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Impact of Sodium-Glucose Cotransporter-2 Inhibitors on Sympathetic Nervous System Activity Detected by Sympathetic Activity Index and LF/HF Ratio in Patients with Type 2 Diabetes Mellitus

Sodyum-Glukoz Kotransporter-2 İnhibitörlerinin Tip 2 Diyabetli Hastalarda Sempatik Aktivite İndeksi ve LF/HF Oranı ile Belirlenen Sempatik Sinir Sistemi Aktivitesi Üzerine Etkisi

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

ABSTRACT

Objective: Cardiac autonomic neuropathy is a serious microvascular complication of type 2 diabetes mellitus that affects a significant portion of patients. Due to decreased parasympathetic activity, the sympathetic nervous system becomes dominant, causing several problems that lead to increased cardiovascular morbidity and mortality. Sodium-glucose cotransporter-2 inhibitors have been shown to reduce sympathetic nervous system activity previously. This is a promising finding for restoring the impaired sympathovagal balance in cardiac autonomic neuropathy. The aim of this study is to evaluate the effect of at least 6 months of sodium-glucose cotransporter-2 inhibitor treatment on sympathetic nervous system activity with sympathetic activity index and heart rate variability parameters in patients with type 2 diabetes mellitus.

Methods: Holter-electrocardiogram recordings of 50 patients who were using a sodium-glucose cotransporter-2 inhibitor (empagliflozin or dapagliflozin) for at least 6 months and 50 patients who did not were analyzed retrospectively. The sympathetic activity index and heart rate variability parameters of these 2 groups, which were similar in terms of age, gender, hemoglobin A1c, and duration of diabetes, were compared.

Results: The ratio of low-frequency to high-frequency power reflecting the sympathovagal balance [−1.495 (−2.165/−1.196) vs. −1.224 (−1.619/−0.863), $P = .008$] and sympathetic activity index [1.44 (1.06/2.76) vs. 2.47 (1.42/3.68), $P = .009$] was lower in the sodium-glucose cotransporter-2 inhibitor group than in the control group. In addition, the sympathetic activity index was correlated with the ratio of low-frequency to high-frequency power ($r = 0.418$, $P < .001$).

Conclusion: Sodium-glucose cotransporter-2 inhibitor treatment for at least 6 months was found to result in lower values of sympathetic activity index and the ratio of low-frequency to high-frequency power in patients with type 2 diabetes mellitus. These findings indicate lower sympathetic nervous system activity, which supports the sympathoinhibitor effects of sodium-glucose cotransporter-2 inhibitors.

Keywords: Cardiac autonomic neuropathy, gliflozins, sympathetic activity index, sympathovagal balance

ÖZET

Amaç: Kardiyak otonom nöropati, tip 2 diyabet hastalarının önemli bir kısmını etkileyen ciddi bir mikrovasküler komplikasyondur. Parasempatik sinir sistemi aktivitesinin azalması sonucunda sempatik sinir sinir sistemi (SSS) baskın hale gelerek kardiyovasküler morbidite ve mortalite artışına yol açan çeşitli sorunlara neden olur. Sodyum-glukoz kotransporter-2 (SGLT2) inhibitörlerinin SSS aktivitesini azalttığı önceki çalışmalarda gösterilmiştir. Bu bulgu, kardiyak otonomik nöropatide bozulmuş olan sempatovagal dengenin düzeltilmesi için ümit vericidir. Bu çalışmanın amacı, tip 2 diyabetik hastalarda, en az 6 aylık SGLT2 inhibitörü tedavisinin SSS aktivitesi üzerine olan etkisini sempatik aktivite indeksi (SAI) ve kalp hızı değişkenliği parametreleri ile değerlendirmektir.

Yöntemler: En az 6 aydır bir SGLT2 inhibitörü (empagliflozin ya da dapagliflozin) kullanan 50 hasta ile oral antidiyabetik tedavilerinde bir SGLT2 inhibitörü bulunmayan 50 hastanın,

Akif Serhat Balcıoğlu, M.D.
Enes Çelik, M.D.
Ekrem Aksu, M.D.
Ahmet Çağrı Aykan, M.D.

