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Effects of SGLT2 Inhibitors as an Add-on Therapy to Metformin on Electrocardiographic Indices of Ventricular Repolarization

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Background: According to EMPA-REG OUTCOME, trial use of empagliflozin in patients with a history of cardiovascular disease improves hospitalization for heart failure and decreases cardiovascular morbidity and mortality. Recent studies have shown that a prolonged T-peak to T-end interval on the resting electrocardiography is associated with an increased risk of cardiovascular mortality. Tp-e/corrected QT interval (QTc) ratio is a reliable index of prolonged ventricular repolarization.

Objectives: In this study, we examined the effects of sodium glucose co-transporters 2 (SGLT2) inhibitors as an add-on therapy to metformin on electrocardiographic indices of ventricular repolarization.

Methods: Electrocardiographic recordings before combination therapy along with three months and six months follow-up of 141 consecutive patients who were switched from monotherapy to combination therapy with two oral agents due to inadequate glycemic control were derived. QT interval (QT), QTc, Tp-e intervals and Tp-e/QT, Tp-e/QTc ratios were calculated and analyzed.

Results: After the six month follow-up, there was a significant decrease in the QT interval in patients who were using SGLT2 inhibitors as an add-on therapy to metformin compared to other glucose-lowering agents (373.4 ± 9.9 ms vs. 385.4 ± 12.5 ms, 382.9 ± 11.2 ms; $p < 0.001$ respectively). Furthermore, Tp-e/QT and Tp-e/QTc ratios were significantly lower in this patient population compared to control groups (0.186 ± 0.023 vs. 0.196 ± 0.021, 0.191 ± 0.017; $p < 0.001$ and 0.174 ± 0.021 vs. 0.199 ± 0.022, 0.195 ± 0.016; $p < 0.001$ respectively).

Conclusion: Our data showed that using SGLT2 inhibitors as an add-on therapy to metformin favorably alters ventricular repolarization indices in patients with type 2 diabetes mellitus.

Key Words: Diabetes mellitus • Repolarization • 12-lead electrocardiogram

INTRODUCTION

Diabetes mellitus (DM) is one of the most prevalent endocrine diseases in the world. It is well known that patients with DM are predisposed to serious cardiovascular morbidity and mortality as a result of oxidative stress, endothelial dysfunction and vascular remodeling caused by DM.[1] Cardiac autonomic neuropathy which affects the sympathetic autonomic nervous system may also predispose malignant ventricular arrhythmias in the diabetic patient population.[2,3] Electrical instability and increased dispersion of repolarization which is caused by ionic current remodeling and prolonged action potential duration were observed in diabetic animal models.[4,5]

Prolonged dispersion of ventricular repolarization is a reliable electrocardiographic indicator for ventricular arrhythmias and is evaluated by various methods, such

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as QT interval (QT), corrected QT interval (QTc) and QT dispersion.[6,7] According to recent studies, T-wave peak to T-wave end intervals (Tp-e interval) on electrocardiogram (ECG); can be used as an index of transmural dispersion of repolarization.[7,8] Tp-e/QT and Tp-e/QTc ratios may also be a useful index in terms of predicting ventricular tachyarrhythmias.[9]

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are a novel class of glucose-lowering drugs which have favorable effects on the cardiovascular system. The EMPA-REG OUTCOME trial showed that use of empagliflozin in patients with a history of cardiovascular disease was associated with lower rates of mortality from cardiovascular causes [38% relative risk reduction (RRR)], mortality from all-causes (32% RRR) and hospitalization for heart failure (35% RRR).[10] Although the underlying mechanism is not evident, the most possible explanations were about the direct cardiac effects of inflammation,[11] oxidative stress,[12] and ionic dyshomeostasis.[13]

In the present study, we tested the hypothesis that treatment with empagliflozin may improve repolarization heterogeneity in patients with type 2 diabetes mellitus compared to other glucose-lowering medications.

