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Original

Therapeutic Effects of a Sodium Glucose Cotransporter 2 Inhibitor in Diabetic Patients with Chronic Kidney Disease

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SUMMARY

Multiple large-scale clinical trials have indicated that sodium glucose cotransporter 2 (SGLT2) inhibitors reduce the incidence of cardiovascular events, deterioration of renal function and mortality. However, the therapeutic effects of SGLT2 inhibitors are supposed to be limited in patients with reduced renal function considering the mechanism of their action. In this study, a SGLT2 inhibitor, ipragliflozin was given to 30 type 2 diabetic patients with nephropathy whose estimated glomerular filtration rate (eGFR) was not lower than 30 mL/min/1.73 m^2. After 12 to 16 weeks, hemoglobin A1c decreased by 0.6% ($p<0.001$), body weight was reduced by 1.8 kg ($p<0.01$) and blood pressure was lowered by −10/−6 mmHg ($p<0.001$/$p<0.001$). This was accompanied by reductions in serum uric acid (−0.7 mg/dL, $p<0.001$), triglycerides (−25 mg/dL, $p=0.028$) and γ-glutamyl transferase (−8 U/L, $p=0.001$). On the other hand, plasma B-type natriuretic peptide also decreased by 12% ($p=0.020$) and urinary albumin excretion was reduced by 23% ($p=0.018$) although the eGFR was not significantly changed. It is concluded that ipragliflozin is effective in lowering blood glucose even in patients with diabetic kidney disease and is beneficial in improving the accompanying obesity and hypertension. In addition, ipragliflozin is thought to have favorable influences on the metabolisms of uric acid and lipids. These properties of ipragliflozin is expected to bring about protective effects against the progression of nephropathy and the development of cardiovascular disease resulting in the improvement of prognosis in diabetic patients with mild to moderate chronic kidney disease.

Key words : sodium glucose cotransporter 2 inhibitors, ipragliflozin, diabetes mellitus, chronic kidney disease, blood pressure

INTRODUCTION

The prevalence of diabetes mellitus (DM), especially type 2 diabetes mellitus (T2DM), is rapidly increasing in this modern societies. The long-term duration of inadequate control of blood glucose brings about the development of microangiopathy such as neuropathy, retinopathy and nephropathy. Progression of these diabetic complications results in loss of vision and needs for renal replacement therapy such as con-

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tinuation of maintenance hemodialysis which greatly reduces the patient's activity of their daily life. In addition, DM is a major risk factor for atherosclerosis as well and the incidence of cardiovascular diseases such as stroke and coronary heart disease. It is several-fold higher in patients with DM than in non-diabetic subjects[1]. The complications of such cardiovascular diseases are the major causes of mortality in patients with DM. Therefore, the care should be directed to not only in lowering the blood glucose but also preventing the development of such microangiopathies and cardiovascular diseases in order to improve the long-term prognosis of diabetic patients. Among the classes of oral hypoglycemic agents, biguanides have been shown to improve the long-term prognosis of DM patients[2,3]. In addition, recent clinical studies have demonstrated that the sodium-glucose cotransporter-2 (SGLT2) inhibitors also reduced cardiovascular events and mortality in patients with T2DM[4,5]. However, the mechanism by which the SGLT2 inhibitors inhibit the incidence of cardiovascular events is not fully understood.

On the other hand, it is recognized that the existence of chronic kidney disease (CKD) manifested by proteinuria and reduced renal function can not only progress to end-stage renal disease but also increases the risk of developing cardiovascular diseases[6,7]. Considering that DM is the major cause of CKD, the management of cardiovascular risks such as blood pressure and blood glucose in diabetic CKD patients seems a matter of primary importance in clinical practice aiming at the maximum improvement of long-term prognosis. The hypoglycemic effect of SGLT2 inhibitors is supposedly lessened in patients with reduced renal function, however, there is an interest in if the cardiovascular risk is lowered by SGLT2 inhibitors, because the co-existence of DM and CKD greatly increases the risk of developing cardiovascular events.

