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Sodium-Glucose Cotransporter-2 Inhibitor Immediately Decreases Serum Uric Acid Levels in Type 2 Diabetic Patients

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Background: Sodium-glucose cotransporter-2 (SGLT2) inhibitors are new antihyperglycemic drugs for type 2 diabetes. SGLT2 inhibitors ameliorate cardiovascular morbidity and mortality as well as kidney disease progression by reducing body weight (BW), blood pressure (BP), visceral adiposity, albuminuria, and serum uric acid and blood glucose levels. However, it is not clear which effects are pronounced, and what mechanisms are associated with these effects.

Material/Methods: This study recruited patients with type 2 diabetes who were prescribed an SGLT2 inhibitor for the first time in our outpatient department. Clinical parameters were measured before and 6 months after the administration of the SGLT2 inhibitor, without the addition of new drugs and dose changes for all prescribed drugs.

Results: This study recruited 24 patients with type 2 diabetes. No significant differences in BP, glycated hemoglobin (HbA1c) levels, and low-density lipoprotein cholesterol levels were observed after SGLT2 inhibitor administration. In contrast, BW and serum uric acid levels decreased significantly, and the fractional excretion of uric acid (FEUA) increased significantly after administration. While no significant relationships were observed between serum uric acid and FEUA with respect to the percentage changes from baseline values, the percentage changes in serum uric acid levels from baseline were significantly and positively associated with those in serum creatinine levels.

Conclusions: Serum uric acid levels were immediately decreased owing to the administration of SGLT2 inhibitor, but BP, blood glucose, and serum lipid levels were unchanged. These changes in serum uric acid levels may be associated with changes in renal function.

MeSH Keywords: Diabetes Mellitus, Type 2 • Sodium-Glucose Transporter 2 • Uric Acid

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Background

Diabetes mellitus (DM) is a worldwide public health and economic challenge. The latest edition of the International Diabetes Federation (IDF) Diabetes Atlas shows that 463 million adults are currently living with DM [1]. DM is largely composed of type 2 diabetes. Type 2 diabetes is a major risk factor for cardiovascular disease, and the presence of both type 2 diabetes and cardiovascular disease increases the risk of death [2,3]. In addition, kidney disease develops in approximately 35% of patients with type 2 diabetes [4] and is associated with increased mortality [5]. Since 1998, diabetic kidney disease is the leading cause for introducing dialysis in Japan [6].

Intensive glycemic control can delay the onset and progression of the early stages of diabetic microvascular complications in type 2 diabetic patients [7,8]. Therefore, sodium-glucose cotransporter-2 (SGLT2) inhibitors were developed as new antihyperglycemic drugs for type 2 diabetes [9]. SGLT2 inhibitors ameliorate hyperglycemia in type 2 diabetic patients by decreasing renal glucose reabsorption [10], and reducing cardiovascular morbidity and mortality as well as the progression of kidney disease [11–14]. SGLT2 inhibitors exert cardiorenal protective effects by reducing body weight (BW) [15,16] and visceral adiposity due to inhibition of glucose reabsorption and promoting the use of fatty acids instead of glucose as an energy source [17], blood pressure (BP) due to inhibition of sodium reabsorption [18], albuminuria due to inhibition of glomerular hyperfiltration via tubuloglomerular feedback [19], serum uric acid [20] as well as blood glucose levels due to inhibition of glucose reabsorption. However, it is unclear which effects are pronounced and what mechanisms are associated with these effects. Therefore, we have performed this study to clarify them.

Material and Methods

Patients

This study included type 2 diabetic patients, whose blood glucose levels were inadequately controlled with diet/exercise therapy in combination with various antihyperglycemic drugs including insulin therapy, in the outpatient department of Hamamatsu University School of Medicine, University Hospital between May 2018 and May 2019. We recruited 24 patients prescribed SGLT2 inhibitors for the first time.