MATERIAL AND METHODS

Study design and population

In this retrospective study, subjects were selected from the type 2 DM patients who were admitted to the cardiology outpatient clinic between October 2018 and April 2019. Patients who were on metformin treatment previously and had switched from monotherapy to combination therapy with two oral agents due to inadequate glycemic control were evaluated. The major classes of oral anti-diabetic medications selected for combination therapy were sulfonylureas (SU) dipeptidyl peptidase 4 (DPP-4) inhibitors and sodium-glucose co-transporter (SGLT2) inhibitors. All pharmacological therapies were initiated by endocrinologists who were unaware of the study. Patients who had type 1 or other specific types of DM, atrial fibrillation, chronic kidney disease at stage 4 or higher, used antiarrhythmic drugs affecting QT duration, had any type of bundle branch block on ECG, were older than 80 and younger than 18 years old, and could not tolerate the treatment were excluded. A total of 268 patients were analyzed. After exclusion, 141 patients were included (details are shown in Figure 1).

Study protocol

The included patients were divided into 3 groups according to the type of combination therapy. Patients who had; SGLT2 inhibitors for combination formed group 1, DPP-4 inhibitors for combination formed group 2, and SU for combination formed group 3. All patients were evaluated in terms of age, gender, coronary artery disease, hypertension, hyperlipidemia, and other concomitant diseases. The standard 12-lead ECGs that were obtained on combination therapy with two oral antidiabetic agents (48-72 hours before switching from metformin to combination therapy) at; three and six months after combination treatment. All ECGs were analyzed for calculating QT and QTc intervals, Tp-e interval and Tp-e/QT, Tp-e/QTc ratios.

Electrocardiography

The 12-lead ECGs were recorded at a paper speed of 25 and 50 mm/s (Nihon Kohden, Tokyo, Japan) at rest in the supine position. An appropriate ECG was defined as having at least 10 analyzeable leads for the required measurements. Otherwise, the ECG was considered to be inadequate. ECG measurements of QT and Tp-e intervals were performed by 2 different cardiologists who were blind to the patient data. An average value for each lead was calculated. The QT interval was measured from the onset of the QRS complex to the point at which the tangent of the maximal downslope of the descending limb of the T wave crossed the isoelectric baseline and was corrected for HR with the Bazett formula: QTc = QT/(R – R)1/2 interval[14] (as shown in Figure 2). The Tp-e interval was defined as the interval from the peak of the T wave to the end of the T wave. Measurements of the Tp-e interval were performed from precordial leads.[15] Finally, the Tp-e/QT and Tp-e/QTc ratios were calculated from these measurements. Intraobserver and interobserver coefficients of variation [standard deviation (SD) of the differences between two observations divided by the mean value and expressed as a percent] were found to be 1.3% and 2.1% respectively.