In the present study, we examined the effects of a SGLT2 inhibitor on the factors relating to the risks of cardiovascular diseases and renal injury in T2DM patients presenting CKD.

METHODS

The subjects enrolled in this study were 31 type 2 diabetes mellitus patients with 7.0% or higher hemoglobin A1c (HbA1c) and/or 180 mg/dL or higher postprandial blood glucose and stage G1-G3 CKD. Patients with estimated glomerular filtration rate (eGFR) lower than 30 mL/min/1.73 m^2 or patients showing nephrotic level proteinuria were excluded and patients receiving insulin injection therapy or already taking a SGLT2 inhibitor were not included. The eGFR was calculated from the serum creatinine level and age by the following equation[8] : $eGFR = 194 \times Age^{-0.287} \times sCr^{-1.094}$ ($\times 0.739$ for females) mL/min/1.73 m^2.

They were given 50 mg ipragliflozin once daily in the morning for 12 to 16 weeks in addition to other drugs which were not changed during the study period. Office blood pressure (BP) was measured with a sphygmomanometer in the sitting position after resting for at least 20 min at each visit every 4 weeks. Before and after 12 to 16 weeks of starting ipragliflozin, non-fasting blood samples were drawn from the antecubital subcutaneous vein. In addition to the routine blood chemistry and blood cell counts, plasma B-type natriuretic peptide (BNP) was assayed using chemiluminescent enzyme immunoassay. Urine samples were also collected at the visits before and after 12 to 16 weeks. Urinary albumin was measured by an immunoturbidimetric method and corrected using the urinary creatinine level. Then, the urinary albumin excretion (UAE) was expressed in mg albumin to g creatinine ratio (mg/gCr).

The study protocol was in accordance with the recommendations of the World Medical Association for biomedical research involving human subjects (Fortaleza version, 2013) and was approved by the institutional review board (No. 27032). Informed consent was obtained from all subjects after explaining the study objective and design.

Clinical data were expressed as means ± standard deviations (SD). Statistical analyses were performed using Stat View software (version 5.0 ; SAS Institute Inc, Carey, North Carolina, USA). Values before and after the study period were compared by paired t-test. However, Wilcoxon signed-rank test was applied for the data with skewed distribution. A P value of less than 0.05 was considered to be statistically significant.

Table 1 Baseline characteristics of the study subjects

Age, years	63.5±11.3
Gender, male/female	18/12
Body mass index, kg/m^2	28.0±4.8
Systolic blood pressure, mmHg	131.4±13.2
Diastolic blood pressure, mmHg	78.9±12.5
Heart rate, bpm	76.7±11.3
Duration of diabetes mellitus, years	10.3±10.4
Complications	
Hypertension	25 (83%)
Dyslipidemia	23 (77%)
Hyperuricemia	12 (40%)
Coronary artery disease	5 (17%)
Arrhythmia	4 (13%)
Chronic glomerulonephriis	3 (10%)

Data are the mean±SD.

RESULTS

Among the 31 patients who started ipragliflozin, a 67-year-old women stopped taking ipragliflozin after 3 days because of pollakisuria and she withdrew the consent to continue the study protocol. Other 30 patients showed good adherence to the therapy and fulfilled the whole study periods. Table 1 shows the baseline characteristics of these 30 patients. The 23 patients were overweight with body mass index (BMI) higher than 25 kg/m^2 of which 10 had obesity with BMI higher than 30 kg/m^2 resulting in the group mean BMI as overweight level. The majority of patients were accompanied with other lifestyle-related diseases such as hypertension, dyslipidemia and hyperuricemia.

Table 2 lists the drugs concurrently prescribed during the study period of 12 to 16 weeks. Although the patients under insulin injection therapy were excluded, 28 of 30 patients were taking oral hypoglycemic agents other than SGLT2 inhibitors. Dipeptidyl peptidase 4 inhibitors were most frequently used followed by α-glucosidase inhibitors and glinides. Because the study subjects include a considerable number of patients with reduced renal function, few patients were given biguanides, sulfonylureas or thiazolidine derivatives. As antihypertensive medications, angiotenisn II receptor blockers and calcium channel blockers were frequently used to lower blood pressure and reduce proteinuria.