Department of Cardiology, Kahramanmaraş Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey

Corresponding author:
Akif Serhat Balcıoğlu
✉ serhatbalcioglu@gmail.com

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24-saatlik Holter-EKG kayıtları geriye dönük olarak incelendi. Yaş, cinsiyet, hemoglobin A1c ve diyabet süreleri açısından benzer olan bu 2 grubun SAI ve kalp hızı değişkenliği parametreleri karşılaştırıldı.

Bulgular: Sempatovagal dengeyi yansıtan LF/HF oranı [1,44 (1,06/2,76)'e karşı 2,47 (1,42/3,68), *P* = ,009] ve SAI [−1,495 (−2,165/−1,196)'e karşı −1,224 (−1,619/−0,863), *P* = ,008], SGLT2 inhibitörü grubunda kontrol grubundan daha düşüktü. Ayrıca SAI'nin LF/HF oranı değerleri ile korele olduğu görüldü (*r* = 0,418, *P* < ,001).

Sonuç: Bu çalışmada, tip 2 diyabet hastalarında en az 6 aylık SGLT2 inhibitörü tedavisinin daha düşük SAI ve LF/HF oranı değerleri ile sonuçlandığı görülmüştür. Bu bulgular daha düşük SSS aktivitesine işaret etmekte olup SGLT2 inhibitörlerinin sempatoinhibitör etkileri olduğunu desteklemektedir.

Anahtar kelimeler: Gliflozinler, kardiyak otonom nöropati, sempatik aktivite indeksi, sempatovagal denge

The prevalence of diabetes, of which 90% is type 2 diabetes mellitus (T2DM), is increasing inexorably and it is estimated to affect 578 million people globally in 2030.[1] As with the macrovascular complications of T2DM, cardiac autonomic neuropathy (CAN), a microvascular complication, increases cardiovascular morbidity and mortality by leading to QT interval prolongation, arrhythmias, impaired heart rate variability (HRV), blood pressure dysregulations such as orthostatic hypotension and reverse-dipping pattern, and silent myocardial ischemia and infarction.[2,3] Cardiac autonomic neuropathy, in which sympathetic activity becomes dominant due to the deterioration of the balance between the parasympathetic and sympathetic innervation of the heart, can be encountered in more than half of T2DM patients.[3,4] It has no definitive treatment and starts very early, to be more precise, it can be detected after the first year of T2DM.[2,3] The earliest sign of CAN, even in the subclinical stage, is a decrease in HRV.[5]

Heart rate variability consists of physiological cyclic fluctuations in the time interval between consecutive heartbeats and was found to be impaired in patients with CAN due to the sympathovagal imbalance.[6,7] Time- and frequency-domain measurements obtained from 24-hour Holter-electrocardiogram (ECG) recordings are reliable and are the widely used methods in the evaluation of HRV.[8] While some of these parameters specifically evaluate parasympathetic nervous system (PNS) activity, others evaluate both PNS and sympathetic nervous system (SNS) activities.[6] The ratio of low-frequency (LF) to high-frequency (HF) power (LF/HF ratio) obtained from the frequency-domain measurements is used to estimate the ratio between SNS and PNS activity.[6] In addition, a novel HRV-derived autonomic measure, the sympathetic activity index (SAI) is proposed to assess the time-varying SNS function.[9]

Among the various drug classes used in the treatment of T2DM, sodium-glucose cotransporter-2 (SGLT2) inhibitors have been shown to improve cardiovascular outcomes that go beyond their blood glucose control benefits, such as reducing heart failure hospitalizations and both cardiovascular and all-cause mortality.[10-12] Some of these benefits of SGLT2 inhibitors have been attributed to their sympathoinhibitor effects, as they have been shown to reduce SNS activity markers such as tyrosine hydroxylase and noradrenaline in preclinical studies, and to decrease sympathetic nerve activity demonstrated by iodine-123-meta-iodobenzyl-guanidine scintigraphy in clinical studies.[13-16] Moreover, the lack of compensatory heart rate increase in response to the decrease in blood pressure caused by these drugs and the lower risk of atrial fibrillation, atrial flutter, and serious ventricular arrhythmias observed in clinical studies in favor of SGLT inhibitors support that they may modulate the cardiovascular autonomic function by reducing SNS activity.[10-12,17,18]

The aim of this study is to investigate the SAI, LF/HF ratio, and other HRV measures obtained from 24-hour Holter-ECG recordings in T2DM patients receiving an SGLT2 inhibitor versus those not receiving it.

