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ORIGINAL ARTICLE

The effect of SGLT2 inhibitors on cardio-electrophysiological balance index in diabetic patients with preserved ejection heart failure

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Abstract

Background: Heart failure with preserved ejection fraction (HFpEF) is a syndrome commonly associated with type 2 diabetes mellitus (DM). The use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors, which have been shown to have cardioprotective effects in HFpEF, has increased in frequency. The index of cardio-electrophysiological balance (iCEB) is a marker that can be calculated for electrocardiography (ECG) and has been proven to be a good predictor of ventricular arrhythmia. This study aimed to investigate the effects of SGLT-2 inhibitors on the iCEB and the iCEBc in HFpEF patients with type 2 DM.

Methods: We retrospectively analyzed the data of 76 patients with type 2 DM with HFpEF who were started on SGLT-2 inhibitors. We compared the ECG parameters obtained at baseline and six-month follow-up.

Results: The mean age of the patients included in the study was 64.7±8.9 years. When ECG parameters before and after treatment were compared, iCEB (4.33±1.95 vs. 4.24±1.50, p=0.006) and iCEBc (4.67±1.35 vs. 4.59±1.36, p<0.001) values were found to be lower compared to before treatment.

Conclusions: The iCEB and iCEBc values of patients decreased considerably with the use of SGLT-2 inhibitors. These results suggest that SGLT-2 inhibitors may reduce the risk of ventricular arrhythmia in patients with HFpEF.

Keywords: Diabetes Mellitus, Index of Cardio-Electrophysiological Balance, Sodium-Glucose Co-Transporter-2 Inhibitors, Preserved Ejection Fraction Heart Failure.

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INTRODUCTION

Diabetes mellitus (DM), with its rampant prevalence and various adverse cardiovascular consequences, is a chronic disease that needs to be understood in all its aspects (1). With increasing sedentary life and obesity, type 2 DM, which constitutes nearly 90% of the diabetic group in recent years, poses a higher risk of adverse cardiovascular disease compared to type 1 (2). Among the adverse cardiovascular outcomes in patients with type 2 DM, heart failure (HF) is important in terms of morbidity and mortality (3, 4). Epidemiologic and clinical data over the past 20 years have shown that the prevalence of HF in type 2 DM is very high and that the prognosis in patients with HF with type 2 DM is worse than in patients without type 2 DM (5). In antidiabetic drug studies, the rate of HF is reported to be up to 30% in the diabetic population (6). Type 2 DM causes unique adverse changes in the myocardium independent of traditional risk factors, such as coronary artery disease, hypertension (HT), and valvular heart disease, increasing the risk of all three phenotypes of HF, i.e., preserved, reduced, and midrange ejection fraction (HFpEF, HFrEF, and HFmrEF, respectively) (7). However, the most common type of HF in type 2 DM is HFpEF, which accounts for approximately half of the population (8, 9).

HFpEF is a phenotype of HF associated with type 2 DM, advanced age, female gender, HT, obesity, and atrial fibrillation, with normal systolic function (EF≥50%) and impaired diastolic function (7). It is a syndrome characterized by left ventricular (LV) diastolic dysfunction, increased LV filling pressure, decreased LV volume, and coronary microvascular dysfunction (10). The mechanisms for explaining these pathologies are not yet precise. However, increased oxidative and metabolic stress, systemic inflammation, and myocardial fibrosis with type 2 DM are thought to be involved in the development of HFpEF (7).

Until recently, conventional HF drugs were not effective in treating HFpEF. However, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, an antidiabetic drug group, have revitalized treatment with favorable results for HFpEF (11). In the EMPEROR-Preserved study of nearly 6,000 patients, empagliflozin reduced the risk of cardiovascular death and hospitalization with HFpEF, independent of type 2 DM (12). Another large cohort study of HFpEF and HFmrEF patients treated with another SGLT-2 inhibitor, dapagliflozin, found that it reduced the risk of worsening HF and cardiovascular death (13). Increasing evidence has elevated SGLT-2 inhibitors to the preferred option for the treatment of all types of HF.