Renal function and urinary albumin or protein excretion levels were not considered while recruiting patients. Steroid users were excluded due to the potential influence on blood glucose levels. This study was approved by the Ethics Committee of Hamamatsu University School of Medicine (No. 17-242) and adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Study protocols

We measured patient height, BW, BP, and heart rate, and collected blood and urine samples before and 6 months after SGLT2 inhibitor administration in our outpatient department. The primary physicians were prohibited from adding new drugs and changing the dosages or types of all prescribed drugs for 6 months after the administration of SGLT2 inhibitors. The primary physicians were entrusted to adequately treat the patients with diet/exercise. There were no restrictions on the type of SGLT2 inhibitor.

Clinical data

Patients' clinical parameters, such as age, sex, height, BW, body mass index (BMI), and BP, were recorded during visits to our outpatient department before and 6 months after SGLT2 inhibitor administration. Concentrations of some clinical parameters were measured in the clinical laboratory of the Hamamatsu University School of Medicine, University Hospital using blood and urine samples. The estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine (Cr) concentrations using the Japanese eGFR equation [21]. The fractional excretion of uric acid (FEUA) was calculated as (urinary uric acid×serum Cr)/(urinary Cr×serum uric acid)×100. Similarly, the fractional excretion of glucose (FEglu) was calculated as (urinary glucose×serum Cr)/(urinary Cr×blood glucose)×100. The percentage change in serum uric acid from the baseline values to those 6 months after SGLT2 inhibitor administration, was calculated as (serum uric acid in 6 months after administration–serum uric acid before administration)/serum uric acid before administration×100. The percentage changes in other clinical parameters were calculated in the same way.

Statistical analyses

The results were expressed as means±standard deviation. The significance of differences between the clinical parameters before and after SGLT2 inhibitor administration was determined using Student's *t*-tests for paired samples. Because the urinary albumin/Cr and urinary protein/Cr did not show normal distributions, the data was expressed as medians (interquartile range). Logarithmic transformation was applied to the data before performing *t* tests. The correlations between serum uric acid levels and clinical parameters 6 months after SGLT2 inhibitor administration were evaluated using Pearson's product-moment correlation tests. The relationships between the changes in serum uric acid levels and clinical parameters from baseline to 6 months after SGLT2 inhibitor administration were assessed in the same way. Multiple linear regression

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Table 1. Patient characteristics.

Age (year)	63.7±12.7
Sex	Male 14/Female 10
Diabetic mellitus duration (year)	14.0±6.1
Stage of diabetic kidney disease	Stage 1: 9/Stage 2: 9/Stage 3: 6
Height (cm)	160.9±10.0
Body weight (kg)	70.6±12.7
Body mass index (kg/m^2)	27.1±4.2
Systolic blood pressure (mmHg)	134.9±12.5
Diastolic blood pressure (mmHg)	74.6±11.9
Heart rate (/min)	78.3±11.2
Hemoglobin A1c (%)	8.24±1.26
Creatinine (mg/dL)	0.97±0.40
eGFR (mL/min/1.73 m^2)	63.3±24.7
Urinary albumin/creatinine (mg/g)	33.6 [19.2–375.3]
Urinary protein/creatinine (g/g)	0.096 [0.067–0.41]
Antihypertensive drugs usage	15 (62.5%)
Antihyperlipidemic drugs usage	14 (58.3%)
Antihyperuricemic drugs usage	4 (20.0%)
Antidiabetic drugs usage	24 (100%)
	Insulin: 11 (45.8%), GLP-1 receptor agonist: 4 (16.6%),
	Biguanide: 14 (58.3%), Thiazolidinedione: 3 (12.5%),
	Sulfonylurea: 4 (16.7%), DPP-4 inhibitor: 14 (58.3%), a-glucosidase inhibitor: 4 (16.7%), Glinide: 1 (4.2%)

eGFR – estimated glomerular filtration rate; DPP-4 – dipeptidyl peptidase-4; GLP-1 – glucagon-like peptide-1.