ABBREVIATIONS

CAN	Cardiac autonomic neuropathy
ECG	Electrocardiogram
HF	High-frequency power
HRV	Heart rate variability
LF	Low-frequency power
PNS	Parasympathetic nervous system
SAI	Sympahetic activity index
SNS	Sympathetic nervous system
SGLT2	Sodium-glucose cotransporter-2
T2DM	Type 2 diabetes mellitus

Methods

Study Design and Patient Characteristics

In this study, we retrospectively examined the clinical, laboratory, and ambulatory-ECG data of approximately 700 T2DM patients whose 24-hour Holter-ECG recordings were available in the hospital information management system. Of these patients, those with the following characteristics were excluded: T2DM for less than 5 years; any acute coronary syndrome within 1 year prior to Holter-ECG recordings; known heart failure and/or cardiomyopathies; moderate or severe valvular heart disease; abnormal thyroid function tests; non-sinus rhythm on Holter-ECG; use of any anti-arrhythmic drugs that may affect HRV, including beta-blockers and non-dihydropyridine calcium channel blockers; Holter-ECG recordings shorter than 22 hours and/or not of sufficient quality for examination; and absence of hemoglobin A1c (HbA1c) values close to the date of Holter-ECG recordings. The use of glucagon-like peptide-1 agonists was another reason for exclusion as they may influence HRV parameters.[19]

Patients outside these exclusion criteria were screened for the use of an SLGT2 inhibitor for at least 6 months duration prior to Holter recordings. Patients who provided the required duration for the use of drugs were called by phone and asked whether they took their medications uninterruptedly. Subjects whose SGLT2 inhibitor treatment was discontinued or who did not use their medication regularly were also excluded from the study. After all exclusions, 50 patients whose antidiabetic therapy includes an SGLT2 inhibitor, which can be dapagliflozin

or empagliflozin, constituted the SGLT2 inhibitor group, and 50 patients with similar age, gender, and HbA1c values using antidiabetic drugs except an SGLT2 inhibitor formed the control group.

The study was designed and performed in accordance with the principles stated in the Helsinki Declaration and was approved by the local medical research ethics committee (Approval Date: January 21, 2022; Approval Number: 13). All participants were informed before the study and their written consent was obtained.

Holter-ECG Recordings

The 24-hour Holter-ECG recording was obtained using digital recorders (CardioDay® for Windows Version 2.5, GE Healthcare, GETEMED Medizin- und Informationstechnik AG/Germany). Time- and frequency-domain HRV parameters and the SAI were measured and calculated by using the automatic features of the software. Time-domain HRV measures include the following parameters: standard deviation (SD) of normal-to-normal (NN) intervals (SDNN), SD of the average NN intervals for each 5-minute segment of a 24-hour recording (SDANN), mean of the SDs of all the NN intervals for each 5-minute segment of a 24-hour recording (SDNNI), percentage of successive RR intervals that differ by >50 milliseconds (pNN50), and root mean square of successive RR interval differences (RMSSD). We also examined the frequency domain parameters: the absolute power of the LF (0.04-0.15 Hz) band (LF power) and absolute power of the HF (0.15-0.4 Hz) band (HF power).[8] In addition, we calculated the LF/HF ratio which reflects the sympathovagal balance. A lower LF/HF ratio indicates lower SNS activity, while a higher ratio indicates higher SNS activity.[6] All assessments and measurements were performed in accordance with standards set by the European Society of Cardiology Task Force and the North American Society of Pacemaker and Electrophysiology.[8]

The SAI relies on an appropriate combination of Laguerre coefficients derived from the use of Laguerre functions, which have unique properties in the time and frequency domains of HRV.[9] The calculation method of the SAI is detailed elsewhere.[9] The Holter-ECG software we use gives the lowest value of the SAI measured throughout the entire recording in numerically (Figure 1). As expected, lower SAI values indicate lower SNS activity.

Clinical, Laboratory, and Echocardiographic Findings

We obtained the clinical, laboratory, and echocardiographic data of all patients included in the study from the hospital information management system (MIA-MED, version 1.0.1.4155). Existing ECG recordings were used for resting heart rate values. A maximum difference of 30 days was allowed between the dates of the data to be used for statistical analysis and the dates of Holter-ECG recordings.