Table 2 Medications concurrently given with ipragliflozin in study subjects.

Drug	Number of subjects (%)
Oral hypoglycemic agent	
Biguanide	5 (17%)
Thiazolidine derivatives	1 (3%)
Sulfonylurea	3 (10%)
Glinide	8 (27%)
Dipeptidyl peptidase 4 inhibitor	24 (80%)
α-glucosidase inhibitor	13 (43%)
Antihypertensive drug	
Diuretic	9 (30%)
β-blocker	9 (30%)
Other adrenergic inhibitor	4 (13%)
Calcium channel blocker	18 (60%)
ACE inhibitor	2 (7%)
Angiotenisn II receptor blocker	27 (90%)
Lipid-lowering drug	23 (77%)
Antihyperuricemic drug	12 (40%)
Antiplatelet drug	9 (30%)
Anticoagulant	3 (10%)
Antianginal drug	5 (17%)
Antiarrhythmic drug	1 (3%)

The physical findings of study subjects before and after taking ipragliflozin are shown in Table 3. Body weight was significantly reduced by 1.8 kg during the 12 to 16 weeks of giving ipragliflozin. Systolic and diastolic BPs were also significantly reduced by 10.4/6.2 mmHg after taking ipragliflozin for 12 to 16 weeks. On the other hand, the heart rate was not significantly changed by ipragliflozin administration.

Table 4 shows the changes in blood cell counts before and after 12 to 16 weeks of starting ipragliflozin. The number of erythrocytes, hemoglobin concentration and hematocrit were significantly increased suggesting the occurrence of dehydration and hemoconcentration by the ipragliflozin treatment. The changes in blood chemistry data are shown in Table 5. As naturally expected, highly significant reductions in non-fasting blood glucose and HbA1c were observed after taking ipragliflozin for 12 to 16 weeks. The liver enzymes such as aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyltransferase (γ-GTP) were also reduced significantly at the end of study period. Although the serum proteins were not significantly changed and the change in

Table 3 Blood pressure, heart rate and body weight before and after 12 to 16 weeks after starting ipragliflozin

Variable	Before	After 12-16 weeks	P value
Systolic BP, mmHg	131.4±13.2	121.0±11.4	<0.001
Diastolic BP, mmHg	78.9±12.5	72.7±10.5	<0.001
Heart rate, bpm	76.7±11.3	74.6±11.4	0.127
Body weight, kg	73.2±14.3	71.4±14.2	<0.001

Data are the mean±SD. BP, blood pressure.

Table 4 Peripheral blood cell counts before and after 12 to 16 weeks after starting ipragliflozin

Variable	Before	After 12-16 weeks	P value
White blood cell, $\times 10^3/mm^3$	7.64±1.88	7.89±1.51	0.543
Red blood cell, $\times 10^6/mm^3$	4.59±0.75	4.90±0.71	<0.001
Blood hemoglobin, g/dL	13.7±2.2	14.5±2.2	<0.001
Hematocrit, %	41.1±6.2	44.1±6.2	<0.001
Platelet, $\times 10^3/mm^3$	235±60	230±40	0.526

Data are the mean±SD.

Table 5 Data of blood chemistry before and after 12 to 16 weeks after starting ipragliflozin

Variable	Before	After 12-16 weeks	P value
Aspartate transaminase, U/L	26±14	23±9	0.002
[min-max]	[10-79]	[11-53]	
Alanine transaminase, U/L	33±24	29±21	0.002
[min-max]	[11-108]	[7-106]	
γ-glutamyltransferase, U/L	47±51	39±46	0.001
[min-max]	[12-288]	[11-263]	
Total protein, g/dL	7.0±0.5	7.1±0.5	0.093
Albumin, g/dL	4.0±0.4	4.1±0.4	0.134
Na, mEq/L	139.5±3.0	140.6±2.1	0.020
K, mEq/L	4.3±0.4	4.4±0.5	0.214
Urea nitrogen, mg/dL	21.8±10.7	23.2±10.4	0.082
Creatinine, mg/dL	1.24±0.47	1.32±0.56	0.010
Uric acid, mg/dL	6.3±1.4	5.6±1.2	<0.001
Plasma glucose, mg/dL	166±33	146±34	0.004
Hemoglobin A1c (NGSP), %	7.5±0.7	6.9±0.7	<0.001
HDL-cholesterol, mg/dL	50±16	51±15	0.628
LDL-cholesterol, mg/dL	105±44	105±41	0.463
Triglycerides, mg/dL	192±88	167±72	0.028
[min-max]	[70-409]	[65-347]	