SGLT-2 inhibitors are antidiabetic agents that reduce glucose reuptake from the renal proximal tubules, leading to increased urinary glucose excretion (5). In addition to providing glycemic control, primarily through glucosuria with their renal effect, these inhibitors reduce the number of major cardiovascular events and hospitalizations due to HF, independent of type 2 DM, thanks to their positive systemic effects (12, 13). Although the mechanisms of their beneficial cardiac effects are unclear, the standard views are that they improve myocardial remodeling, myocardial fibrosis and hypertrophy, and increase cardiac energy production (14, 15). In addition, their effect on arrhythmia has also been studied. Although the direct effects of SGLT-2 inhibitors on sodium and calcium (L-type) ion channels have been demonstrated in animal studies, their effects on other stages of cardiac action potential still need to be determined (16).

As in many cardiovascular diseases, the risk of malignant arrhythmias increases in the presence of HF (17). One of the most important baseline tests for predicting the development of malignant arrhythmias is 12-lead surface electrocardiography (ECG). QT and heart rate-corrected (QTc) distances, which indicate ventricular repolarization for ECG, are classic electrocardiac parameters used to predict ventricular arrhythmias (18). In addition, a somewhat newer parameter, the Tp-e (Tpeak-Tend) distance and the ratio of Tp-e to QT and QTc are predictive markers of ventricular arrhythmia (19). Increases in all of these electrocardiac parameters and rates have previously been shown to be associated with ventricular arrhythmogenesis (20). The index of cardio-electrophysiological balance (iCEB), calculated as the QT distance divided by the QRS distance in ECG, is a new and popular marker for predicting ventricular arrhythmia. Noninvasive and enabling the simple measurement of iCEB, it is used as a surrogate of cardiac wavelength, which indicates susceptibility to ventricular arrhythmia and can only be measured by an invasive electrophysiological study (21, 22). Our study aimed to evaluate the effect of SGLT-2 inhibitors on the iCEB and the iCEBc in HFpEF patients with type 2 DM.

MATERIALS AND METHODS

All of the procedures performed in our study comply with the ethical standards of the corporate committee. Our study also complies with the ethical standards of the Declaration of Helsinki. This study was approved by the clinical research Ethics Committee of the Etlik City Training and Research Hospital (Date: 14.06.2023, Number: AEŞH-EK1-2023-272).

Study population

Our single-center observational study was conducted retrospectively by examining patients with type 2 DM with a diagnosis of HFpEF who had been started on SGLT-2 inhibitors (dapagliflozin or empagliflozin) in the internal medicine outpatient clinic between November 2022 and June 2023. Data were obtained from 98 of 147 patients.

Patients with acute HF, low EF (<50%), advanced valvular heart disease, prosthetic valvular heart disease, complete bundle branch block, atrial fibrillation, advanced renal failure (grade 4–5), hepatic failure, active infection, electrolyte abnormalities, malignancy, and patients taking antiarrhythmic drugs at baseline or throughout treatment were excluded. The study was conducted with a total of 76 patients, minus 22 due to exclusion criteria. The participants' baseline demographic, laboratory, and echocardiographic data were recorded by reviewing the hospital records system. The 12-lead surface ECG data obtained from the hospital registry system were evaluated at baseline and six months after SGLT-2 inhibitors were administered.

Electrocardiography

The recording speed of 12-lead ECG data for all patients was 25 mm/sec and the amplitude was 10 mm/mV. To ensure adequate amplification when measuring ECG parameters, the recordings were computerized and evaluated by two different cardiologists. The intraobserver and interobserver coefficients of variation were <5%. In the case of differing results, mean measurements were taken as the basis. In ECG recordings, heart rate, QRS duration, QT interval, and Tp-e interval were measured manually. The distance from the beginning to the end of the QRS wave was defined as the QRS duration. The QT interval was defined as the time from the beginning of the QRS to the end of the T wave. The QTc was calculated by Bazett's formula (QTc=QT/√RR). The Tp-e interval was determined by measuring the distance from the peak of the T wave to the end of the T wave in lead V5 (23). Using these measurements, the Tp-e/QT and Tp-e/QTc ratios were calculated. The iCEB was obtained by dividing the QT interval, and the iCEBc was obtained by dividing the QTc interval by QRS duration (D2 or V5) (22).

Statistical analysis

Statistical analyses were conducted using the IBM SPSS 23.0 statistical software package. Before performing significance tests, the Levene test was used to determine the homogeneity of variances and the Kolmogorov–Smirnov test was used to evaluate whether continuous variables were normally distributed. The dependent groups t-test was used to compare the ECG data of patients at admission and six months after admission. The significance level was set to $p<0.05$ for all statistical analyses.