Statistical analysis

Statistical analyses were performed using SPSS soft-

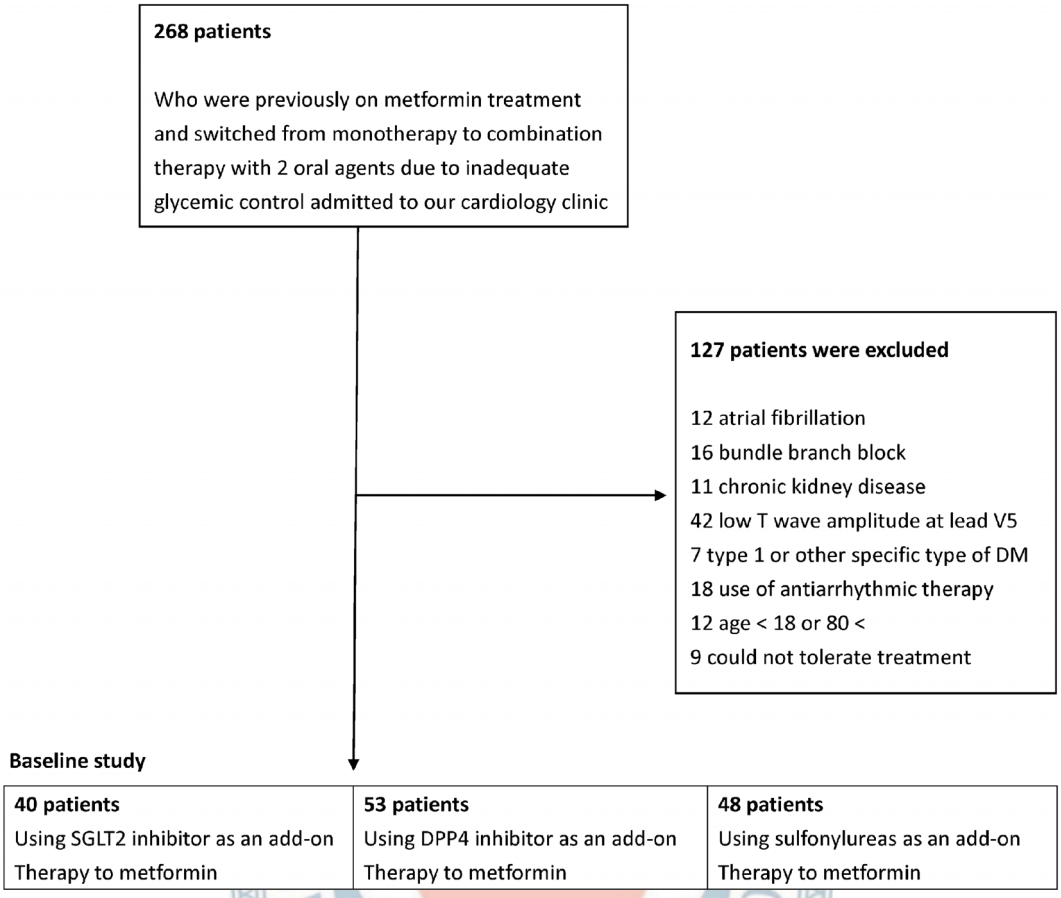

Figure 1. *Flow chart of the study design. DM, diabetes mellitus; DPP4, dipeptidyl peptidase 4; SGLT2, sodium glucose co-transporters 2.*

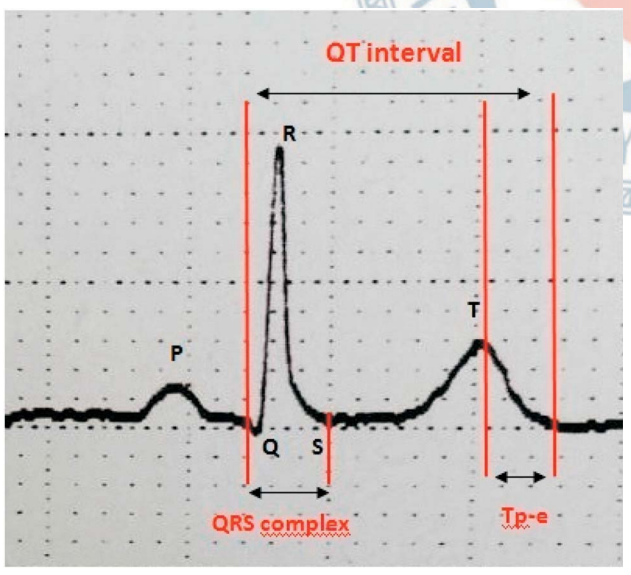

Figure 2. *Assessment of QRS, Tp-e and QT intervals.*

ware (version 20.0; SPSS Inc., Chicago, IL, USA). In this study, data were expressed as mean ± SD for continuous variables and as counts and percentages for categorical variables. $p < 0.05$ was considered statistically significant. Fitness to a normal distribution of continuous variables was analyzed with the Kolmogorov-Smirnov test. Inter-observer agreement between 2 cardiologists was calculated using Cohen's kappa coefficient. A kappa coefficient (κ) < 0 indicated no agreement, 0.0-0.20 indicated none to slight, 0.21-0.40 indicated fair, 0.41-0.60 indicated moderate, 0.61-0.80 indicated substantial, and 0.80 indicated almost perfect agreement. Chi-square and Fisher's exact tests were used for comparison of categorical variables. An analysis of variance test (ANOVA) was used to analyze intra-group data and a multivariant analysis of variance (MANOVA) test was used to analyze inter-group data. Homogeneity of variances was calculated with the Levene test and the Lilliefors significance correction test. Post hoc analysis was done with either the Tukey HSD or Games-Howell tests. Correlations of continuous variables were evaluated using Pearson's cor-

relation analysis or its nonparametric counterpart Spearman's test.

RESULTS

Our study sample involved 141 patients with T2DM. Of these 141 patients; 40 patients (28.3%) formed group 1, 53 patients (37.5%) formed group 2, and 48 patients (34.2%) formed group 3. The baseline characteristics of all 3 groups are presented in Table 1. There were no statistically significant differences in terms of age, sex, baseline glycated hemoglobin(HbA1c) levels, number of hypertensives, heart failure and hyperlipidemia patients among all 3 groups.