analyses were conducted to evaluate the relationships between the changes in serum uric acid levels from baseline to 6 months after SGLT2 inhibitor administration, and changes in FEUA or serum Cr concentration. Age, sex, and change in BMI were selected as independent variables because these parameters are commonly included in multiple linear regression analyses. P values <0.05 were considered statistically significant. Statistical analyses were performed using IBM®SPSS® Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

This study included 24 type 2 diabetic patients (14 males and 10 females). Their baseline characteristics are presented in Table 1. Most patients were middle-aged or older (63.7±12.7 years). Their BMI was 27.1±4.2 kg/m^2, falling within the obesity category [22]. Assessment of renal functions included a serum Cr of 0.97±0.40 mg/dL, eGFR of 63.3±24.7 mL/min/1.73 m^2, and median urinary albumin/Cr levels of 33.6 mg/g. According to the 2014 classification of diabetic nephropathy, 9, 9, and 6 patients were stage 1, 2, and 3, respectively [23]. The mean HbA1c level was 8.24±1.26%, and the patients did not achieve adequate glycemic control. Patients' medical regimens are also shown in Table 1.

Comparisons of each parameter before and 6 months after SGLT2 inhibitor administration

Table 2 shows the comparisons of each parameter before and 6 months after SGLT2 inhibitor administration in the patients included in this study. No significant differences were observed in systolic and diastolic BPs, HbA1c, serum low-density lipoprotein cholesterol, serum triglyceride, urinary albumin, and protein excretion before and after SGLT2 inhibitor administration. However, a significant decrease in BW, BMI, and serum uric acid level (before administration; 6.13±1.36 mg/dL *vs.* after administration; 5.20±1.11 mg/dL, p<0.01) and a significant increase in hemoglobin was observed between those values before and after SGLT2 inhibitor administration. Moreover, a significant

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Table 2. Comparisons of each parameter before and 6 months after sodium-glucose cotransporter-2 inhibitor administration.

	Before administration	After administration	P-value
Body weight (kg)	70.58±12.70	68.90±13.13	<0.01
Body mass index (kg/m^2)	27.12±4.20	26.44±4.19	<0.01
Systolic blood pressure (mmHg)	134.9±12.5	137.1±15.0	0.45
Diastolic blood pressure (mmHg)	74.6±11.9	77.9±12.0	0.077
Heart rate (/min)	78.3±11.2	80.0±11.6	0.65
Hemoglobin (g/dL)	13.73±1.61	14.78±1.44	<0.01
Blood urea nitrogen (mg/dL)	18.08±6.95	19.20±4.59	0.38
Cr (mg/dL)	0.97±0.41	0.93±0.36	0.31
eGFR (mL/min/1.73 m^2)	63.25±24.66	63.88±22.95	0.67
Hemoglobin A1c (%)	8.24±1.26	8.15±1.26	0.70
Low-density lipoprotein cholesterol (mg/dL)	111.2±29.3	119.9±37.2	0.12
Triglyceride (mg/dL)	174.0±118.1	181.3±107.8	0.64
Uric acid (mg/dL)	6.13±1.36	5.20±1.11	<0.01
Log urinary albumin/Cr (mg/g)	1.72±0.88	1.88±0.75	0.14
Log urinary protein/Cr (g/g)	–0.84±0.63	–0.80±0.69	0.76
Fractional excretion of glucose (%)	1.46±3.80	27.81±19.18	<0.01
Fractional excretion of uric acid (%)	5.98±2.59	7.71±3.22	0.039

eGFR – estimated glomerular filtration rate, Cr – creatinine.

increase in FEglu and FEUA was observed after SGLT2 inhibitor administration compared to those before administration.