Data are the mean±SD. AST：aspartate transaminase, ALT：alanine transaminase, γ-GTP：γ-glutamyltransferase, HDL：high-density lipoprotein, LDL：low-density lipoprotein, NGSP：National Glycohemoglobin Standardization Program.

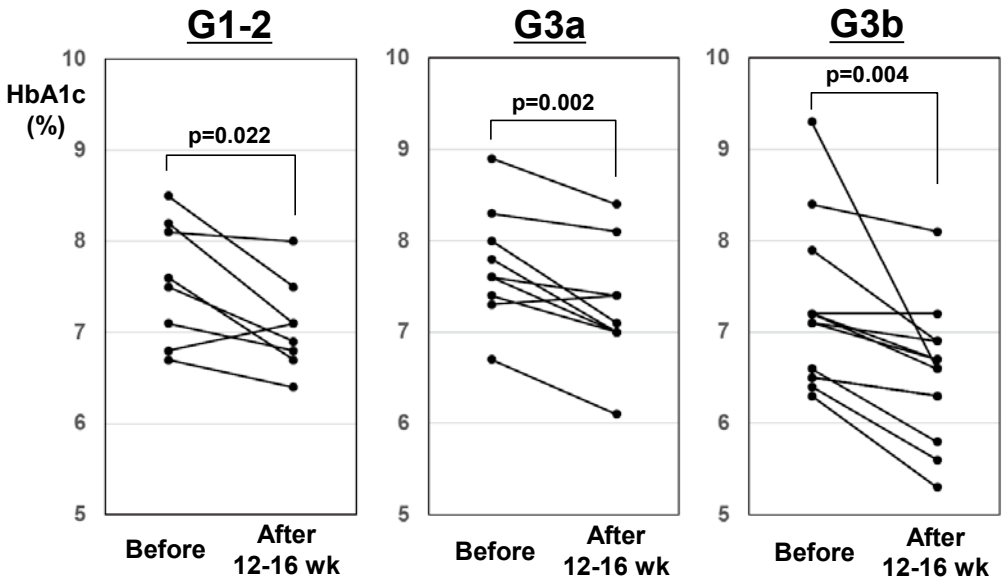

Figure 1 Changes in hemoglobin A1c (HbA1c) before and after taking ipragliflozin for 12 to 16 weeks in CKD patients grouped by the stage of eGFR reduction ; G1-2 ≥60, G3a 45-59 and G3b 30-44 mL/min/1.73 m^2. Data are mean ± SD.

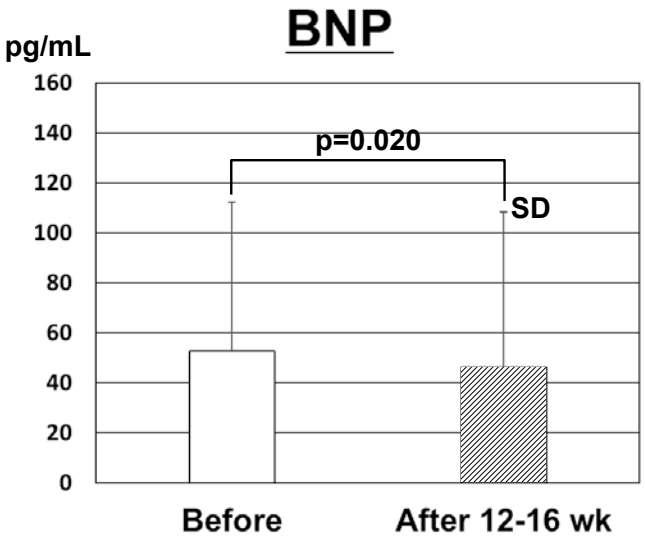

Figure 2 Changes in plasma B-type natriuretic peptide (BNP) before and after taking ipragliflozin for 12 to 16 weeks. Data are mean ± SD.

