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Factors Influencing Change in Serum Uric Acid After Administration of the Sodium-Glucose Cotransporter 2 Inhibitor Luseogliflozin in Patients With Type 2 Diabetes Mellitus

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Abstract

Although sodium-glucose cotransporter 2 (SGLT2) inhibitors lower serum uric acid, their long-term effect on uric acid metabolism is not well understood. We analyzed pooled data from studies wherein patients with type 2 diabetes mellitus received luseogliflozin, an SGLT2 inhibitor. Upon stratifying patients by baseline glycated hemoglobin (HbA_{1c}) or serum uric acid, lower HbA_{1c} or higher serum uric acid level was associated with a greater reduction in serum uric acid after treatment. At week 12 of treatment, significant increases in urinary glucose/creatinine (Cr) ratio and urinary uric acid clearance/Cr clearance ratio (C_{UA}/C_{Cr} ratio) and a significant reduction in serum uric acid were observed. Comparison of the subgroups of patients with a reduction or an increase in serum uric acid showed that the increase subgroup had a higher estimated glomerular filtration rate (eGFR) at baseline, and the eGFR was significantly reduced, associated with a significant reduction in the C_{UA}/C_{Cr} ratio. Multiple regression analysis showed that the reduction in serum uric acid in the luseogliflozin group was strongly associated with baseline high serum uric acid, low HbA_{1c} levels, and an increase in eGFR. Luseogliflozin was shown to reduce serum uric acid by enhancing urinary uric acid excretion in association with increased urinary glucose. Treatment with luseogliflozin resulted in increased serum uric acid in some patients, which may be due to reduced glomerular filtration of uric acid via the tubuloglomerular feedback. SGLT2 inhibitors reduced serum uric acid desirably in patients with type 2 diabetes mellitus with low HbA_{1c} and high serum uric acid.

Keywords

insulin resistance, long term, luseogliflozin, sodium-glucose cotransporter 2 inhibitor, uric acid

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are antidiabetic drugs that reduce blood glucose by inhibiting SGLT2, which is expressed in the proximal tubules of the kidney and is responsible for glucose reabsorption.[1] SGLT2 inhibitors have been reported to have pleiotropic effects, including beneficial effects on blood pressure, body weight, lipids, and hepatic and renal function, in addition to blood glucose– and serum uric acid–lowering effects.[2] Many pooled analyses and meta-analyses have shown that the lowering effect of SGLT2 inhibitors is a class effect.[3–9] Recently, a pooled analysis of data from large clinical studies of canagliflozin showed that canagliflozin significantly suppressed gout.[10] Moreover, real-world data of 300 000 patients with type 2 diabetes mellitus (T2DM) from a nationwide commercial insurance database in the United States showed that SGLT2 inhibitors significantly inhibited the development of gout compared with glucagon-like peptide-1 receptor agonists.[11]

Regarding the relationship between serum uric acid and glucose metabolism, a nutrition survey in the United States showed that serum uric acid increased in the presence of insulin resistance, which precedes the development of diabetes mellitus (DM), and decreased along with a worsening of DM.[12] SGLT2 inhibitors have been reported to reduce serum uric acid by enhancing urinary uric acid excretion through the effect of increased urinary glucose on glucose transporter-9 (GLUT9).[13] This mechanism may also explain the trend toward lower serum uric acid in patients with DM.

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On the other hand, few reports have thoroughly analyzed the long-term effect of SGLT2 inhibitors on serum uric acid levels from the aspect of their mechanism of action. The present study retrospectively analyzed data from phase II and III studies of luseogliflozin, an SGLT2 inhibitor, to determine the long-term effect of luseogliflozin on uric acid metabolism.

Methods

Study Design and Analysis Methodology

This pooled analysis was a retrospective analysis after anonymization on the basis of data obtained from previous clinical studies.[14–16] The clinical studies were conducted in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice after approval by the institutional ethics committee of each participating study site. All participants provided written informed consent before study enrollment.

The clinical studies were 2 phase II studies (JapicCTI-090908[14] and JapicCTI-101191[15]) and 1 phase III study (JapicCTI-111661[16]) studies wherein Japanese patients with T2DM received only luseogliflozin as an antidiabetic drug in a placebo-controlled manner. The duration of treatment was 12 weeks in the phase II studies and 24 weeks in the phase III study, and all 3 studies were placebo-controlled, randomized, double-blind, parallel-group comparative studies and included laboratory variables for 2-hour pooled urine at baseline and week 12 (Table S1). All patients were in the non–insulin-dependent stage, including 5 with gout and 10 treated with uric acid–lowering drugs (allopurinol in all, K^+, Na^+-citrate in 3). Patients in the placebo group were on a dietary treatment and were not treated with antidiabetic medications.