Relationships between serum uric acid levels and clinical parameters 6 months after SGLT2 inhibitor administration

The levels of some clinical parameters are expected to change following the administration of SGLT2 inhibitors, including blood glucose, BP, lipids, albuminuria and proteinuria. However, the levels of other clinical parameters do not change significantly with SGLT2 inhibitor administration. Contrarily, because serum uric acid was one of the markers that changed following the administration of SGLT2 inhibitors in this study, we focused on serum uric acid levels. Serum uric acid levels were significantly associated with renal function after SGLT2 inhibitor administration (serum creatinine; R=0.76, p<0.01 and eGFR; R=–0.51, p=0.011, respectively). However, no significant relationships were observed between serum uric acid level and FEUA (Table 3).

Relationships between the percentage changes in serum uric acid levels and clinical parameters from baseline to 6 months after SGLT2 inhibitor administration

Evaluation of the relationships between the percentage changes in serum uric acid levels and clinical parameters from baseline to 6 months after SGLT2 inhibitor administration, indicated that the percentage change of serum uric acid levels correlated with that of renal function (serum Cr; R=0.47, p=0.020, and eGFR; R=–0.47, p=0.022). However, the percentage change in serum uric acid levels was not associated with that of other clinical parameters including FEUA (FEUA; R=0.14, p=0.58) (Table 4).

Multiple linear regression analyses of the percentage changes in serum uric acid levels from baseline to 6 months after SGLT2 inhibitor administration

Multiple linear regression analyses, to evaluate the relationships between the percentage changes in serum uric acid and those of FEUA or serum Cr after adjusting for age, sex, and the percentage changes of BMI from baseline to 6 months after SGLT2 inhibitor administration, showed no significant relationships between the percentage changes in serum uric acid levels and those of FEUA after adjustment (Models 1 and 2). In contrast, significant relationships were observed between the percentage changes in serum uric acid and those of serum Cr after adjustment (Model 3; β=0.41, p=0.038 and Model 4; β=0.42, p=0.041) (Table 5).

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Table 3. Relationships between serum uric acid levels and clinical parameters 6 months after sodium-glucose cotransporter-2 inhibitor administration.

	R	P-value
Age (year)	–0.44	0.030
Height (cm)	0.32	0.13
Body weight (kg)	0.36	0.083
Body mass index (kg/m^2)	0.21	0.32
Systolic blood pressure (mmHg)	–0.47	0.022
Diastolic blood pressure (mmHg)	–0.047	0.83
Heart rate (/min)	–0.35	0.24
Hemoglobin (g/dL)	–0.11	0.61
Blood urea nitrogen (mg/dL)	0.32	0.13
Cr (mg/dL)	0.76	<0.01
eGFR (mL/min/1.73 m^2)	–0.51	0.011
Hemoglobin A1c (%)	0.22	0.31
Low-density lipoprotein cholesterol (mg/dL)	0.41	0.053
Triglyceride (mg/dL)	–0.052	0.81
Log urinary albumin/Cr (mg/g)	0.25	0.25
Log urinary protein/Cr (g/g)	0.17	0.45
Fractional excretion of glucose (%)	0.12	0.59
Fractional excretion of uric acid (%)	0.38	0.11

eGFR – estimated glomerular filtration rate, Cr – creatinine.

Table 4. Relationships between the percentage changes in serum uric acid levels and clinical parameters from baseline to 6 months after sodium-glucose cotransporter-2 inhibitor administration.

	R	P-value
Body weight (kg)	0.19	0.40
Body mass index (kg/m^2)	0.19	0.40
Systolic blood pressure (mmHg)	–0.19	0.41
Diastolic blood pressure (mmHg)	–0.082	0.72
Heart rate (/min)	–0.069	0.83
Hemoglobin (g/dL)	–0.35	0.090
Blood urea nitrogen (mg/dL)	0.22	0.30
Cr (mg/dL)	0.47	0.020
eGFR (mL/min/1.73 m^2)	–0.47	0.022
Hemoglobin A1c (%)	0.21	0.33
Low-density lipoprotein cholesterol (mg/dL)	0.028	0.90
Triglyceride (mg/dL)	0.060	0.78
Log urinary albumin/Cr (mg/g)	–0.21	0.35
Log urinary protein/Cr (g/g)	0.14	0.56
Fractional excretion of glucose (%)	–0.13	0.58
Fractional excretion of uric acid (%)	0.14	0.58

eGFR – estimated glomerular filtration rate, Cr – creatinine.

