Annals of Clinical Case Reports

Research Article
Published: 21 Oct, 2023

The Effects of Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors on the Alterations of Plasma Renin Activity and Aldosterone Concentration in Type 2 Diabetes Mellitus

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Abstract

SGLT-2 inhibitors (SGLT-2i) have shown that an inhibition of sodium glucose cotransporter-2 in the renal tubule results in an excretion of urinary glucose and Na. The purpose of this study is to examine alterations of Plasma Renin Activity (PRA) and Aldosterone Concentration (PAC) after treatment with SGLT-2 inhibitor in Type 2 Diabetes mellitus (T2D).

We measured PRA and PAC after resting at supine position for 30 min in 18 T2D patients (age 68 ± 18 years old, male: female = 12:6) after treatment with SGLT-2 inhibitors (tofogliflozin: 9 cases, empagliflozin: 4 cases, canagliflozin: 4 cases dapagliflozin: 1 case) for more than 1 months, and also selected as control 18 non-diabetic patients adjusted for age and sex from 2014 to 2016. Moreover, we could measure each metabolic parameters such as blood glucose, HbA1c, serum lipids level, urinary Na/creatinine and blood pressure, and PRA and PAC before and after treatment with SGLT-2 inhibitors (SGLT-2i) for 1-month in 7 T2D patients. We analyzed these results with paired and unpaired *t* test using JMP12.2.0.

SGLT-2i significantly increased PRA and PAC levels compared with control as follows; PRA in control group and SGLT-2i group 0.9 ± 0.5 ng/ml/h and 5.8 ± 8.9 ng/ml/h, $p<0.04$, PAC in control group and SGLT-2i group 72 ± 36 pg/ml, 99 ± 44 pg/ml and $p<0.05$. Moreover, when we examined each metabolic parameter before and after treatment with SGLT-2i for 1-month in 7 T2D patients, each body weight, blood pressure, and HbA1c was significantly decreased compared with before treatment in 6 T2D patients ($p<0.04$). PRA value after treatment with SGLT-2i was significantly increased compared with before (before 3.25 ± 3.13, after 5.98 ± 4.78, $p<0.05$), but not PAC. Moreover, correlation between the alterations of PRA and PAC and urinary Na/creatinine and hematocrit were measured. Alterations of PRA tend to be correlated with PAC ($r=0.73$) and alteration of PAC correlated with that of hematocrit ($r=0.736$), respectively.

SGLT-2i increases urinary sodium excretion, which affects macula densa in juxta-glomerular apparatus, and finally stimulates secretion of renin, but the alteration of aldosterone and hematocrit was correlated. SGLT-2i-induced increases in urinary sodium excretion affect stimulation of renin secretion and SGLT-2i-induced increase in urinary glucose excretion may affect on osmotic diuresis and finally aldosterone secretion which may act sodium reabsorption.

OPEN ACCESS

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Received Date: *29 Sep 2023*

Accepted Date: *16 Oct 2023*

Published Date: *21 Oct 2023*

Citation:

Mori I, Tangiku M, Fujioka K, Fuwa M, Tani H, Maeda A, et al. The Effects of Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors on the Alterations of Plasma Renin Activity and Aldosterone Concentration in Type 2 Diabetes Mellitus. Ann Clin Case Rep. 2023; 8: 2503.

ISSN: 2474-1655.

Introduction

Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors (SGLT-2i) are the newest drug class for the treatment of type 2 diabetes [1-2]. In 2013 these drugs have shown that an inhibition of sodium glucose cotransporter-2 in the renal tubule results in an excretion of urinary glucose and Na [3-5]. Treatment with SGLT2 inhibitors resulted in no changes of natriuretic effects during two weeks [6]. Previous studies in healthy volunteers or patients with type 2 diabetes have suggested that SGLT2 inhibitors cause transient increases in 24-h sodium excretion [7,8]. The purpose of this study is to examine alterations of Plasma Renin Activity (PRA) and Aldosterone Concentration (PAC) after treatment with SGLT-2 inhibitor in Type 2 Diabetes mellitus (T2D). The purpose of this study is to examine alterations of Plasma Renin Activity (PRA) and Aldosterone Concentration (PAC) after treatment with SGLT-2 inhibitor in T2D.

Methods

We measured PRA and PAC after resting at supine position for 30 min and measured PRA

and PAC in 18 T2D patients (age 68 ± 18 years old, male: female = 12:6, Tofogliflozin 8 cases Canagliflozin 4 cases Empagliflozin 4 cases Dapagliflozin 2 cases) after treatment with SGLT-2i for more than 1 months, and also selected as control 18 non-diabetic hypertensive patients adjusted for age and sex from 2014 to 2016. PRA and PAC were measured by EIA. We analyzed these results with *t* test using JMP12.2.0.