To investigate the effect of baseline glycated hemoglobin (HbA_{1c}) or serum uric acid on change in serum uric acid, patients in the placebo and luseogliflozin groups in the 3 studies were stratified by baseline HbA_{1c} or serum uric acid, and the mean levels of serum uric acid over 24 weeks were calculated for each subgroup. More specifically, patients were classified into 3 subgroups according to baseline HbA_{1c} ($\leq$7.5%, 7.6%-8.4%, and $\geq$8.5%) and 4 subgroups according to baseline serum uric acid ($\leq$ 5.0, 5.1-6.0, 6.1-7.0, and $\geq$7.1 mg/dL). In this analysis, pooled analysis set 1 (a total of 501 patients: 311 in the luseogliflozin group and 190 in the placebo group) was defined as the population of patients in the full analysis set (FAS) of each study who received luseogliflozin at a dose of 2.5 or 5 mg, which are the clinical doses with no dose-response differences in terms of serum uric acid–lowering effect[8] (Figure S1). The FAS included all patients who received at least 1 dose of the study drug and had at least 1 efficacy variable measured after the start of the study treatment. Subsequently, pooled analysis set 2 (a total of 480 patients: 297 in the luseogliflozin group and 183 in the placebo group) was defined as the population in pooled analysis set 1, excluding 11 patients who discontinued drug administration by week 12; 9 patients with missing data on variables at baseline or week 12, when urine was pooled; and 1 patient with outliers in metabolic variables of uric acid. In this analysis set, the variables were compared between the luseogliflozin and placebo groups. Next, the data for the luseogliflozin group were classified into the following 3 subgroups according to the change in serum uric acid from baseline to week 12, and various variables, including those of glucose metabolism, uric acid metabolism, and renal function, were compared among the 3 subgroups: serum uric acid increase group ($\geq$0.1 mg/dL), low-responder group ($-$0.9 to 0 mg/dL), and high-responder group (≤ -1.0 mg/dL) (Figure 1). The urinary clearance of uric acid (C_{UA}) was calculated as (urinary uric acid concentration $\times$ 2-hour urine volume)/(serum uric acid concentration $\times$ 120) $\times$ (1.73/body surface area), and the C_{UA} to creatinine clearance (C_{Cr}) ratio (C_{UA}/C_{Cr} ratio) was calculated as (urinary uric acid concentration $\times$ plasma Cr concentration)/(serum uric acid concentration $\times$ urine Cr concentration) $\times$ 100.[17] The estimated glomerular filtration rate (eGFR) was calculated using the formula developed by the Japanese Society of Nephrology for the Japanese population as follows[18]: (194 $\times$ serum $Cr^{-1.094}$ $\times$ $age^{-0.287}$ for men; and 194 $\times$ serum $Cr^{-1.094}$ $\times$ $age^{-0.287}$ $\times$ 0.739 for women). All HbA_{1c} levels were measured in units specified by the Japan Association for Diabetes Education and Care (JADEC) and converted to National Glycohemoglobin Standardization Program units using the validated formula (HbA_{1c} [%] = 1.02 $\times$ JADEC [%] + 0.25%).[19]

Statistical Analysis

Changes in each variable from baseline were compared using a paired *t*-test, and changes in variables from baseline between the placebo group and the luseogliflozin group were compared using an unpaired *t*-test for homoscedasticity and Aspin-Welch's *t*-test for unequal variance. An analysis of variance or the Bonferroni test was used for comparison among the subgroups. Discrete variables were analyzed using the Steel-Dwass test. The relationships of change in serum uric acid from baseline to week 12 with baseline value and change at week 12 were evaluated using regression analysis for the following variables: age, sex, HbA_{1c}, fasting plasma glucose, urinary glucose excretion, urinary glucose/Cr ratio, homeostasis model