serum urea nitrogen was not significant, serum sodium and creatinine were significantly increased after the 12 to 16 weeks of ipragliflozin therapy. As for the serum lipids, the triglycerides were significantly decreased, although the levels of high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)-cholesterols were not affected by ipragliflozin.

Figure 1 shows the changes in HbA1c in patients grouped by eGFR levels. Ipragliflozin, a SGLT2 inhibitor, significantly lowered HbA1c in CKD patients with reduced renal function, namely stage G3a (eGFR 45-59 mL/min/1.73 m^2) and stage G3b (eGFR 30-44 mL/min/1.73 m^2), as well as in patients with 60 mL/min/1.73 m^2 or higher eGFR.

Figure 2 depicts the change in plasma BNP before and after taking ipragliflozin. The plasma BNP was significantly reduced from 52.6 ± 59.4 pg/mL to 46.2 ± 62.1 pg/mL ($p = 0.020$) after the 12 to 16 weeks of

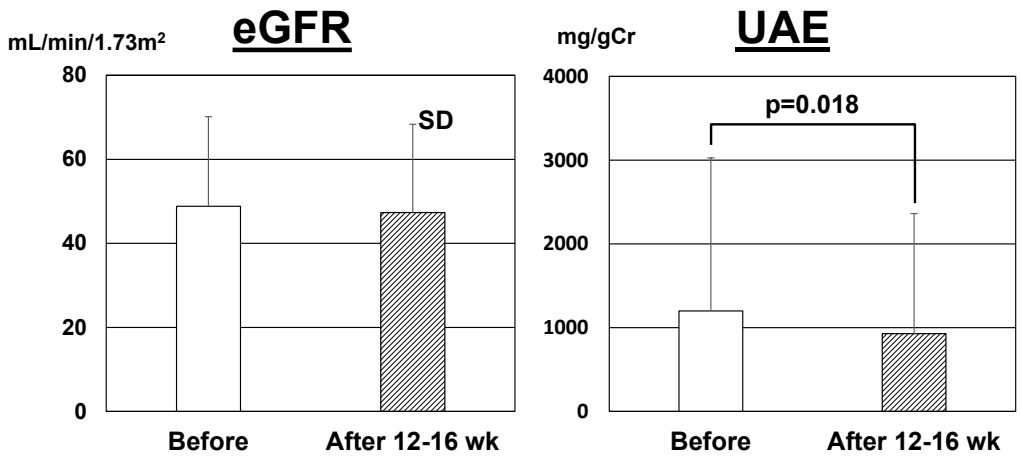

Figure 3 Changes in estimated glomerular filtration rate (eGFR, left panel) and urinary albumin excretion (UAE, right panel) before and after taking ipragliflozin for 12 to 16 weeks. gCr : g creatinine. Data are mean ± SD.

ipragliflozin administration. Figure 3 shows the changes in parameters of nephropathy. Although the serum creatinine was significantly increased, the decrease in calculated eGFR was minimal and insignificant, from to 48.8 ± 19.0 to 47.3 ± 20.0 mL/min/1.73 m^2 ($p = 0.117$) after taking ipragliflozin for 12 to 16 weeks (Figure 3, left panel). On the other hand, the UAE was significantly reduced from 1200 ± 1828 to 928 ± 1436 mg/gCr ($p = 0.018$) by the 12 to 16 weeks ipragliflozin treatment (Figure 3, right panel).

