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RESEARCH ARTICLE

Effect of Sodium-Glucose Cotransporter-2 Inhibitors on Circadian Blood Pressure Rhythm in Patients with Type 2 Diabetes Mellitus

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Abstract

Introduction: The aim of this study was to investigate the effect of sodium-glucose cotransporter-2 (SGLT2) inhibitors on circadian blood pressure rhythm in normotensive patients diagnosed with type 2 diabetes mellitus (DM) who were not on antihypertensives. **Methods:** The study included normotensive patients with type 2 DM who were initiated on SGLT2 inhibitors (empagliflozin, n=31; dapagliflozin, n=36) in addition to an antihyperglycemic agent. **Results:** Systolic blood pressure (SBP) and diastolic blood pressure (DBP) changed from a nondipper to a dipper pattern after treatment in 22.4% (n=15) and 25.4% (n=17) of the patients, respectively. Both SBP and DBP changed from a nondipper to a dipper pattern after treatment in 17.9% (n=12) of all patients. This change in circadian blood pressure was not significantly different for the dapagliflozin and empagliflozin groups ($p>0.05$). Fasting blood sugar and HbA1c levels significantly decreased in both groups after SGLT2 inhibitor treatment ($p<0.001$). Serum creatinine and spot urine microalbumin levels and the microalbumin/creatinine ratio decreased significantly in both groups ($p<0.05$). The posttreatment decrease in spot urine protein and creatinine levels was significantly higher in the dapagliflozin group compared to the empagliflozin group ($p<0.05$). **Conclusion:** The circadian blood pressure pattern changed from a dipper to a nondipper pattern in normotensive type 2 DM patients after they used SGLT2 inhibitors.

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Introduction

Hypertension and diabetes mellitus (DM) are associated with an increased risk of cardiovascular events and death.[1-2] Hypertension is a common comorbid condition in diabetes and affects 60% of DM patients.[3-4] This comorbidity further increases cardiovascular complications in the long run.[5] Uncontrolled nocturnal hypertension, in particular, has been associated with increased cardiovascular risk in patients with diabetes.[6] A nondipper pattern of blood pressure is a high-risk condition for arteriosclerosis, and therefore cerebrovascular events and cardiovascular disease,[7] and has been reported in patients with type 2 DM and insulin resistance. The management of nocturnal hypertension includes reducing circulating volume and preferably diuretics.[8] Sodium-glucose cotransporter-2 (SGLT2) inhibitors are mildly diuretic and produce specific effects on ambulatory blood pressure parameters. These inhibitors have been shown to improve glycemic control and lower blood pressure in type 2 DM patients.[9] The EMPA-REG OUTCOME trial showed that empagliflozin, an SGLT2 inhibitor, significantly reduced cardiovascular mortality by 38%.[10] The underlying mechanism by which SGLT2 inhibitors ameliorate cardiovascular disease is unclear; however, it may not be limited to metabolic parameters, body weight, and blood pressure. Although SGLT2 inhibitors have been reported to reduce systolic blood pressure by [2-5] mmHg, their effect on circadian blood pressure has not been fully elucidated.[11] Therefore, the aim of the present study was to investigate the effect of SGLT2 inhibitors on circadian blood pressure rhythm in normotensive patients with type 2 DM who were not on antihypertensives.

Materials and Methods

Study Design

This single-center prospective observational studywas conducted between 15 December 2019 and 15 June 2020 in the Ankara City Hospital Internal Medicine Clinic. The study was planned in accordance with the Declaration of Helsinki and was granted approval by the Ankara City Hospital Clinical Research Ethics Committee No. 1 (date 16/01/2020, decision number E1/182/2019).

Study participants

The study included normotensive (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg) type 2 DM patients of both sexes aged 18-80 years who used an antihyperglycemic and who were initiated on an SGLT2 inhibitor per indication. The exclusion criteria were as follows: history of using SGLT2 inhibitors, GFR <60 mL/min, genitourinary infection, hypertension and/or using antihypertensives (renin-angiotensin system blockers, calcium channel blockers, diuretics, alpha/beta blockers), malignancy, and immunosuppression.

Study Treatments

Patients who met the inclusion and exclusion criteria were randomized 1:1 to receive dapagliflozin 10 mg and empagliflozin 10 mg. Initially, two 24-hour ambulatory blood pressure measurements were planned: one before initiating SGLT2 inhibitors and one after 12 weeks of treatment. However, due to the coronavirus pandemic, there were delays in follow-up ambulatory blood pressure measurements (ABPMs). The average duration of follow-up was 19 weeks. Patients' diet and exercise habits remained unchanged.