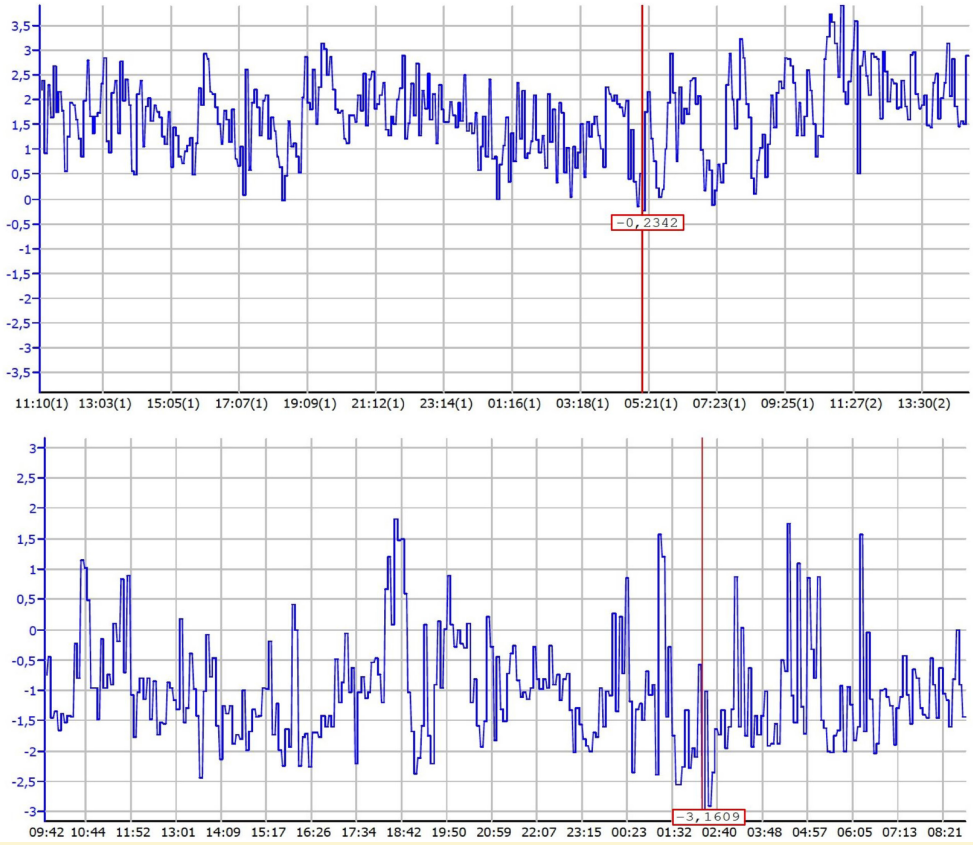

Figure 1. Sympathetic activity index-time graphs of the 2 different patients. The y-axis shows the sympathetic activity index, and the x-axis shows the time in hours. During the entire recording, it is seen that the sympathetic activity is higher in the upper graph and lower in the below one. The lowest SAI values of the patients in the graphics (seen in the red box) were used for statistical analyses.

Statistical Analysis

For all statistical analysis, the Statistical Program for Social Sciences version 22 (IBM Corp., Armonk, NY, USA) was used. Whether the data is normally distributed was examined with Kolmogorov–Smirnov test. Categorical variables were presented as the number of cases with percentages, and continuous variables were presented as mean ± SD or median (25/75% interquartile ranges) according to distribution properties. For examining the differences between groups, the chi-square test was used for categorical variables and Student's *t*-test or Mann–Whitney *U* test for continuous variables. The correlation analysis between HRV parameters and the SAI was performed with the Pearson's or Spearman's tests. A 2-sided *P*-value < .05 was considered statistically significant.

Results

Study Population

The clinical, laboratory, and echocardiographic findings of the patients in both groups are given in Table 1. No significant difference was present between the 2 groups in terms of these characteristics. Of the patients in the SGLT2 inhibitor group, 29 (58%) were using empagliflozin and 21 (42%) were taking dapagliflozin. When the other antidiabetic drugs of the patients were examined, it was seen that almost all the patients were using metformin. In addition, more than half of the patients were using insulin and/or other oral antidiabetic drugs from classes of dipeptidyl peptidase-4 inhibitors, sulfonylureas, and thiazolidinediones. There was no significant difference between the groups in terms of additional antidiabetic drugs (Table 1).