Evaluation of electrocardiographic data

Two different cardiologists who were blind to the patient group data analyzed the ECGs. There was substantial concordance of the two cardiologists for QT, QTc, and Tp-e (QT: $\kappa = 0.76$, $p < 0.001$; QT_c: $\kappa = 0.75$, $p < 0.001$; Tp-e: $\kappa = 0.70$, $p < 0.01$). The ECG data of all 3 groups are shown in Table 2. The mean baseline QT (387.0 ± 9.6 ms, 387.7 ± 11.9 ms, 385.5 ± 9.3 ms; p = 0.868), QTc (419.1 ± 9.7 ms, 418.2 ± 10.1 ms, 409.1 ± 5.8 ms; p = 0.653), Tp-e intervals (79.5 ± 8.4 ms, 90.4 ± 4.3 ms, 87.7 ± 4.5 ms; p = 0.464), Tp-e/QT (0.202 ± 0.017, 0.212 ± 0.024, 0.205 ± 0.017; p = 0.394) and Tp-e/QTc (0.186 ± 0.017, 0.196 ± 0.021, 0.19 ± 0.017; p = 0.294) were similar between all 3 groups and no significant differences were found.

Significant ECG changes were detected as early as 3 months after switching to combination therapy. Although Tp-e, Tp-e/QT and Tp-e/QTc values (79.50 ± 8.45 vs. 79.11 ± 7.99 p = 0.853; 0.2021 ± 0.020 vs. 0.2020 ± 0.025 p = 0.619; 0.1868 ± 0.017 vs. 0.1850 ± 0.022 p = 0.449 respectively) did not significantly changed after 3 months, QT, QTc values (387.00 ± 9.63 vs. 382.70 ± 10.31 p < 0.0001; 419.12 ± 9.71 vs. 415.02 ± 8.53 p < 0.0001) were significantly decreased in group 1 in compared to the baseline ECG. After the 6 months follow-up, there were improvements in all ventricular repolarization indices; QT, QTc and Tp-e intervals were detected in group 1 compared to groups 2 and 3 (373.4 ± 9.9 ms vs. 385.4 ± 12.5 ms, 382.9 ± 11.2 ms; p < 0.001, 402.1 ± 11.1 ms vs. 417.4 ± 10.9 ms, 408.3 ± 49.1 ms; p = 0.043

Table 1. Baseline demographic and biochemical characteristics of all 3 groups

Variable	Group 1 (n = 40)	Group 2 (n = 53)	Group 3 (n = 48)	p value
Age (years, mean ± std)	60.4 ± 5.16	62.6 ± 5.15	62.9 ± 5.15	0.214
Gender (male, n/%)	17 (42.5)	22 (41.5)	20 (41.6)	0.995
BMI (kg/m^2)	29.32 ± 3.21	30.16 ± 4.43	27.89 ± 5.36	0.418
Beta blocker usage (n/%)	18 (45)	24 (45.28)	21 (43.75)	0.053
Non-dihydropyridine calcium channel blocker usage (n/%)	2 (5)	3 (5.66)	2 (4.16)	0.739
Ivabradine usage (n/%)	1 (2.5)	5 (9.43)	4 (8.33)	0.031
Teophylline/aminophylline usage (n/%)	1 (2.5)	2 (3.77)	1 (2.08)	0.561
Coronary artery disease (n/%)	4 (10)	16 (30.1)	15 (31.2)	0.037
Heart failure (n/%)	4 (10)	14 (26.4)	12 (25)	0.118
LVEF (%)	49.85 ± 4.24	46.67 ± 3.78	47.34 ± 2.56	0.068
Hypertension (n/%)	28 (70)	34 (64.1)	26 (54.1)	0.295
Dsylipidemia (n/%)	26 (72.5)	39 (73.5)	28 (58.3)	0.202
COPD (n/%)	5 (12.5)	9 (16.9)	7 (14.5)	0.832
Thyroid dsyfunction (n/%)	6 (15)	5 (9.4)	6 (12.5)	0.712
HbA1c (mg/dl, mean ± std)	8.55 ± 0.17	8.61 ± 0.17	8.59 ± 0.21	0.271
Total cholesterol (mg/dl)	185.28 ± 12.67	177.56 ± 21.65	173.45 ± 8.78	0.048
LDL (mg/dl)	102.01 ± 33.40	97.33 ± 31.42	96.45 ± 32.18	0.116
HDL (mg/dl)	44.15 ± 6.85	48.45 ± 9.06	47.26 ± 5.36	0.279
Triglyceride (mg/dl)	182.26 ± 25.32	165.25 ± 69.30	148.52 ± 59.32	0.043
TSH (mIU/l)	4.24 ± 1.45	4.85 ± 1.97	4.78 ± 0.98	0.471

BMI, body mass index; COPD, chronic obstructive pulmonary disease; HDL, high density lipoprotein; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; TSH, thyroid stimulating hormone.