Results

SGLT-2i significantly increased PRA and PAC levels compared with control as follows; PRA in control group and SGLT-2i group 0.9 ± 0.5 ng/ml/h and 5.8 ± 8.9 ng/ml/h, p<0.04 (Figure 1), PAC in control group and SGLT-2i group 72 ± 36 pg/ml and 99 ± 44 pg/ml p<0.05 (Figure 2). Moreover, when we examined each metabolic parameter before and after treatment with SGLT-2i for 1-month in 10 patients with T2D, each body weight, blood pressure (Figure 3), and HbA1c was significantly decreased compared with before treatment in 10 patients with T2D (p<0.04). PRA value after treatment with SGLT-2i was significantly increased compared with before (before 2.63 ± 2.89, after 4.28 ± 4.71, p<0.05), but not PAC. Correlation between the alteration of PRA and PAC tended to be correlated (r=0.766, P<0.059) (Figure 4, 5). Moreover, correlation between the alterations of PRA and PAC and urinary Na/creatinine and hematocrit were measured. Each alteration of PRA and PAC was not significantly correlated with alteration of urinary Na/creatinine. However, alteration of hematocrit was significantly correlated with alteration of PAC (r=0.736) (Figure 6).

These results suggest that SGLT-2i increases urinary sodium excretion, which affects macula densa in juxta-glomerular apparatus, and finally stimulates secretion of renin. Further studies will be required in diabetic patients concerning about SGLT-2i-mediated alterations of renin-aldosterone secretion.

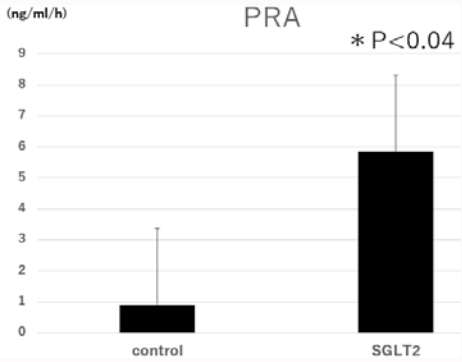

Figure 1: PRA after resting at supine position for 30 min was measured in 18 T2D patients after treatment with SGLT-2 inhibitors for more than 1 moth and 18 non-diabetic hypertensive patients as control adjusted for age and sex from 2014 to 2016. (* P<0.04).

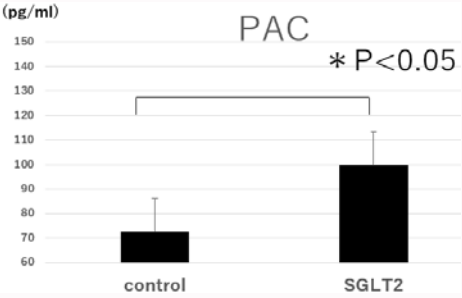

Figure 2: PAC after resting at supine position for 30 min was measured in 18 T2D patients after treatment with SGLT-2 inhibitors for more than 1 months, and also selected as control 18 non-diabetic hypertensive patients adjusted for age and sex from 2014 to 2016. (* P<0.05).

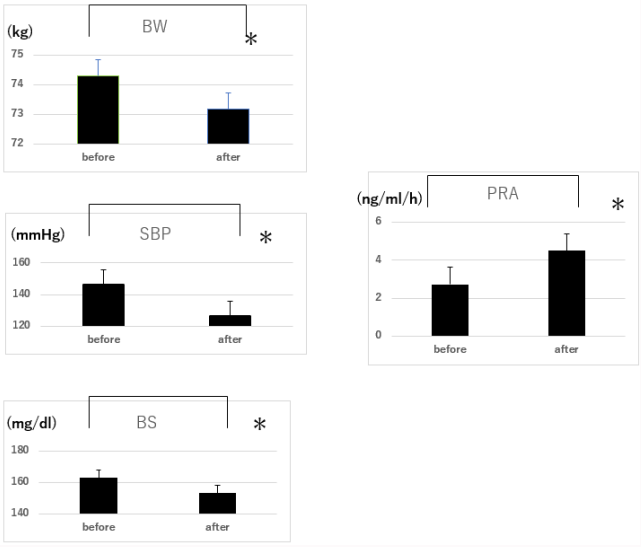

Figure 3: Body weight (BW: kg), systolic blood pressure (SBP: mmHg), PRA (ng/ml/h), and blood glucose level (mg/dl) were shown before and after 1 month. (* P<0.05).

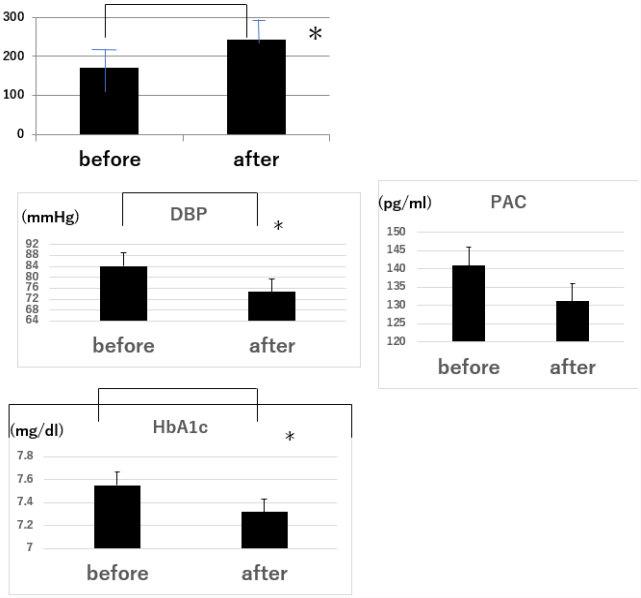

Figure 4: Urinary Na excretion (mEQ/g creatinine), diastolic blood pressure (DBT: mmHg), HbA1c (%) and PAC pg/ml) were shown before and after treatment with SGLT-2i for 1 month. (* P<0.05).