HRV Parameters, SAI, and LF/HF Ratio

Time- and frequency-domain HRV measures are presented in Table 2. Standard deviation of NN intervals, SDANN, and SDNNI values were significantly higher in patients in the SGLT2 inhibitor group compared to those in the control group. Percentage of successive RR intervals that differ by >50 millisec, RMSSD, and HF power values were not different between groups. The LF power, SAI, and LF/HF ratio values of patients using SGLT2 inhibitors were significantly lower than those of patients in the control group (Table 2). In correlation analysis, SAI was correlated positively with LF/HF ratio ($r=0.418$, $P < .001$), SDNN ($r=0.238$, $P=.017$), and SDANN ($r=0.243$, $P=.015$) and inversely with age ($r=-0.249$, $P=.012$). In addition to the SAI, the LF/HF ratio was also found to be correlated with the following parameters: LF power ($r=0.307$, $P=.002$), HF power ($r=-0.473$, $P < .001$), SDNN ($r=0.203$, $P = .043$), SDANN ($r=0.201$, $P=.045$), and duration of T2DM ($r=-0.209$, $P=.037$).

When the SGLT2 inhibitor group was examined in terms of patients receiving empagliflozin or dapagliflozin, HRV parameters, LF/HF ratio, and SAI were not different between these 2 drugs. Holter-ECG data of patients receiving empagliflozin and dapagliflozin were as follows, respectively: SDNN (125.7 ± 29.6 vs. 128.5 ± 29.8, $P=.750$), SDANN (106.2 ± 30.7 vs. 107.3 ± 29.7, $P=.897$), SDNNI [34 (28/51) vs. 30 (23.5/42), $P=.205$], RMSSD [60 (38/91) vs. 62 (28/78), $P=.569$], pNN50 [5 (3.5/7.5) vs. 5 (2.5/11.5), $P=.921$], LF [331.3 (150.7/560.5) vs. 381 (214.9/544.5), $P=.806$], HF [193 (100.7/287.8) vs. 258.6

Table 1. Comparison of the Clinical and Laboratory Characteristics of the Groups

	SGLT2 Inhibitor Group (n=50)	Control Group (n=50)	*P*
Age, years	58.9 ± 10.5	60.1 ± 11.4	.593
Gender, male/female, n (%)	22/28 (44/56)	26/24 (52/48)	.423
Current smoking, n (%)	9 (18)	7 (14)	.585
Hypertension, n (%)	27 (54)	31 (62)	.418
Atherosclerotic cardiovascular disease, n (%)	12 (24)	15 (30)	.499
Body weight, kg	80.3 ± 12.8	83.5 ± 11.9	.201
Body mass index, kg/m^2	29.1 ± 4.3	30.3 ± 5.4	.261
Duration of diabetes, years	7.3 ± 2.2	7.7 ± 2.5	.642
Fasting plasma glucose, mg/dL	143 ± 44.2	147.6 ± 39.7	.228
HbA1c, %	7.41 ± 1.80	7.81 ± 1.95	.263
Total cholesterol, mg/dL	196.8 ± 38.2	201.5 ± 41.3	.510
HDL cholesterol, mg/dL	43.6 ± 11.7	45.1 ± 13.2	.576
LDL cholesterol, mg/dL	124.4 ± 29.9	126.0 ± 33.4	.809
Triglycerides, mg/dL	142.4 ± 69.7	145.0 ± 73.1	.899
Systolic blood pressure, mmHg	127.2 ± 18.9	131.3 ± 21.7	.340
Diastolic blood pressure, mmHg	77.8 ± 11.5	81.2 ± 14.7	.395
Resting heart rate, beats/min	71.7 ± 8.0	74.8 ± 11.8	.093
Left ventricular ejection fraction, %	63.0 ± 5.5	62.4 ± 5.0	.327
Interventricular septum thickness, mm	11.1 ± 1.8	11.4 ± 1.6	.323
Left ventricular posterior wall thickness, mm	10.4 ± 1.5	10.3 ± 1.6	.752
Current medical therapies			
ACEI or ARB, n (%)	24 (48)	27 (54)	.548
Dihydropyridine CCB, n (%)	17 (34)	20 (40)	.534
Diuretics, n (%)	13 (26)	18 (36)	.280
Metformin, n (%)	43 (86)	40 (80)	.424
DPP-4 inhibitors / Sulfonylureas / Thiazolidinediones, n (%)	21 (42)	24 (48)	.546
Insulin, n (%)	18 (36)	15 (30)	.523
Statins, n (%)	23 (46)	27 (54)	.424

