic drugs except of beta blockers, and patients with disorders in serum

electrolytes (potassium K ,sodium Na, magnesium Mg, calcium Ca) were excluded. Demographic data including age, sex and related to co-morbidities were recorded. All the following measurements were recorded before the treatment with empagliflozin and at the end of follow up: SBP, fasting blood glucose, QT dispersion, QTC, SDNN**.**

Heart rate variability (HRV): is the physiological phenomenon of the variation in the time interval between consecutive heart beats in milliseconds, and it may provide a non-invasive tool for the early diagnosis of cardiac autonomic neuropathy(CAN) in patients with DM.[7,8]

SDNN(ms): The Standard deviation of all normal RR intervals in the entire 24 –hour ECG record, and represents one of HRV indices measured by Time-domain method. It reflects the parasympathetic component of autonomic function, and classified into normal SDNN: above 100 ms, and abnormal SDNN below 100ms.[8]

QT dispersion: is defined as the difference between the longest and shortest QT intervals on a standard 12-lead ECG, and this may provide an indirect measure of underlying inhomogeneity of myocardial repolarization. It classified into three subgroups: normal <40 ms,prolonged:40-80 ms, very prolonged ≥80 ms.[9]

Statistical Analysis

Statistical analysis was performed by using IBM SPSS version 20. Basic Descriptive statistics included means, standard deviations (SD) Frequency and percentages.

Differences of distribution examined by using chi-square test or Fisher exact test if it need. Paired sample t-test was performed to compare indices before and after treatment. Correlations were analysed using Spearman's rank correlation coefficient. Variables with p less than 0.05 were included in the model.

RESULTS

A total of 40 patients with T2DM (median age: 52.5 year; 22 males, hypertension in 70%) who presented to the department of endocrinology from September 2019 to September 2020 were included in the study. The baseline characteristics of patients are as given in table(1).

As shown below, 57.5% of the patients had prolonged QTd,25% had very prolonged QTd, and 70% had abnormal SDNN.

Table 1: Demographic characteristics and electrocardiographic parameters of the study population.

Variable	
Age(years)	52.5(42-80)
Sex-n(%)	
Male female	22(55%) 18(45%)
Co=morbidities: HTN T2DM (duration >10 years) CAD HFrEF	 28(70%) 23(57.5%) 15(37.5%) 8(20%)
Follow up duration(day)	56.5
QTd(ms): Normal Prolonged Very prolonged	 7(17.5%) 23(57.5%) 10(25%)
SDNN(ms) Normal Abnormal	 12(30%) 28(70%)

There was a significant relationship between QTd subgroups and presence hypertension (p=0.03) before treatment Table 2**.**

Table 2: Comparison between QTd subgroups and Co=morbidities.

	QTd		
	Normal	**Prolonged**	**Very prolonged**
Hypertension	3(10.7%)	15(53.6%)	10(35.7%)
HFrEF	0	6(75%)	2(25%)

The relationship between SDNN subgroups and presence of hypertension (p=0.04), T2DM with duration longer

than 10 years(p=0.001), HFrEF(p=0.03) was significant, Table 3**.**

Table 3: Comparison between SDNN subgroups and Co=morbidities.

	SDNN	
	Normal	**Abnormal**
Hypertension	6(21.4%)	22(78.6%)
T2DM (duration>10 years)	2(8.7%)	21(91.3%)
HFrEF	0	8(100%)

SBP reduced significantly after the treatment (p<0.05). There wasn't any significant difference in serum electrolyte, mean HR after treatment(p>0.05).

Among ventricular repolarization indices, there is a significant reduction in QTd(62.22±21.4 vs 52.15±22.6 ,p0.003) in particular in very prolonged QTd subgroup,Fig1 and significant increased in SDNN, table(4).

Table (4): Changes in parameters in T2DM patients after treatment with empagliflozin(n=40).

	Before	**After**	**P-value**
Blood glucose	186.10±54.9	125.72±33.3	0.0001
Serum electrolyte			
Na	138.32±3.09	138±2.7	0.6
K	4.17±0.43	4.16±0.4	0.4
Ca	8.9±0.38	8.9±0.4	0.4
Mg	1.9±0.29	1.9±0.33	0.8
SBP	132.3±12.7	124.9±9.8	0.001
Mean HR	77.3±9.5	78.6±11.7	0.2
QTD	62.22±21.4	52.15±22.6	0.003
Normal	31.4±5.6	31.1±6.7	0.9
Prolonged	59.6±10.5	52.2±22.5	0.1
Very prolonged	89.6±10.8	66.6±19.2	0.001
QTc	429.8±23.5	431.9±27.4	0.5
SDNN	89.15±22.2	96.40±21.2	0.03