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Table 5. Multiple linear regression analyses of the percentage changes in serum uric acid levels from baseline to 6 months after sodium-glucose cotransporter-2 inhibitor administration.

	Model 1		Model 2		Model 3		Model 4	
	R=0.39	p=0.48	R=0.40	p=0.66	R=0.63	p=0.015	R=0.65	p=0.035
	β	p	β	p	β	p	β	p
Age (year)	–0.37	0.15	–0.36	0.19	–0.43	0.023	–0.43	0.030
Sex	–0.082	0.75	–0.067	0.82	–0.030	0.87	–0.031	0.88
Change of BMI (%)			0.079	0.78			0.069	0.73
Change of FE_{UA} (%)	0.066	0.80	0.065	0.81				
Change of sCr (%)					0.41	0.038	0.42	0.041

BMI – body mass index, FE_{UA} – fractional excretion of uric acid, sCr – serum creatinine.

Discussion

The results of the present study revealed significantly decreased serum uric acid levels compared to BP, blood glucose, and serum lipids levels after the administration of an SGLT2 inhibitor. In addition, the results indicated that changes in serum uric acid levels may be associated with changes in renal function.

The mechanisms by which SGLT2 inhibitors lower serum uric acid level have not been completely elucidated until now. Previous large-scale clinical trials reported decreased serum uric acid levels after the administration of an SGLT2 inhibitor [24,25]. Moreover, Andrade et al demonstrated a null prevalence of hyperuricemia and significantly higher FEUA values in 720 diabetic participants with glycosuria who were members of a community-based health care program [26]. Lytvyn et al examined plasma uric acid levels and FEUA in type 1 diabetic patients by inducing glycosuria with SGLT2 inhibition while maintaining clamped euglycemia, and reported that glycosuria rather than hyperglycemia increased uricosuria in the patients [27]. In addition, Chino et al found that the urinary excretion rate of uric acid could be increased by SGLT2 inhibitor-induced glycosuria in healthy subjects, and that the increased concentration of glucose in the lumen by SGLT2 inhibition stimulated uric acid excretion via glucose transporter 9 (GLUT9) isoform 2 in the proximal tubule, and inhibited uric acid reabsorption via GLUT9 isoform 2 in the collecting duct in *in vitro* transport experiments [28]. Novikov et al showed disengagement of urate transporter URAT1, responsible for the probenecid-sensitive urate reabsorption, thereby enhancing urate excretion in nondiabetic mice with both genetic and pharmacological inhibition of SGLT2 [29]. These reports suggest that increased uric acid excretion in the proximal tubule due to increased glucose concentration contributes to the lowering effects on serum uric acid levels. However, until now, no obvious evidence has yet been found in patient and animal models of type 2 diabetes. The present study observed significant differences in FEUA between levels before and 6 months after SGLT2 inhibitor treatment. However, there were no significant relationships between serum uric acid and FEUA levels at 6 months after administration of SGLT2 inhibitor, and a percentage change was not observed in serum uric acid and FEUA levels between baseline and 6 months after treatment with an SGLT2 inhibitor. Moreover, no significant relationships were found between FEglu and FEUA levels at 6 months after SGLT2 inhibitor administration (r=0.19 and p=0.44; data not shown), and the percentage change in FEglu and FEUA values between baseline and 6 months after SGLT2 inhibitor treatment (r=0.25 and p=0.31; data not shown) in the present study. The accumulation of visceral fat causes insulin resistance or hyperinsulinemia. The magnitude of insulin resistance and serum uric acid concentration are significantly and positively related, and insulin resistance is also negatively correlated with urinary uric acid clearance [30]. Moreover, normal FEUA is 8.3%. Although the FEUA before SGLT2 inhibitor administration was low (5.98±2.59%) in this study and increased significantly after SGLT2 inhibitor administration to 7.71±3.22% (p=0.039), it remained relatively low. Therefore, the increase in urinary uric acid level may not have contributed greatly to serum uric acid levels, and serum uric acid levels were not significantly and negatively correlated with FEUA in this study.