Discussion

We have examined whether SGLT-2 inhibitors- induced alterations of each PRA and PAC associated with urinary sodium excretion. Baseline PRA and PAC in diabetic patients treated with SGLT-2 inhibitor were significantly increased compared with non-diabetic controls (Figure 1). It suggests that urinary excretion of Na and osmotic diuresis cause increased circulating plasma volume, and finally, up-regulated PRA and PAC for 1-month. As shown Figure

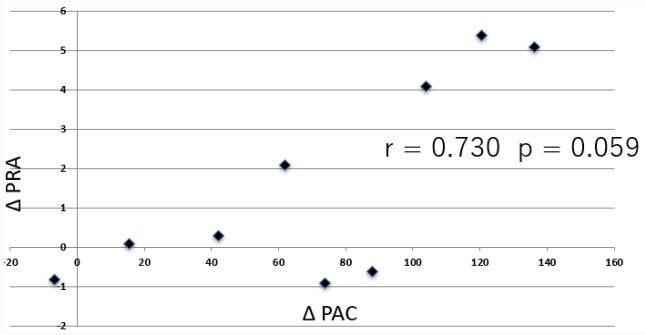

Figure 5: Correlation between alterations of PRA and PAC was shown before and after treatment with SGLT-2i (r=0.730, P=0.059).

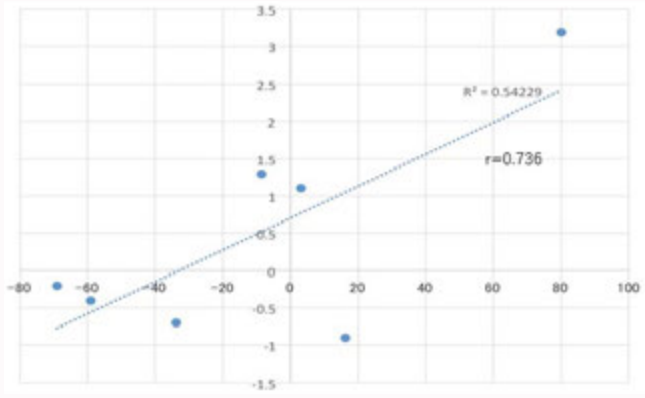

Figure 6: Correlation between alteration of hematocrit and PAC before and after treatment with SGLT-2i (r=0.736 P<0.05).

Table 1: Body Weigh (BW), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Blood Glucose Level (BS), HbA1c, PRA, PAC and urinary sodium excretion (U-Na/CRE) were shown before and after treatment with SGLT-2i for 1 month.

	Before	After	P value
BW (kg)	74.3 ± 21.5	73.2 ± 20.8	0.02
SBP (mmHg)	146 ± 20	126 ± 15	0.01
DBP (mmHg)	84 ± 16	75 ± 11	0.01
BS (mg/dl)	163 ± 64	153 ± 71	0.20
HbA1c (%)	7.5 ± 0.7	7.3 ± 0.7	0.02
PRA (ng/ml/h)	2.63 ± 2.89	4.28 ± 4.71	0.05
PAC (pg/ml)	141 ± 84	131 ± 60	0.55
U-Na/CRE (mEQ/g creatinine)	171.2 ± 141.8	241.8 ± 143.4	0.01

4 urinary Na excretions were significantly increased after treatment with SGLT-2 inhibitors for 1 month. These results are different from previous reports [6] treated with dapagliflozin within 18 days. Our results shown in Figure 5 indicates tendency of correlation between alteration of PRA and PAC which is not significant after treatment with SGLT-2 inhibitor for 1-month, suggesting that PAC regulated with both ACTH and renin-angiotensin system. Actually, as shown in Figure 6, alterations of hematocrit are correlated with those of PAC after treatment with SGLT-2 inhibitors for 1-month. Our data was not enough number of patients and also no examinations of within short effect of SGLT-2-induced changes of each factor.

Conclusion

SGLT-2i increases urinary sodium excretion, which affects macula densa in juxta-glomerular apparatus, and finally stimulates secretion of renin, but the alteration of aldosterone and hematocrit was correlated. SGLT-2i-induced increases in urinary sodium excretion affect stimulation of renin secretion, and SGLT-2i-induced increases in urinary glucose excretion may affect on osmotic diuresis. Finally increased aldosterone secretion may facilitate reabsorption of urinary sodium to regulate serum sodium levels. Father studies may require SGLT-2 inhibitor-induced changes of urinary sodium excretion, PRA and PAC.

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