RESULTS

A total of 76 patients were included in the study. The mean age of the patients was 64.7±8.9 years; 44 (58.2%) of the patients were female. Empagliflozin was started in 47 (61.8%) patients and dapagliflozin in 29 (38.2%). Table 1 shows the baseline demographic and clinical characteristics of the patients who participated in the study.

Table 1. Baseline characteristics of the study population

Demographic characteristics	N=76
Age (years)	64.7±8.9
Male, n(%)	32(41.8)
Hypertension, n(%)	48(63.5)
Hyperlipidemia, n(%)	20(26.1)
Coronary artery disease, n(%)	12(15.3)
BMI, kg/m^2	29.6±2.7
Echocardiographic findings	
LVEF %	62.8±4.3
LV diastolic diameter, mm	46.4±5.1
LV systolic diameter, mm	28.5±3.8
LA diameter, mm	39±2.7
IVS, mm	1.28±0.4
Laboratory characteristics	
Hemoglobin, g/dl	12.7±5.3
Glucose, mg/dl	148±29
Creatinine, mg/dl	1.1±0.3
Platelet, 10^9/l	275±44
Na, meq/L	136±18
K, meq/L	4.1±1.3
HbA1c, %	7.9±0.9
Medications	
Beta-blocker	70(92)
Renin-angiotensin-aldosterone inhibitors	73(96)
Calcium channel blockers	33(43)
Diuretic (hydrochlorothiazide-indapamide)	72(95)
Metformin	74(98)
Sulfonylureas	8(11)
Dipeptidyl dipeptidase-4 inhibitors	27(35)
Thiazolidinediones	5(7.1)
Glucagon-like peptide-1 receptor agonist	3(3.4)
Insulin	49(65)

BMI: body mass index, LV: left ventricle, EF: ejection fraction, IVS: interventricular septum diameter, WBC: white blood cell, HbA1c: glycosylated hemoglobin

When ECG data at admission and six months were compared, the QT interval (368.2±31.3 vs. 361.4±22.6, p=0.008), the QTc interval (397±37.6 vs. 390.8±35.5, p=0.002), the Tp-e interval (101±19 vs. 92±17, p=0.012), the Tp-e/QT (0.28±0.09 vs. 0.23±0.06, p<0.001), the Tp-e/QTc (0.26±0.08 vs. 0.22±0.07, p=0.001), the iCEB (4.33±1.95 vs. 4.24±1.50, p=0.006), and the iCEBc (4.67±1.35 vs. 4.59±1.36, p<0.001) had decreased compared to pretreatment. No significant difference was found between heart rate and QRS duration (Table 2).

Table 2. Pretreatment and posttreatment electrocardiographic changes in the study population

Parameters	Pretreatment	Post-treatment	P
Heart rate, beat/min	87±11	86±10	**0.013**
QT interval, ms	368.2±31.3	361.4±22.6	**0.008**
QTc interval, ms	397±37.6	390.8±35.5	**0.002**
QRS duration, ms	85±16	85±15	**0.198**
Tp-e interval, ms	101±19	92±17	**0.012**
Tp-e/QT	0.28±0.09	0.23±0.06	**<0.001**
Tp-e/QTc	0.26±0.08	0.22±0.07	**0.001**
iCEB	4.33±1.95	4.24±1.50	**0.006**
iCEBc	4.67±1.35	4.59±1.36	**<0.001**

iCEB: index of cardio-electrophysiological balance, ms: milliseconds

DISCUSSION

Our study investigated the effect of SGLT-2 inhibitors on different electrocardiographic parameters and cardiac electrical activity in type 2 DM patients with HFpEF. In these patients, iCEB and iCEBc values were found to have been reduced by SGLT-2 inhibitors. In addition, QT, QTc, Tp-e distances, and Tp-e/QT and Tp-e/QTc ratios had also been considerably decreased. To our knowledge, our study is the first to show the effect of SGLT-2 inhibitors on the iCEB in HFpEF patients with type 2 DM.

The frequency of ventricular arrhythmias can lead to an increase in sudden death with HFpEF. The mechanisms of ventricular arrhythmias in this patient group were multifaceted. These mechanisms comprised i) decreased conduction velocity with ventricular hypertrophy, ii) increased re-entry circuits with ventricular fibrosis, and iii) delayed repolarization caused by the upregulation of potassium channels (17). It was previously shown that the

frequency of ventricular arrhythmias due to repolarization abnormalities, independent of HF, increased in type 2 DM (24). In addition, the role of SGLT-2 inhibitors (which have shown mortality benefits in HF patients) in terms of cardiac arrhythmias has aroused curiosity and guided studies. For these reasons, we formulated our study population from type 2 DM patients with HFpEF who had an increased risk of ventricular arrhythmia. We evaluated the ventricular arrhythmia risk markers of SGLT-2 inhibitors using ECG parameters, a noninvasive, accessible, and simple test.