A significant positive association has been reported between serum uric acid level and obesity in adults [31]. Obesity is linked to the elevation of serum uric acid levels due to overproduction. In other words, visceral fat accumulation induces an elevated influx of plasma free fatty acids into the liver and hepatic portal vein, which stimulates triglyceride synthesis, followed by an associated surge in uric acid production through activation of the uric acid synthesis pathway, namely the pentose phosphate cycle [32,33]. Thus, the amelioration of obesity by SGLT2 inhibitors may have improved serum uric acid levels in this study. However, significant relationships between serum uric acid levels, and serum triglyceride levels

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or BMI 6 months after the administration of SGLT2 inhibitors were not observed. Moreover, significant relationships between the percentage change in serum uric acid levels, and serum triglyceride levels or BMI from baseline to 6 months after the administration of an SGLT2 inhibitor were also not observed. Therefore, whether serum uric acid levels were significantly decreased by amelioration of body weight or serum triglyceride levels could not be determined.

The gut and kidney are responsible for approximately one-third and two-thirds of daily uric acid disposal, respectively. All or nearly all uric acid is readily available for filtration at the glomerulus. Therefore, renal function, namely GFR, is one of the most important determinants of serum uric acid levels. This study observed a significant relationship between serum uric acid levels and serum Cr levels 6 months after SGLT2 inhibitor administration. Significant relationships between the percentage changes of serum uric acid levels and serum Cr levels from baseline to 6 months after SGLT2 inhibitor administration, after adjusting for age, sex, and the percentage change of BMI, were also observed. These results suggest that renal function determined the serum uric acid levels in the present study. However, the lack of significant differences in renal function before and after SGLT2 inhibitor administration was contrary to this hypothesis. Additional large-scale clinical studies are necessary to identify mechanisms contributing to the serum uric acid-lowering effects of SGLT2 inhibitors in type 2 diabetic patients.

Elevated serum uric acid levels are associated with gout attacks [34]. Recent evidence also suggests a significant association between hyperuricemia and chronic kidney disease [35,36], metabolic syndrome [37], hypertension [38], and cardiovascular events [39,40]. These organ damages are mainly mediated by endothelial dysfunction [41]. Therefore, clinicians should consider more aggressive use of SGLT2 inhibitors to decrease serum uric acid levels and protect against some organ damage.

While the previous study indicated that HbA1c reduced by 0.41% due to the administration of dapagliflozin at week 24 in Japanese patients with type 2 diabetes [42], this study demonstrated that HbA1c decreased by only 0.09% using SGLT2 inhibitors. The decreased levels in this study were considerably less compared with those in the previous study. Moreover, although the decreased levels of BW were only 1.68 kg in this study, they were 2.13 kg in the previous study. These results suggest that dietary management was not controlled well and that glucose intake increased after the administration of SGLT2 inhibitors in the patients of this study. This may be why HbA1c levels did not decrease significantly in this study.

This study has some limitations. First, we performed the single-center cohort study. In addition, because we would like to show which effects are pronounced and what mechanisms are associated with these effects among the pleiotropic effects of SGLT2 inhibitors, we prohibited the primary physicians from adding new drugs and changing the dosages or types of all prescribed drugs for 6 months after the administration of SGLT2 inhibitors. Therefore, the sample size was relatively small. As a result, serum uric acid levels may not be correlated with FEUA. These results require confirmation by large-scale clinical studies. Second, although their physicians directed the patients to perform diet and exercise therapies, the levels of adherence may have differed among patients. Finally, the SGLT2 inhibitor was not restricted to a single formulation. For example, 5 mg/day of dapagliflozin was administered to 23 patients while one patient received 50 mg/day of ipragliflozin. Therefore, the different SGLT2 inhibitors likely had only subtle influences on the results.