Primary End Point

To demonstrate the change in circadian blood pressure compared to basal circadian blood pressure after 12 weeks.

Secondary End Points

To determine any changes in HbA1c, fasting blood glucose (FBG), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), alanine aminotransferase (ALT), alkaline phosphatase (ALP), serum urea, creatinine, spot urine protein, spot urine creatinine, spot urine microalbumin, and hemoglobin levels.

Ambulatory Blood Pressure Measurement

All patients underwent 24-hour ABPMs before being initiated on the study drug and after treatment for follow-up. They were asked to resume their normal activities. They were asked to be awake from 07:00 a.m. and 10:00 p.m. and to resume activities of daily living during this time and to rest and/or asleep between 10:00 p.m. and 07:00 a.m. ABPMs were performed using a GE Tenoport V (GE Tenoport V, Chicago, IL, USA). The device was programmed to perform a blood pressure measurementevery 30 minutes from 07:00 a.m. to 10:00 p.m. and every 60 minutes from 10:00 p.m. to 07:00 a.m.

Statistical Analysis

The data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL, USA). The normality of data distribution was tested with the Kolmogorov–Smirnov test. Normally distributed numerical variables were presented as mean ± standard deviation, and nonnormally distributed numerical variables as median (minimum-maximum). Categorical variables were presented as numbers and percentages. Categorical variables were compared using chi-square and Fisher's exact tests. Student's t-test was used for the pairwise comparison of normally distributed numerical variables and the Mann–Whitney U-test for the pairwise comparison of nonnormally distributed numerical variables.The difference between before and after SGLT2 inhibitor treatment was analyzed by independent samples t-test and the Wilcoxon test for numerical variables and the McNemar test for categorical variables. Changes in laboratory and ABPMs between the treatment groups were compared by repeated measure mixed model analysis. $p<0.05$ (*) was accepted as statistically significant.

Results

The clinical and demographic findings are presented in detail in Table 1. The average duration of follow-up was similar between the empagliflozin and dapagliflozin groups, 19 weeks. The two groups were also similar in terms of the drugs used by the patients (Table 2). Blood pressure measurements before and after treatment according to the SGLT2 inhibitor groups are shown in detail in Table 3. Pretreatment APBMs were similar between the two groups. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) changed from a nondipper to a dipper pattern after treatment in 22.4% (n=15) and 25.4% (n=17) of the patients, respectively. Both SBP and DBP changed from a nondipper to a dipper pattern after treatment in 17.9% (n=12) of all patients. Among these, 66.6% (n=8) were on dapagliflozin and 34.4% (n=4) on empagliflozin. This change in circadian blood pressure was not significantly different between the two groups ($p>0.05$). In the dapagliflozin group, the mean daytime DBP significantly increased after treatment (72.6±8.5 mmHg vs. 75.2±7.9 mmHg, $p=0.034$). The remaining ambulatory blood pressure parameters did not significantly change. In the empagliflozin group, ABPMs did not significantly change after treatment ($p>0.05$). The pretreatment laboratory results were similar between the dapagliflozin and empagliflozin groups (Table 4). In the dapagliflozin group, mean FBG,creatinine, potassium, ALT, AST, GGT, ALP, and HbA1c levels significantly decreased, and mean urea and hemoglobin levels significantly increased after treatment ($p<0.05$, Table 4). In the empagliflozin group, mean FBG, ALT, AST, GGT, ALP, and HbA1c significantly decreased, and mean urea and hemoglobin levels significantly increased after treatment ($p<0.05$, Table 4). When the two groups were compared, only the change in creatinine levels was significantly different between the two groups, being higher in the dapagliflozin group (Table 4). The pretreatment spot urine findings of the two groups were similar. In the dapagliflozin group, mean spot urine protein, spot urine creatinine, and spot urine microalbumin levels and the spot urine microalbumin/creatinine ratio were significantly lower after treatment ($p<0.05$). In the empagliflozin group, mean spot urine microalbumin levels and the spot urine microalbumin/creatinine ratio were significantly lower after treatment ($p<0.05$). The posttreatment decrease in spot urine protein and creatinine levels was significantly higher in the dapagliflozin group compared to the empagliflozin group ($p<0.05$, Table 5)

Discussion

Our study is one of the few to demonstrate the effect of SGLT2 inhibitors on circadian blood pressure in normotensive type 2 DM patients.