Our study used a newer ECG parameter, the iCEB, in addition to the classic repolarization parameters used as ventricular arrhythmia risk markers. The iCEB is an ECG parameter that estimates the invasively measurable cardiac wavelength, which is associated with both the repolarization and depolarization of cardiac electrical activity. The iCEB was previously shown to be associated with ventricular arrhythmias, independent of torsade de pointes (21, 22). A recent study showed that SGLT-2 inhibitors reduced iCEB and iCEBc values within physiological limits in diabetic patients without HF (25). Our study evaluated patients with HFpEF in whom SGLT-2 inhibitors have achieved breakthroughs in treating HFpEF. Our study found that SGLT-2 inhibitors also lowered the iCEB and iCEBc in patients with HFpEF. This decrease in iCEB values was related to the shortened QT distance, as there was no significant change in QRS duration compared to the baseline.

In ECG, the classic ventricular repolarization and torsadogenicity parameter is the QT interval. The duration of the QT interval depends on heart rate; accordingly, the QTc value is more commonly used (26). Modern computer-based ECG devices can calculate QTc automatically. However, the use of different correction formulas is less sensitive to identifying individuals at high risk of ventricular arrhythmias (27). Therefore, we manually calculated QTc using Bazett's formula in the current study. Although different results were obtained in previous studies that evaluated the effect of SGLT-2 inhibitors on QT and QTc distances, the common conclusion is that they do not prolong QT and QTc (25, 28, 29). In our study, QT and QTc distances, among the ventricular repolarization parameters, were significantly decreased with the use of SGLT-2 inhibitors.

In our study, the changes that SGLT-2 inhibitors caused on Tp-e distance, a proarrhythmogenic marker for ECG, were also evaluated. The Tp-e distance is a parameter showing the distribution of transmural repolarization. An increase in this distance has been associated with malignant arrhythmias and sudden cardiac death (30). Previous studies provided evidence that SGLT-2 inhibitors favorably modified the Tp-e distance in diabetic patients (25, 28). Our study supports existing research, as it was observed that Tp-e distances lessened with the use of SGLT-2 inhibitors. In addition, since both Tp-e distance and QT, as well as QTc distances may vary according to body weight, Tp-e/QT and Tp-e/QTc ratios were recently used to increase the sensitivity of these parameters in predicting arrhythmogenicity (20). In our study, Tp-e/QT and Tp-e/QTc ratios decreased with SGLT-2 inhibitor treatments, as did QT, QTc, and Tp-e distances.

Previous studies suggested that SGLT-2 inhibitors reduced the risk of arrhythmias through cardioprotective mechanisms, such as having direct effects on myocyte ion channels, lowering blood pressure, reducing afterload and preload, improving myocardial fibrosis and hypertrophy, and sympathetic nervous system blockade (15, 31). Since our study was retrospective, it is impossible to explain the causality of the favorable effects of SGLT-2 inhibitors on the iCEB and other proarrhythmic predictive parameters. However, our results suggest that SGLT-2 inhibitors contribute to lowering the risk of ventricular arrhythmia in type 2 DM patients with HFpEF in addition to enabling glycemic control.

In conclusion, in type 2 DM patients with HFpEF, SGLT-2 inhibitors meaningfully reduced QT, QTc, Tp-e, Tp-e/QT, Tp-e/QT, Tp-e/QTc, iCEB, and iCEBc parameters. Prospective and comprehensive cohort studies are needed to prove the association of the results in our study with a reduced risk of malignant arrhythmias.

The primary limitation of this study is that it was single-center focused and included a small sample. The patients in the sample group had no data on the severity of HF. Another major limitation was that arrhythmias or sudden cardiac deaths that may develop in patients could not be followed up due to the retrospective study design.

Declarations

The authors have no conflicts of interest to declare. The authors declared that this study has received no financial support.

This study was approved by the clinical research Ethics Committee of the Etlik City Training and Research Hospital (Date: 14.06.2023, Number: AEŞH-EK1-2023-272).

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