Conclusions

Serum uric acid levels were immediately decreased by the administration of SGLT2 inhibitors, unlike BP, albuminuria, proteinuria, and blood glucose, and serum lipids levels. The changes in serum uric acid levels by SGLT2 inhibitor administration may be associated with changes in renal function.

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References:

1. IDF Diabetes Atlas 9th edition 2019 *https://www.diabetesatlas.org/en/*
2. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR et al: Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. Lancet, 2010; 375: 2215–22
3. Beckman JA, Creager MA, Libby P: Diabetes and atherosclerosis: Epidemiology, pathophysiology, and management. JAMA, 2002; 287: 2570–81
4. de Boer IH, Rue TC, Hall YN et al: Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA, 2011; 305: 2532–39
5. Afkarian M, Sachs MC, Kestenbaum B et al: Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol, 2013; 24: 302–8
6. Annual Dialysis Data Report 2016, JSDT Renal Data Registry Masakane I, Taniguchi M, Nakai S, et al. & on behalf of Japanese Society for Dialysis Therapy Renal Data Registry Committee: Annual dialysis data report 2016, JSDT renal data registry. Renal Replacement Therapy, 2018; 4: 45
7. Shichiri M, Kishikawa H, Ohkubo Y, Wake N: Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care, 2000; 23(Suppl. 2): B21–29
8. Ismail-Beigi F, Craven T, Banerji MA et al., ACCORD trial group: Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet, 2010; 376: 419–30
9. Heise T, Seewaldt-Becker E, Macha S et al: Safety, tolerability, pharmacokinetics and pharmacodynamics following 4 weeks' treatment with empagliflozin once daily in patients with type 2 diabetes. Diabetes Obes Metab, 2013; 15: 613–21
10. Gallo LA, Wright EM, Vallon V: Probing. SGLT2 as a therapeutic target for diabetes: Basic physiology and consequences Diab Vasc Dis Res, 2015; 12: 78–89
11. Zinman B, Wanner C, Lachin JM et al., EMPA-REG OUTCOME Investigators: Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med, 2015; 373: 2117–28
12. Neal B, Perkovic V, Mahaffey KW et al., CANVAS Program Collaborative Group: Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med, 2017; 377: 644–57
13. Wanner C, Inzucchi SE, Lachin JM et al., EMPA-REG OUTCOME Investigators: Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med, 2016; 375: 323–34
14. Perkovic V, Jardine MJ, Neal B et al., CREDENCE Trial Investigators: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med, 2019; 380: 2295–306
15. Kovacs CS, Seshiah V, Swallow R et al., EMPA-REG PIO™ Trial Investigators: Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: A 24-week, randomized, placebo-controlled trial. Diabetes Obes Metab, 2014; 16: 147–58
16. Rosenstock J, Jelaska A, Frappin G et al., EMPA-REG MDI Trial Investigators: Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes Care, 2014; 37: 1815–23
17. Ridderstråle M, Andersen KR, Zeller C et al., EMPA-REG H2H-SU Trial Investigators: Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: A 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol, 2014; 2: 691–700
18. Tikkanen I, Narko K, Zeller C et al., EMPA-REG BP Investigators: Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. Diabetes Care, 2015; 38: 420–28
19. Barnett AH, Mithal A, Manassie J et al: EMPA-REG RENAL trial investigators. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: A randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol, 2014; 2: 369–84
20. Chino Y, Samukawa Y, Sakai S et al: SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. Biopharm Drug Dispos, 2014; 35: 391–404
21. Matsuo S, Imai E, Horio M et al: Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis, 2009; 53: 982–92