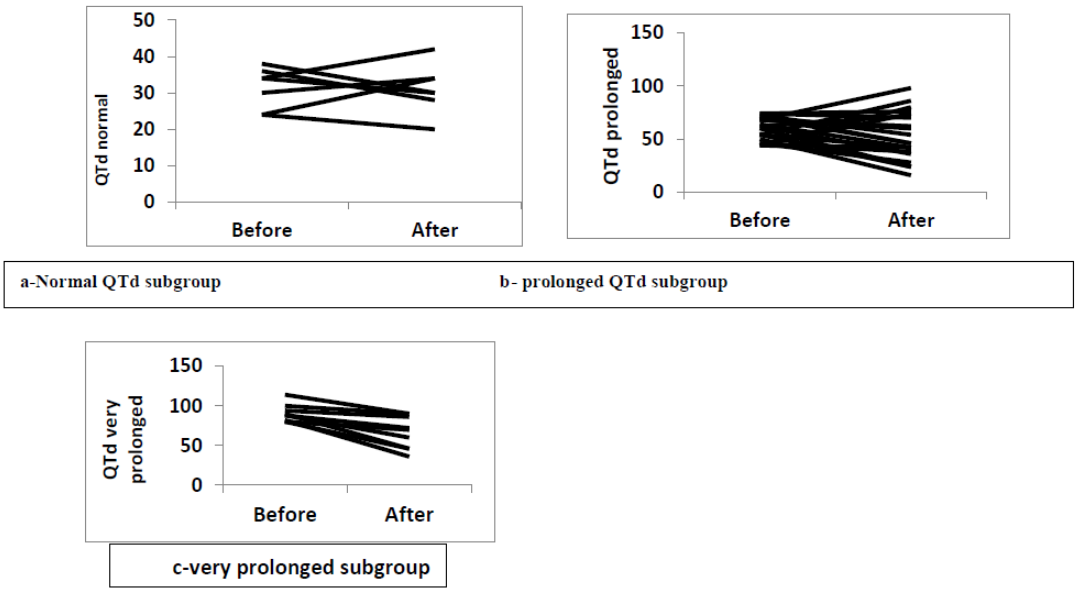

Figure 1: Changes in QTd after administration empagliflozin in the three subgroups of QTd, with decreasing rate by 100% in very prolonged subgroup.

There was a positive correlation between changes in SBP and changes in QTd (Spearman's =0.6, P=0.0001) and a negative correlation with changes in SDNN Figure 2**.**

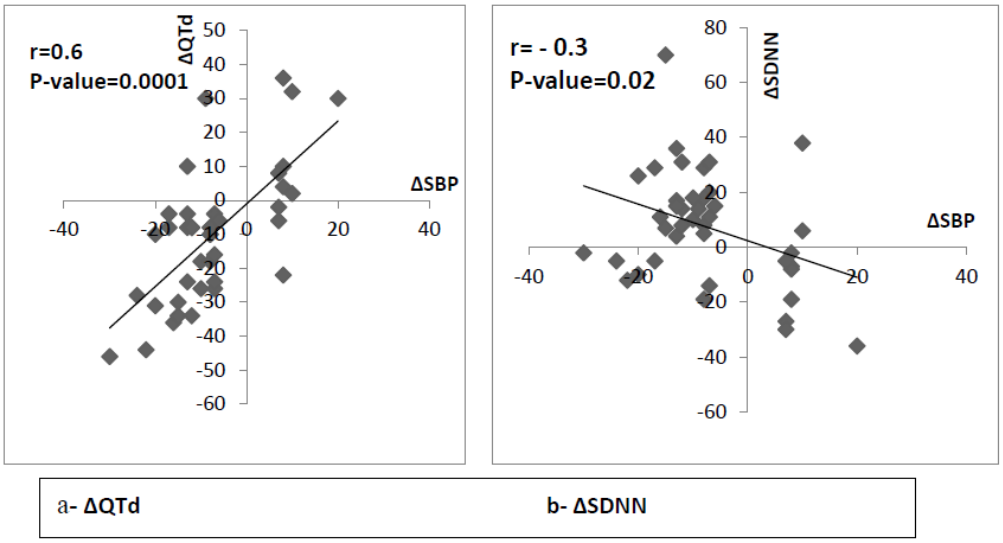

Figure 2: Correlation of changes in SBP with changes in QTd(a) and changes in SDNN(b).