DISCUSSION

In the present study, the long-term treatment with a SGLT2 inhibitor, ipragliflozin, not only improved blood glucose control but also reduced body weight and blood pressure without increasing heart rate in diabetic patients with CKD. In addition, ipragliflozin significantly reduced serum uric acid, triglycerides, liver enzymes and plasma BNP. As to the indices of renal injury, serum creatinine was slightly increased, however, urinary albumin excretion was significantly reduced.

In diabetic patients complicated by CKD, the comprehensive management of cardiovascular risk factors is critically required because both DM and CKD are major risks for developing cardiovascular diseases and organ injuries. Therefore, alleviation of cardiovascular risk factors other than blood glucose should be considered in selecting the anti-diabetic drug therapy so as to improve the prognosis of such patients. Regarding the effects of oral hypoglycemic agents on the long-term prognosis of diabetic patients, the United Kingdom Prospective Diabetes Study (UKPDS) has demonstrated that the intensive blood-glucose lowering therapy with biguanide for an average of 10.7 years reduced all-cause mortality as compared with the control group with a diet therapy alone or the group given sulfonylureas[2]. The prospective study registered diabetic patients with atherothrombosis also showed the lower mortality in patients given biguanide than those not given[3]. However, the evidence of improving the long-term prognosis such as mortality and the incidence cardiovascular events is lacking as to other classes of orally-administered hypoglycemic agents. Thereafter, the sodium-glucose cotransporter-2 (SGLT2) inhibitors were introduced to the clinical practice of managing diabetic patients and the large-scale randomized controlled trials such as the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) study[4] and the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program[5] have shown that the SGLT inhibitors reduced the incidence of cardiovascular events and mortality.

As to the mechanism by which SGLT2 inhibitors reduce cardiovascular events, the facilitated urinary excretion of glucose is expected to cause osmotic diuresis and thereby reduce blood pressure and the risk of developing cardiovascular diseases. Although

SGLT2 inhibitors facilitate water diuresis along with urinary excretion of glucose, the increase in urinary sodium excretion takes place transient and is not significant after 24 hours a SGLT2 inhibitor is started[9,10]. This water diuresis rather than natriuresis induced by SGLT2 inhibitors may have caused the increase in serum sodium concentration observed in the diabetic patients given ipragliflozin in the current study. However, SGLT2 inhibitors have been shown to reduce body weight and blood pressure, as seen in the present study, and these effects are supposedly brought about by the diuretic effect[11,12].

This diuretic effect of SGLT2 inhibitors is thought to contribute to reduce the incidence of heart failure. Patients with diabetes mellitus are at high risk of developing heart failure and their mortality is greatly increased by the presence of heart failure[13~15]. Not only the incidence of heart failure with reduced ejection fraction but also the incidence of heart failure with preserved ejection fraction is increased in diabetic patients and the existence of reduced left ventricular diastolic function also increases the mortality of patients[16~18]. In the present study, plasma BNP, a marker of left ventricular load[19], was significantly decreased by ipragliflozin in addition to body weight and blood pressure reductions. Also the large-scale clinical trials such as EMPA-REG[4], CANVAS Program[5] and Dapagliflozin Effect on Cardiovascular Events (DECLARE)[20] have demonstrated that SGLT2 inhibitors reduce hospitalization due to heart failure in type 2 diabetic patients with cardiovascular risks. Thus, it seems certain that SGLT2 inhibitors reduce the risk of developing heart failure and the diuretic effect is involved in the mechanism of their preventive effects.

In the present study, blood hematocrit and hemoglobin concentration were significantly increased after taking ipragliflozin. This may be understood as the results of hemoconcentration caused by the diuretic action of SGLT2 inhibitors. However, it has been reported that empagliflozin increased plasma erythropoietin in patients with type 2 diabetes[21]. It is speculated that inhibition of tubular glucose reabsorption by SGLT2 inhibitors reduces renal energy and oxygen consumption which alleviates the hypoxia of renal interstitial tissue resulting in a decrease of inflammatory cytokine release and potentiation of erythropoietin production by the fibroblasts[22~25].