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; DPP-4, dipeptidyl peptidase-4; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n, numbers; SGLT2, sodium-glucose cotransporter-2; HbA1c, hemoglobin A1c.
Data are presented as mean ± standard deviation.

Table 2. Comparison of 24-Hour Holter-ECG Findings, Heart Rate Variability Parameters, and Sympathetic Activity Index Between SLGT2 Inhibitor and Control Groups

	SGLT2 Inhibitor Group (n=50)	Control Group (n=50)	*P*
24-hour Holter-ECG findings			
Recording duration, hours*	23.7 ± 1.2	23.3 ± 0.8	.200
Mean heart rate, beats/min*	79.5 ± 9.8	82.5 ± 8.6	.255
Mean RR interval, milliseconds	766.5 (724.7/863)	750.5 (717/804.2)	.190
Time-domain heart rate variability parameters			
SDNN, milliseconds*	126.9 ± 29.4	110.7 ± 34.7	.013
SDANN, milliseconds*	106.6 ± 30.0	92.1 ± 32.9	.023
SDNNI, milliseconds	32 (25/46.75)	25.5 (18.75/38)	.021
RMSSD, milliseconds	61 (36/85.25)	56 (37/66)	.442
pNN50, %	5 (3/9.5)	4 (2.75/7)	.211
Frequency-domain heart rate variability parameters			
LF power, ms^2	348.5 (178.5/549.4)	512.5 (317.4/915.9)	.004
HF power, ms^2	193.5 (103.5/345.2)	207.3 (111.1/422.8)	.549
LF/HF ratio	1.44 (1.06/2.76)	2.47 (1.42/3.68)	.009
Sympathetic activity index	−1.495 (−2.165/−1.196)	−1.224 (−1.619/−0.863)	.008

HF, high frequency; LF, low frequency; pNN50, percentage of successive RR intervals that differ by >50 milliseconds; RMSSD, root mean square of successive RR interval differences; SDANN, standard deviation of the average normal-to-normal intervals for each 5-minute segment of a 24-hour recording; SDNN, standard deviation of normal-to-normal intervals; SDNNI, mean of the standard deviations of all the normal-to-normal intervals for each 5-minute segment of a 24-hour recording; SGLT2, sodium-glucose cotransporter-2.
Data are presented as median (25%/75% interquartile ranges).
*Data presented as mean ± standard deviation.

(109.5/415.5), *P*=.258], LF/HF ratio [1.71 (1.19/3.22) vs. 1.28 (0.98/1.89), *P*=.114], and the SAI [−1.429 (−2.195/−1.133) vs. −1.555 (−2.158/−1.235), *P*=.510].

Discussion

In this study, we examined the effects of SGLT2 inhibitors on the SAI, a novel indicator of SNS activity, and on HRV parameters, which reflects both SNS and PNS functions, in patients with T2DM. For this purpose, 24-hour Holter ECG recordings of patients with similar T2DM duration and glycemic control levels, who used an SGLT2 inhibitor for at least 6-month duration and who did not have an SGLT2 inhibitor in their antidiabetic treatment, were compared. The main finding of our study is that at least 6 months of SGLT2 inhibitor treatment resulted in lower values of the SAI and LF/HF ratio compared to the control group. In addition, we observed improvements in the HRV parameters which reflect SNS activity in favor of SLGT2 inhibitors and a significant correlation between the SAI and LF/HF ratio. To the best of our knowledge, this study is the first to confirm the sympathoinhibitor effects of SGLT2 inhibitors with the SAI values calculated from 24-hour Holter-ECG recordings.