In their meta-analysis, Zaccardi et al. showed that SGLT2 inhibitors decreased HbA1c by 7–10 mmol/mol (0.6–0.9%) independently of other antidiabetic treatments.[12] In our study, we observed a similar decrease in HbA1c levels. Our finding is consistent with the available literature.[13] However, SGLT2 inhibitors were not found to be associated with reduced blood pressure, HbA1c levels, or body weight.[14]

A dapagliflozin study by Lambers et al. reported a reduction in 24-hour SBP (mean 5.6±11.6 mmHg), daytime SBP (mean 8.8±12.25 mmHg), and nighttime SBP (mean 1.9±12.5 mmHg) [15]. In that study, the mean basal 24-hour SBP (131±12 mmHg), 24-hour DBP (77±7mmHg), daytime SBP (138±12 mmHg), and ni

Table 1. The distribution of demographic characteristics

Demographic characteristics	All subjects n = 67
Age (years)	52.4±8.4
Sex, n (%)	
Female	28 (41.8)
Male	39 (58.2)
BMI, kg/m2	29.0±3.5
Smoker, n (%)	
No	46 (68.7)
Yes	21 (31.3)
Alcohol use, n (%)	
No	63 (94.0)
Yes	4 (6.0)
Comorbidity, n (%)	
Hyperlipidemia	60 (89.6)
Thyroid disease	5 (7.5)
Anemia	3 (4.5)
Asthma	4 (6.0)
COPD	2 (3.0)
CAD	1 (1.5)
Other	
Crohn's disease	1 (1.5)
Alzheimer's	1 (1.5)
Epilepsy	1 (1.5)

Abbreviations: BMI: Body Mass Index, COPD Chronic Obstructive Pulmonary Disease, CAD coronary artery disease

Table 2. Distribution of drugs used before SGLT2 inhibitor treatment according to treatment groups

Drugs	Dapagliflozin n = 36	Empagliflozin n = 31	p
Metformin,n (%)	30 (83.3)	29 (93.5)	0.364
Statin, n (%)	14 (38.9)	8 (25.8)	0.304
DPP-4i, n (%)	7 (19.4)	7 (22.6)	0.772
Sulfonylurea,n (%)	7 (19.4)	6 (19.4)	0.999
Insulin, n (%)	8 (22.2)	5 (16.1)	0.758
Glitazones, n (%)	-	1 (3.2)	0.940
Glinides, n (%)	1 (2.8)	-	0.999

Categorical variables are presented as numbers (%).
Abbreviations: DPP-4i: Dipeptidyl Peptidase Inhibitor

pared to our basal blood pressure measurements. We ascribed this difference to the fact that Lambers et al. included patients on diuretics and with uncontrolled hypertension. The lack of nocturnal BP dipping in our patients may have been due to our having excluded patients on antihypertensives and those with uncontrolled hypertension.

An empagliflozin study by Tikkanen et al. reported a mean baseline 24-hour SBP of 131.3±13.0 mmHg and a mean baseline 24-hour DBP of 75.1±8.3 mmHg. They did not report data for other blood pressure parameters .[16] After treatment, they reported a reduction in 24-hour SBP (2.99±8.86 mmHg), 24-hour DBP (1.1±4.96 mmHg), daytime SBP (3.4±9.55 mmHg), daytime DBP (-1.28±5.41 mmHg), nighttime SBP (2.22±10.21 mmHg), and nighttime DBP (0.8±6.21 mmHg). It should be noted that their study included hypertensive and diabetic patients. Since the true effects of SGLT2 inhibitors on blood pressure are confounded by various variables in different populations, including BMI, ethnicity, basal blood pressure, and circadian blood pressure pattern, the results in the literature may need to be improved. Assessment of the effects of SGLT2 inhibitors on ABPMs requires ABPM data obtained after discontinuation of the drug. The improvement in blood pressure may result not only from the SGLT2 inhibitor but also from reduced sodium intake.

The literature reports conversion from a nondipper pattern to a dipper pattern in ABPMs after 14 days of dapagliflozin treatment.[17] In our study, change from a nondipper to a dipper pattern was seen in 17.9% of participants.

Posttreatment subgroup analyses by Baker et al. demonstrated that higher initial blood pressure (>140/90 mmHg) was associated with a greater reduction in BP .[18] In our study, we did not find any significant changes in 24-hour, daytime, or nighttime SBP or DBP values and ascribed this finding primarily to low baseline blood pressure and confounding factors such as diet and exercise.