The serum creatinine concentration was significantly increased after taking ipragliflozin for 12-16 weeks in the current study, although the change in eGFR was not significant. It has been also shown in the large-scale clinical trials such as EMPA-REG OUTCOME and CANVAS Program that SGLT2 inhibitors transiently cause GFR reduction for a few months, however, the recovery of GFR value take place in the long-term treatment[26,27]. This GFR reduction is supposedly caused by diuretic action of SGLT2 inhibitors. In addition, SGLT2 inhibitors have been shown to increase afferent arteriolar resistance and reduce intraglomerular capillary pressure which is supposed to result in a reduction of glomerular filtration[28,29]. This decrease in intraglomerular capillary pressure may cause GFR reduction on the one hand, but on the other hand it is expected to reduce albuminuria which is associated with the progression of nephropathy. Indeed, albuminuria was significantly reduced in the present study similar to EMPA-REG OUTCOME and CANVAS Program[26,27]. According to the hyperfiltration theory, the increase in intraglomerular capillary pressure, glomerular hypertension, is assumed to play an important role in the development of diabetic nephropathy[30]. In EMPA-REG OUTCOME and CANVAS Program[26,27], long-term renal outcomes such as doubling of serum creatinine and end-stage kidney disease requiring renal-replacement therapy is significantly inhibited by SGLT2 inhibitors[26,27]. Therefore, the reduction of albuminuria by a SGLT2 inhibitor observed in this study supposedly implies renal protection in the long-term treatment of diabetic patients. This renoprotective effect is thought to benefit especially to the CKD patients involved in this study presenting albuminuria/proteinuria and/or reduced renal function.

Thiazide and loop diuretics are generally used in the treatment of hypertension, heart failure and renal dysfunction. However, they sometimes cause adverse effects such as hypokalemia, hyperuricemia, dyslipidemia and impaired glucose tolerance. Importantly, it has been indicated that the occurrence of such adverse effects hampers the protective effects of diuretics against cardiovascular diseases[31,32]. Although

ipragliflozin exhibited diuretic effects reducing body weight and blood pressure in diabetic CKD patients in the present study, the change in serum potassium was insignificant and serum uric acid was significantly reduced. Probably, serum potassium was not decreased because ipragliflozin mainly elicited water diuresis and the natriuretic effect was not prominent. Regarding the decrease in serum uric acid, it is speculated that the inhibition of SGLT2 causes an increase in glucose reabsorption and uric acid excretion through glucose transporter 9 (GLUT9) in the proximal tubuli[33]. These favorable effects of SGLT2 inhibitors on the metabolism of electrolytes and uric acid seem advantageous in preventing cardiovascular diseases in diabetic patients.

SGLT2 inhibitors have been also shown to exhibit favorable influence on serum lipid profile such as an increase in HDL-cholesterol although the changes in LDL-cholesterol and triglycerides seem inconsistent[11]. In the current study, serum triglycerides were significantly decreased, while HDL- and LDL-cholesterols were not significantly changed. In addition, serum liver enzymes such as AST, ALT and γ-GTP were significantly decreased by ipragliflozin. It is speculated that reduced load of carbohydrates to the liver reduces production of triglycerides and deposition of lipid in the liver. The experimental studies have indicated that SGLT2 inhibitors lower inflammatory cytokines in the liver and inhibit the development of fatty liver in obese type 2 diabetic rats[34]. Considering that the cardiovascular risk is increased by the existence of nonalcoholic fatty liver disease[35], these effects of SGLT2 inhibitors are supposed to benefit to prevent cardiovascular diseases in diabetic patients.

In summary, the present study showed that ipragliflozin, a SGLT2 inhibitor, not only improved blood glucose control but also reduced body weight and blood pressure in type 2 diabetic patients with CKD. These effects are supposedly caused by its diuretic effect, however, usual adverse effects of diuretics such as hypokalemia was not observed and serum uric acid and triglycerides were rather decreased. As to the indices of renal injury, albuminuria was significantly decreased and the change in eGFR was minimal. It is suggested that these properties of a SGLT2 inhibitor are advantageous in controlling blood pressure as well as blood glucose and preventing cardiovascular diseases and the progression of nephropathy in diabetic patients with CKD.

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