Cardiac autonomic neuropathy, with a prevalence of up to 60% among diabetic patients in some series, is a serious microvascular complication of T2DM that increases cardiovascular morbidity and mortality.[2-4] Since the longest nerves are affected first in neuropathies, PNS activity decreases due to vagus nerve dysfunction.[20] This impairs the sympathovagal balance, resulting in SNS dominance.[3] As a result, resting tachycardia and impaired HRV occur before overt clinical manifestations appear.[3] Because CAN usually begins in the first years of diabetes, we aimed to examine a population with a higher probability of CAN by including patients with T2DM for at least 5 years.[3] However, to identify the number of patients with definite CAN in the study population, we could not perform cardiovascular autonomic reflex tests, which is the gold standard in the diagnosis of CAN, due to the retrospective design of the study.

Sodium-glucose cotransporter-2 inhibitors have been suggested to reduce SNS activity, based on results from previous preclinical and clinical studies.[13-16] However, there are inconsistencies between the results of previous Holter-ECG studies examining the effects of these drugs on heart rate variability parameters.[16,21,22] The differences in outcomes may be attributable to the differences in study durations and patient characteristics. In a relatively small population study comparing 12-week dapagliflozin (n=26) to 12-week glimepiride (n=19) treatments, dapagliflozin did not appear to affect HRV parameters.[21] In fact, the difference between the change in the LF/HF ratio from baseline to 12 weeks was greater with dapagliflozin but was not statistically significant between the 2 groups.[21] Similarly, in the EMPA-HEART CardioLink-6 trial comparing empagliflozin and control groups with 33 patients each, 24 weeks of empagliflozin treatment did not change HRV parameters, including the LF/HF ratio.[22] We, on the other hand, found lower values of LF/HF ratio, which indicates lower SNS activity, in patients who received at least 24 weeks of SGLT2 inhibitor therapy compared to those who did not. However, due to the design of our study, we could not detect the 6-month changes of this ratio within the groups. The reason why the level of improvement in LF/HF ratio with dapagliflozin did not reach

statistical significance in Ang et al's[21] study may be explained by the duration of treatment being short to improve HRV parameters and the small number of patients in the study. The lack of change in the LF/HF ratio in the EMPA-HEART CardioLink-6 study may be due to the 1.8 years longer mean duration of T2DM in the empagliflozin group since statistical comparison of duration of diabetes between groups was not presented in the article (11.9 ± 9.4 years vs 10.1 ± 7.2 years).[22] The severity of CAN is known to increase with longer duration of diabetes, and therefore, more patients at the stage of irreversible CAN might be present in the empagliflozin group.[23] On contrary, our study population had a relatively shorter duration of T2DM with a mean 7.5 years, and groups were similar in terms of T2DM duration.

In another empagliflozin versus placebo study, the EMBODY trial, patients with T2DM were randomized to empagliflozin 10 mg/day or placebo 15 days after an acute myocardial infarction.[16] After 24 weeks of empagliflozin treatment, an improvement of 11.7 milliseconds in SDNN ($P < .01$), 11.7 milliseconds in SDANN ($P = .02$), and 6.5 milliseconds in RMSSD ($P = .01$) was observed according to baseline values, while LF/HF ratio decreased from 2.77 ± 2.21 to 2.37 ± 1.55 ($P = .01$).[16] Consistent with these results, we also found similar HRV parameters (SDNN, SDANN, and SDNNI) to be higher and LF/HF ratio lower in the SGLT2 inhibitor group compared to the control group. As SDNN and its derivatives reflect both PNS and SNS activities, increases in their values and decreases in the LF/HF ratio indicate a reduction in the SNS activity.[6] However, we did not observe any significant difference in RMSSD, pNN50, and HF power values, which mainly reflects PNS activity, between the groups.[6]

Our study distinguishes itself from previous trials by confirming the decrease in SNS activity, indicated by HRV parameters in patients using SGLT2 inhibitors, with the SAI for the first time. In fact, the SAI, which is calculated with complex formulas including both time- and frequency-domain HRV parameters, is quite important as it expresses SNS activity as a single numerical value.[9] The Holter-ECG software we use in our hospital gives the lowest value of the SAI determined in the SAI-hour graph for each patient (Figure 1). Our analyses examining this value showed that the SAI was lower in the SGLT2 inhibitor group than in the control. This finding is consistent with differences in other HRV parameters such as SDNN, SDANN, SDNNI, and LF/HF ratio, supporting the sympathoinhibitor effects of SGLT2 inhibition. Moreover, the lack of difference in LF/HF ratio and SAI between patients receiving empagliflozin and dapagliflozin in our study may indicate that the reduction in SNS activity with these drugs is not due to a specific SGLT2 inhibitor, but rather a group effect.