The antihypertensive effect of SGLT2 inhibitors is usually attributed to natriuretic effects that are secondary to diuresis; however, the relevant mechanisms are not clearly understood. Multiple studies have sugges

Table 3. Changes in ambulatory blood pressure after treatment according to treatment groups

Spot Urine Findings	Dapagliflozin n = 36 *Before Treatment / After Treatment*		p	Empagliflozin n = 31 *Before Treatment / After Treatment*		p	Δp
24 hours							
SBP (mmHg)	119.3±15.9	122.2±15	0.141	120±12.4	120.9±14.6	0.739	0.515
DBP (mmHg)	71.2±8.1	73.3±7.5	0.088	74.0±8.5	73.5±7.6	0.729	0.164
Daytime							
SBP (mmHg)	121.1±16.9	124.7±15.3	0.095	122.4±13.3	122.8±14.3	0.872	0.369
DBP (mmHg)	72.6±8.5	75.2±7.9	0.034*	76.3±9.5	75.8±8.0	0.811	0.043*
Nighttime							
SBP (mmHg)	115.0±13.8	116.9±15.2	0.360	111.7±22.8	116.4±16.1	0.293	0.550
DBP (mmHg)	68.1±8.0	69.1±7.4	0.448	69.5±8.6	69.0±8.8	0.789	0.498
Systolic Dipping (%)	5 [(-5.5)-(15.9)]	5.5 [(-3.3)-(19.9)]	0.187	5.3 [(-12.2) -(21.6)]	5 [(-11.4)-(16)]	0.603	0.267
Diastolic Dipping (%)	6.7 [(-10.5)-(20.9)]	7.9 [(-5.3) -(20.3)]	0.239	6.8 [(-5.8)-(30.2)]	7.9 [(-8.4) -(27.5)]	0.814	0.574
Average heart rate (rpm)	76.9±8.5	78.4±7.6	0.792	77.4±10.0	79.0±9.6	0.257	0.914

Normally distributed numerical variables were presented as mean±standard deviation, and nonnormally distributed numerical variables as median (minimum-maximum).

Δp = significance of the difference between posttreatment changes in the two groups

Abbreviations: SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure

ted that these mechanisms are associated with diuresis, reduced weight, reduced vascular thickness, and reduced insulin resistance.[19]

The literature indicates that 52.8% of patients with DM have concomitant hyperlipidemia [20]. In our study, this rate was 89%. This may have been due to a lack of or inadequate antihyperlipidemic treatment due to reasons related to the physician or the patient. A study by Eriksson et al. on nonalcoholic fatty liver disease patients found that dapagliflozin significantly decreased ALT, AST, and GGT levels [21]. We similarly found a significant decrease in ALT, AST, GGT, and ALP levels after SGLT2 inhibitor therapy. This finding may be associated with hepatosteatosis and changes in weight. A study by List et al. demonstrated significant hematocrit elevation after 12 weeks of dapagliflozin treatment [22]. Merlin et al. found a 3-7% increase in plasma hemoglobin, albumin, and urea levels secondary to dehydration in patients on SGLT2 inhibitors.[23] In our study, mean hemoglobin, albumin, and urea levels significantly increased after treatment in both treatment groups. We evaluated this finding to reflect hemoconcentration secondary to diuresis. In our study, spot urine microalbumin and microalbumin/creatinine were reduced in both treatment groups. Reduced microalbuminuria may be due to decreased intraglomerular pressure after SGLT2 treatment. It has been reported that SGLT2 inhibitors reduce the risk of renal disease progression by 45%, regardless of atherosclerotic cardiovascular disease status.[24] The major limitations of our study are its single-center design (which limits the generalizability of the results), the small sample size, not having a placebo control group, and not having assessed dietary sodium intake. Moreover, we did not find a significant decrease in 24-hour, daytime, or nighttime SBP or DBP. Since follow-up ABPMs were made during the coronavirus pandemic, our results

Table 4. Changes in laboratory results after treatment according to treatment groups