Table 2. ECG parameters at pre-treatment, 3rd and 6th month of treatment periods of all 3 groups

Variable	Group 1	Group 2	Group 3	p value
Pre-treatment				
QT	387.00 ± 9.63	387.74 ± 11.90	385.98 ± 9.43	0.868
QTc	419.12 ± 9.71	418.23 ± 10.14	409.76 ± 50.32	0.653
Tpe	79.50 ± 8.45	90.45 ± 43.85	87.68 ± 44.16	0.464
Tpe/QT	0.2021 ± 0.020	0.2125 ± 0.024	0.2059 ± 0.017	0.394
Tpe/QTc	0.1868 ± 0.017	0.1966 ± 0.021	0.1918 ± 0.017	0.294
3rd month of treatment				
QT	382.70 ± 10.31	385.43 ± 12.56	384.37 ± 10.62	< 0.0001
QTc	415.02 ± 8.53	417.85 ± 9.31	409.73 ± 50.39	< 0.0001
Tpe	79.11 ± 7.99	86.15 ± 11.33	88.11 ± 44.46	0.853
Tpe/QT	0.2020 ± 0.025	0.2065 ± 0.027	0.2067 ± 0.018	0.619
Tpe/QTc	0.1850 ± 0.022	0.1972 ± 0.023	0.1920 ± 0.018	0.449
6th month of treatment				
QT	373.48 ± 9.91	385.92 ± 11.64	383.20 ± 11.44	< 0.001
QTc	402.15 ± 11.12	417.45 ± 10.99	409.24 ± 44.46	0.043
Tpe	71.50 ± 10.98	85.66 ± 11.35	89.72 ± 47.51	0.014
Tpe/QT	0.1765 ± 0.023	0.2029 ± 0.023	0.2098 ± 0.018	< 0.01
Tpe/QTc	0.1743 ± 0.021	0.1996 ± 0.022	0.1937 ± 0.017	<0.001

ECG, electrocardiography; QT, QT interval; QTc, corrected QT interval.

and 71.5 ± 10.9 ms vs. 85.6 ± 11.3 ms, 89.9 ± 4.8 ms; p = 0.014 respectively). In addition, Tp-e/QT and Tp-e/QTc ratios were significantly reduced in group 1 compared to groups 2 and 3 (0.186 ± 0.023 vs. 0.196 ± 0.021, 0.191 ± 0.017; p < 0.01 and 0.174 ± 0.021 vs. 0.199 ± 0.022, 0.195 ± 0.016; p < 0.001 respectively). This reduction reached statistical significance. There was no significant correlation between gender, age, HbA1c levels, comorbid conditions with QT, QTc and Tp-e intervals and Tp-e/QT, Tp-e/QTc ratios.

DISCUSSION

The main finding of our study was the ventricular repolarization dispersion assessed by using QT, QTc, Tp-e intervals, and Tp-e/QT, Tp-e/QTc ratios were favorably altered after using SGLT2 inhibitors as an add-on therapy to metformin in patients with type 2 DM. This reduction reached statistical significance compared to other oral antidiabetic treatment combinations after six months.

A recently conducted EMPA-REG OUTCOME trial showed that there was a positive correlation between the use of empagliflozin, an SGLT inhibitor, and reduction in cardiovascular death and heart failure in patients with type 2 DM who were at high risk of cardiovascular disease. The most plausible underlying mechanisms for cardiovascular benefits are changes in arterial stiffness, cardiac oxygen demand, and the cardio-renal system.[10] According to a study conducted by Kusaka et al., empagliflozin therapy significantly reduced left ventricular weight, cardiomyocyte size, cardiac interstitial fibrosis, and cardiac interstitial macrophage infiltration in a genetic prediabetes/metabolic syndrome rat model after ten weeks of treatment.[16]