As mentioned above, in addition to their antidiabetic benefits, SLGT2 inhibitors are suggested to have ameliorative effects on autonomic functions based on the results of both clinical and preclinical studies. Cardiac autonomic neuropathy has fatal complications and has not been a definitive treatment so far. Resting tachycardia, impaired HRV, QT prolongation, and several arrhythmias seen in CAN are based on the disruption of the balance between SNS and PNS activities. The lower SAI and lower LF/HF ratios in patients using SGLT2 inhibitors compared to non-users may be promising in seeking treatments to regress CAN because drugs that can reduce or correct the sympathovagal imbalance appear to be reasonable options.

This study has several limitations. The first of these is that it is a retrospective study. However, only patients whose all clinical data could be accessed and who were confirmed to have been using SGLT2 inhibitor or other oral antidiabetic drugs continuously for at least 6 months were included in the study. There was no significant difference between the SGLT2 inhibitor and control groups in terms of age, gender, and other clinical features. More importantly, the patients had similar glycemic control levels according to their HbA1c values at the time of Holter-ECG recordings. Second, we do not know how many of the patients have definite CAN as cardiovascular autonomic reflex tests were not performed. However, care was taken to ensure that they had sufficient duration of diabetes to have CAN. Third, since it was a retrospective study, 24-week changes in the SAI and HRV parameters could not be obtained within the groups. Prospective randomized studies are needed to overcome these limitations and test the effects of SGLT2 inhibitors on the SAI in populations with a definite diagnosis of CAN.

Conclusion

In this study, treatment with an SGLT2 inhibitor for at least 6 months was found to result in lower values of SAI and LF/HF ratio in patients with T2DM. These findings indicate a decrease in SNS activity, which supports the sympathoinhibitor effects of SGLT2 inhibitors.

Visual summary of the article can be seen in Figure 2.

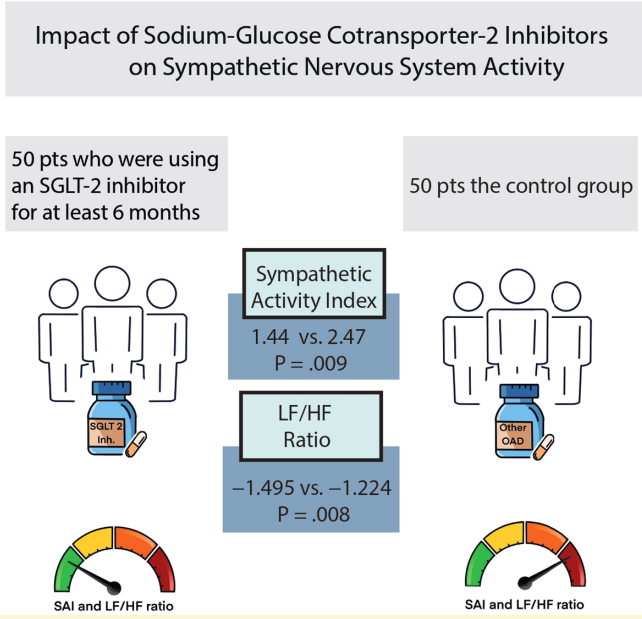

Figure 2. A visual summary of the article.

Ethics Committee Approval: This study approved by the Medical Research Ethics Committee of Kahramanmaraş Sütçü İmam University (Approval Date: January 21, 2022; Approval Number: 13).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Author Contributions: Concept – A.S.B., E.Ç., E.A., A.Ç.A.; Design – A.S.B.; Supervision – A.Ç.A.; Data Collection and/or Processing – E.Ç.; Analysis and/or Interpretation – E.Ç.; Literature Review – A.S.B., E.A.; Writing – A.S.B.; Critical Review – E.A., A.Ç.A.

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