There was a negative correlation between changes in glycemia and changes in QTd (Spearman's = -0.2, P=0.07) and a positive correlation with changes in SDNN (Spearman's = 0.1, P=0.3),Figure 3**.**

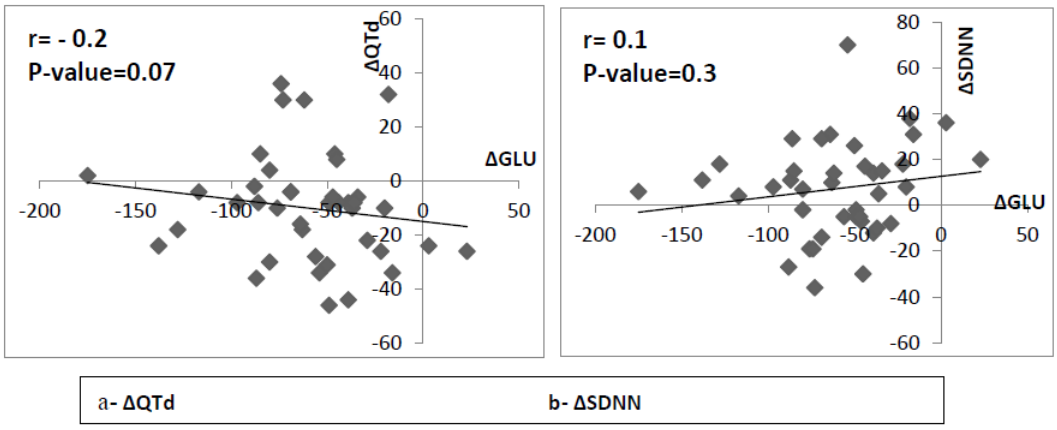

Figure 3: Correlation of changes in glycemia with changes in QTd(a) and changes in SDNN(b).

DISCUSSION

This prospective study demonstrated changes in heart rate variability and QT dispersion in patients with T2DM aged 42 to 80 years after treatment with empagliflozin. This changes include reduction in SBP and QTd(more significantly in the very prolonged QTD subgroup), increasing in SDNN. Reduction in SBP was correlated with decreased QTd and increased in SDNN. Reduction in glycemia was correlated with increased in QTd and decreased in SDNN without any statistical significance.

The exact mechanism responsible for cardio protective effects of empagliflozin in patients with T2DM is not fully understood, and there are many supposed mechanisms.

Systemic effects of empagliflozin are modulated by hemodynamic actions via natriuresis (sustained reduction in intravascular volume and BP lead to reduction in cardiac preload and afterload),[10,11] and metabolic actions via glycosuria and increasing circulating levels of ketones which are taken up by myocardial cells leading to decreased of myocardial oxygen consumption and cardiac sympathetic nerve activity.[12,13]

Direct effects could potentially mediate through their abilities to attenuate cardiac inflammation, oxidative stress, mitochondrial dysfunction and ionic dyshomeostasis. As result of the previous mechanisms improving both systolic and diastolic LV function, prevent cardiac arrhythmia in cardiac ischemic/ reperfusion, and improving cardiac morphologic changes.[14,15]

The results of our study are consistent with the results of a previous studies.

Sato et al 2017 in Japan showed that treatment with empagliflozin reduced SBP(133±18 vs 126±12 mmHg) without changes in heart rate, QTd(48.8 vs 44.2 ,p 0.006), more significantly in the very prolonged QTd subgroup, and positive correlation of changes in SBP with changes in QTd (Spearman's = 0.32, P=0.03).[16] Shimizu et al,2020 found similar results in multicenter randomized trial included patients with acute myocardial infarction with T2DM which revealed improvement in SDNN after treatment with empagliflozin without significant difference in comparison with placebo.[6]

In contrast to that, Vinay et al ,2020 showed that treatment with empagliflozin reduced SBP(may explain reduced left ventricular mass index observed by MRI) ,but without significant changes in SDNN(100.2±45.8 vs 108.3±29.9,p:0.4) and this difference with our study might be explained by the low number of patients with HFrEF in Canadian study(3% vs 20%) and normal SDNN in most patients.[17]

CONCLUSION

Empagliflozin appears to be a promising option in reducing lethal cardiovascular complications in patients with T2DM by its effects on impaired ventricular repolarization heterogeneity and impaired HRV.

List of abbreviations
T2DM: Type 2 Diabetes Mellitus

HFrEF: Heart failure with reduced ejection fraction.

SDNN: standard deviation of NN.

HTN: hypertension

CAD: Coronary artery disease

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