Laboratory Findings	Dapagliflozin n = 36 *Before Treatment / After Treatment*		p	Empagliflozin n = 31 *Before Treatment / After Treatment*		p	Δp
Hemoglobin (g/dL)	14.6±1.5	15.1±1.3	0.002*	14.5±1.9	15.0±1.5	0.034*	0.786
HDL (mg/dL)	45.4±9.6	45.6±8.0	0.591	44.6±9.1	46.6±8.8	0.101	0.267
LDL (mg/dL)	126.7±29.7	112.6±28.9	0.085	115.6±22.9	109.7±33.0	0.301	0.428
Triglycerides (mg/dL)	167.5 (72 -656)	210 (68-425)	0.943	166 (55 -432)	164.5 (60 -835)	0.648	0.399
Fasting blood sugar (mg/dL)	175.5 (116-440)	125.0 (80-533)	<0.001*	161 (108-388)	119 (90-262)	<0.001*	0.755
Creatinine (mg/dL)	0.81±0.14	0.77±0.12	-0.009	0.81±0.13	0.81±0.15	0.779	0.049*
GFR(mL/min/1.73 m2)	95.2±9.5	95.0±19.1	0.981	97.8±9.6	97.1±11.1	0.525	0.800
Albumin (g/dL)	4.5±0.3	4.6±0.3	0.079	4.6±0.4	4.7±0.2	0.239	0.927
Urea(mg/dL)	31.9±7.5	35.1±9.0	-0.050	29.8±6.5	33.5±6.9	0.001*	0.706
Urea (mg/dL)	31.9±7.5	35.1±9.0	-0.050	29.8±6.5	33.5±6.9	0.001*	0.706
Sodium (mmol/L)	139.3±2.3	139.4±1.8	0.832	139.5±2.7	139.4±1.9	0.953	0.939
Potassium (mmol/L)	4.6±0.3	4.4±0.4	-0.050	4.6±0.4	4.4±0.3	0.036*	0.478
Phosphorus (mg/dL)	3.5±0.5	3.7±0.5	0.048*	3.5±0.5	3.8±0.8	0.040*	0.174
Magnesium (mg/dL)	1.8±0.2	1.9±0.2	0.008*	1.8±0.2	1.9±0.2	0.043*	0.516
Calcium (mg/dL)	9.5±0.4	9.8±0.5	0.048*	9.5±0.4	9.8±0.4	0.027*	0.880
ALT (U/L)	25 (9-164)	20 (13-100)	0.025*	3 (10-142)	27 (16-69)	0.022*	0.981
AST (U/L)	18 (10-117)	15 (4-63)	0.001*	22.5 (11-89)	18 (10-71)	0.002*	0.558
GGT (U/L)	27 (9-147)	24 (10-96)	0.011*	35 (16-159)	26 (16-107)	-0.031	0.591
ALP (U/L)	84 (55-159)	76 (53-163)	0.012*	90 (54-143)	82 (54-125)	0.035*	0.984
HbA1c (%)	9.2±1.6	7.7±1.5	<0.001*	9.1±2.0	7.6±1.2	<0.001*	0.690

Abbreviations: WBC: White Blood Cell, MPV: Mean Corpuscular Volume, RDW: Red Cell Distribution Width GFR: Glomerular Filtration Rate, HbA1c: Hemoglobin A1c, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, ALT: Alanine Aminotransferase, AST: Aspartame Aminotransferase, GGT: Gamma-Glutamyltransferase, ALP: Alkaline Phosphatase

Table 5. Changes in spot urine findings after treatment according to treatment groups

Spot Urine Findings	Dapagliflozin n = 36 *Before Treatment / After Treatment*		p	Empagliflozin n = 31 *Before Treatment/ After Treatment*		p	Δp
Spot urine protein (mg/L)	138.8 (14-390.3)	70.4 (9.8-340.0)	0.011*	83.9 (22.2-768.8)	62.8 (17.5-170.0)	0.722	0.043*
Spot urine creatinine (mg/dL)	132.5 (28.2-336.6)	81.1 (21.5-312.0)	0.001*	106.3 (21.6-179.2)	69.1 (24.8-182.5)	0.721	0.049*
Spot urinemicroalbumin (mg/L)	12.4 (0.1-76.1)	3.6 (0.6-34.3)	0.011*	7.2 (2.4-450)	3.8 (0.4-15.3)	-0.050	0.991
Urine protein/ creatinine (mg/g Cr)	104.7 (10.9-260)	86.8 (38-200)	0.778	78.9 (51-877)	90.8 (52.8-233)	0.139	0.737
Urine microalbumin/creatinine (mg/g Cr)	9.3 (0.3-75.8)	4.4 (1.4- 65.5)	-0.050	6.7 (3-513.4)	5.4 (1.5-32)	0.017*	0.352

Δp = Significance Of The Difference Between Posttreatment Changes In The Two Groups

p < 0.05 İndicates Statistical Significance

may have been affected by psychosocial risk factors such as stress, anxiety, and irregular sleep. The circadian blood pressure pattern changed from a dipper to a nondipper pattern in normotensive type ² DM patients after they used SGLT² inhibitors, but the mechanism by which this occurred is not clear. The changes in circadian blood pressure were not significantly different for the dapagliflozin and empagliflozin groups. Moreover, ²⁴-hour, daytime, and nighttime SBP and DBP did not significantly change. SGLT² inhibitors show more effective blood pressure reduction in poorly controlled hypertensive type ² DM patients.

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