22. Baker S, Barlow S, Cochran W et al: Overweight children and adolescents: A clinical report of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol, Nutr, 2005; 40: 533–43
23. Wada T, Haneda M, Furuichi K et al., Research Group of Diabetic Nephropathy, Ministry of Health, Labour, and Welfare of Japan: Clinical impact of albuminuria and glomerular filtration rate on renal and cardiovascular events, and all-cause mortality in Japanese patients with type 2 diabetes. Clin Exp Nephrol, 2014; 18: 613–20
24. Bailey CJ, Gross JL, Pieters A et al: Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: A randomised, double-blind, placebo-controlled trial. Lancet, 2010; 375: 2223–33
25. Cefalu WT, Leiter LA, Yoon KH et al: Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52-week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet, 2013; 382: 941–50
26. Andrade JA, Kang HC, Greffin S et al: Serum uric acid and disorders of glucose metabolism: The role of glycosuria. Braz J Med Biol Res, 2014; 47: 917–23
27. Lytvyn Y, Škrtić M, Yang GK et al: Glycosuria-mediated urinary uric acid excretion in patients with uncomplicated type 1 diabetes mellitus. Am J Physiol Renal Physiol, 2015; 308: F77–83
28. Chino Y, Samukawa Y, Sakai S et al: SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. Biopharm Drug Dispos, 2014; 35: 391–404
29. Novikov A, Fu Y, Huang W et al: SGLT2 inhibition and renal urate excretion: Role of luminal glucose, GLUT9, and URAT1. Am J Physiol Renal Physiol, 2019; 316: F173–85
30. Facchini F, Chen YD, Hollenbeck CB, Reaven GM: Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA, 1991; 266: 3008–11
31. Oyama C, Takahashi T, Oyamada M et al: Serum uric acid as an obesity-related indicator in early adolescence. Tohoku J Exp Med, 2006; 209: 257–62
32. Tanaka K, Ogata S, Tanaka H et al., Osaka Twin Research Group, Hayakawa K: The relationship between body mass index and uric acid: A study on Japanese adult twins. Environ Health Prev Med, 2015; 20: 347–53
33. Fabregat I, Revilla E, Machado A: Short-term control of the pentose phosphate cycle by insulin could be modulated by the nadph/nadp ratio in rat adipocytes and hepatocytes. Biochem Biophys Res Commun, 1987; 146: 920–25
34. Lin KC, Lin HY, Chou P: The interaction between uric acid level and other risk factors on the development of gout among asymptomatic hyperuricemic men in a prospective study. J Rheumatol, 2000; 27: 1501–5
35. Iseki K, Oshiro S, Tozawa M et al: Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. Hypertens Res, 2001; 24: 691–97
36. Chonchol M, Shlipak MG, Katz R et al: Relationship of uric acid with progression of kidney disease. Am J Kidney Dis, 2007; 50: 239–47
37. Ishizaka N, Ishizaka Y, Toda E et al: Association between serum uric acid, metabolic syndrome, and carotid atherosclerosis in Japanese individuals. Arterioscler Thromb Vasc Biol, 2005; 25: 1038–44
38. Ward HJ: Uric acid as an independent risk factor in the treatment of hypertension. Lancet, 1998; 352: 670–71
39. Alderman MH, Cohen H, Madhavan S, Kivlighn S: Serum uric acid and cardiovascular events in successfully treated hypertensive patients. Hypertension, 1999; 34: 144–50
40. Zoppini G, Targher G, Negri C et al: Elevated serum uric acid concentrations independently predict cardiovascular mortality in type 2 diabetic patients. Diabetes Care, 2009; 32: 1716–20
41. Park JH, Jin YM, Hwang S et al: Uric acid attenuates nitric oxide production by decreasing the interaction between endothelial nitric oxide synthase and calmodulin in human umbilical vein endothelial cells: A mechanism for uric acid-induced cardiovascular disease development. Nitric Oxide, 2013; 32: 36–42
42. Kaku K, Kiyosue A, Inoue S et al: Efficacy and safety of dapagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise. Diabetes Obes Metab, 2014; 16: 1102–10.

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