Although the EMPA-REG OUTCOME study showed favorable effects of SGLT-2 inhibitors in patients with a history of cardiovascular disease, a CVD-REAL study which compared SGLT-2 inhibitors with other glucose-lowering agents in patients without established cardiovascular disease demonstrated similar results in terms of hospitalization for heart failure and all-cause mortality.[17] Despite the favorable effects of SGLT-2 inhibitors on the cardiovascular system, underlying mechanisms that cause cardiovascular benefits were not investigated in this trial. Several reports which studied the effects of empagliflozin in genetic diabetic mouse models suggested the improvement of cardiac morphologic alterations by decreasing the cardiomyocyte cross-sectional area, interstitial collagen I and III depositions, interstitial fibrosis and interstitial macrophage infiltration. The reduction of cardiac fibrosis was associated with the attenua-

tion of the expression of the pro-fibrotic signaling pathway, serum and glucocorticoid-regulated kinase 1 and epithelial sodium channel.[18,19] SGLT-2 inhibitors may also play a crucial role in modulating cardiac Ca2+ and Na+ homeostasis. It is well known that there is a strong association between the depletion of myocardial intracellular Na+ concentration by inhibition of Na+/Ca2+ or Na+/H+ exchangers and improvement in heart failure and cardiac hypertrophy.[20-22] In another study, SGLT-2 inhibitors favorably altered ventricular repolarization heterogeneity which was a predictor of fatal arrhythmias and sudden cardiac death in patients with type 2 DM.[23]

It has been established that electrical instability due to the heterogeneity of cardiac action potential durations lead to cardiac arrhythmias.[24] The human myocardium consists of three myocyte types; endocardial, epicardial, and mid-myocardial M cells.[25] Although these myocytes share anatomical and physiological similarities, they have different electrophysiological properties. While the longest action potential duration was observed in M cells, the earliest completion of action potential was observed in the epicardial cells. The peak of the T wave represents the end of the epicardial action potential, and the end of the T wave represents the end of the mid-myocardial action potential. Therefore, the Tp-e interval demonstrates transmural dispersion of ventricular repolarization.[26] According to recent studies a prolonged T-peak to T-end interval on the resting ECG is associated with increased risk of cardiovascular mortality.[27] Moreover, the Tp-e/QTc ratio is a more sensitive index of prolonged dispersion of ventricular repolarization than Tp-e and QTc intervals.[9]

Common pathological conditions such as atherosclerosis, impaired ventricular function, and repolarization abnormalities may cause sudden cardiac death in patients with type 2 DM.[28] Moreover, alterations in cardiac autonomic activity in patients with DM lead to ventricular arrhythmias owing to increased heterogeneity of ventricular repolarization.[29] Therefore, any treatment modality which decreases ventricular repolarization heterogeneity may improve cardiovascular morbidity and mortality related to DM.

In our study, we observed beneficial alterations in QT, QTc and Tp-e intervals in patients who used SGLT-2 inhibitors as an add-on therapy to metformin. We also observed favorable alterations in Tp-e/QT and Tp-e/QTc ratios. These alterations reached statistical significance compared to other glucose-lowering combinations.

Limitations

The main limitation of our study was the small number of patients. Another limitation was that it may prove beneficial to take into account other factors that might potentially contribute towards increasing susceptibility of developing ventricular arrhythmias such as bundle branch block or atrial fibrillation. Although we analyzed three major classes of oral antidiabetic medications selected for combination therapy, other groups of antidiabetic medications were not included. Large-scale prospective randomized studies in a larger population would provide more precise results and responses as to the underlying mechanism of the cardiovascular benefits of SGLT-2 inhibitors. Furthermore, this study mentioned the clinical ECG parameters, which are not validated by the clinical outcomes. Further studies with larger cohorts are needed to confirm our data.

CONCLUSION

In conclusion, SGLT-2 inhibitors as an add-on therapy to metformin has shown a notable decrease in QT, corrected QT and Tp-e intervals and Tp-e/QT and Tp-e/QTc ratios on the ECG in patients with T2DM compared to other glucose-lowering agents. Improvement in Tpe/QT and Tp-e/QTc ratios during follow-up reached statistical significance compared to other glucose-lowering medications. Although several studies investigating SGLT-2 inhibitors have shown cardiovascular benefits of this drug class, the potential mechanisms are not fully understood. According to our study, these favorable alterations in ventricular indices may be a possible explanation for the cardiovascular benefits of this drug class. To the best of our knowledge, this is the first study to investigates the favorable effects of SGLT inhibitors on ventricular repolarization indices.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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