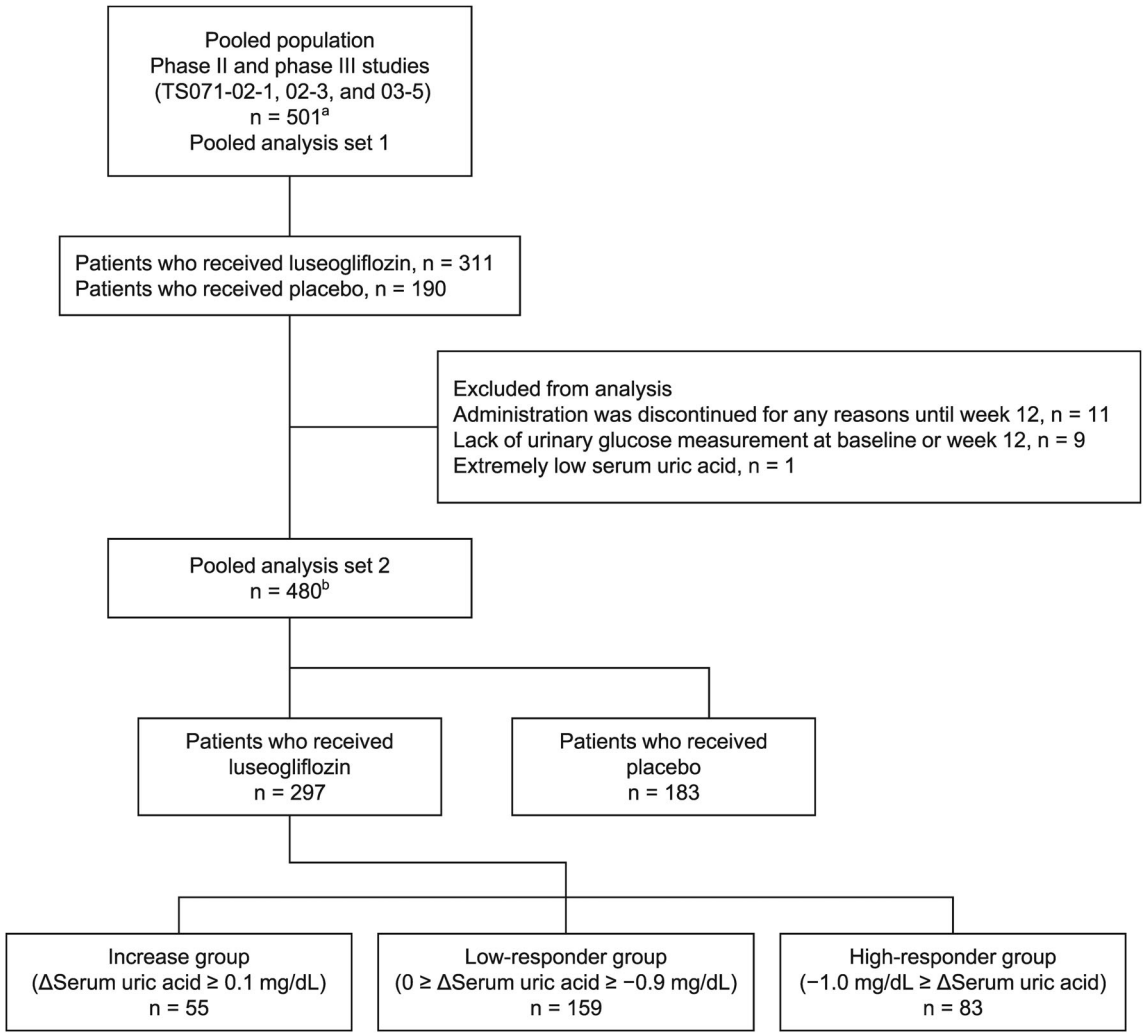

Figure 1. Flowchart of patient disposition. [a]Patients after administration of 2.5 mg and 5 mg of luseogliflozin or placebo. [b]Patients with data for baseline and week 12.

assessment-insulin resistance (HOMA-R), homeostasis model assessment-beta cell function, adiponectin, serum uric acid, urinary uric acid excretion, urinary uric acid/Cr ratio, C_{UA}, C_{UA}/C_{Cr} ratio, serum Cr, urinary Cr excretion, eGFR, urinary Na/Cr ratio, urine pH, urine volume, body weight, hematocrit, uric acid–lowering drug use, antihypertensive drug use, angiotensin receptor blocker use, diuretic use, and lipid-lowering drug use. In addition, baseline HbA_{1c}, baseline serum uric acid, and changes in HOMA-R and eGFR from baseline to week 12 were included as covariates in the adjusted model, and their relationships with change in serum uric acid were evaluated using multiple regression analysis. Statistical analyses were performed using SAS software version 9.04 (SAS Institute Inc., Cary, North Carolina) and SPSS Statistics 27 (IBM, Armonk, New York), and a P value of $<.05$ was considered significant.

Results

To determine the effect of baseline HbA_{1c} or serum uric acid levels on luseogliflozin-induced reduction in serum uric acid, patients in the pooled analysis set 1 were stratified by baseline HbA_{1c} into 3 subgroups ($\leq$7.5%, 7.6%-8.4%, and $\geq$8.5%). Notably, a lower baseline HbA_{1c} was associated with a greater reduction in serum uric acid in the luseogliflozin group than in the placebo group (Figure 2A). Similarly, when patients were stratified by baseline serum uric acid into 4 subgroups ($\leq$5.0, 5.1-6.0, 6.1-7.0, and $\geq$7.1 mg/dL), a higher baseline serum uric acid was associated with a greater reduction in serum uric acid in the luseogliflozin group than in the placebo group (Figure 2B). The reduction in serum uric acid was significantly greater in the luseogliflozin group than in the placebo group from week 2 onward until the final time point in the 3 studies (Figure S1).

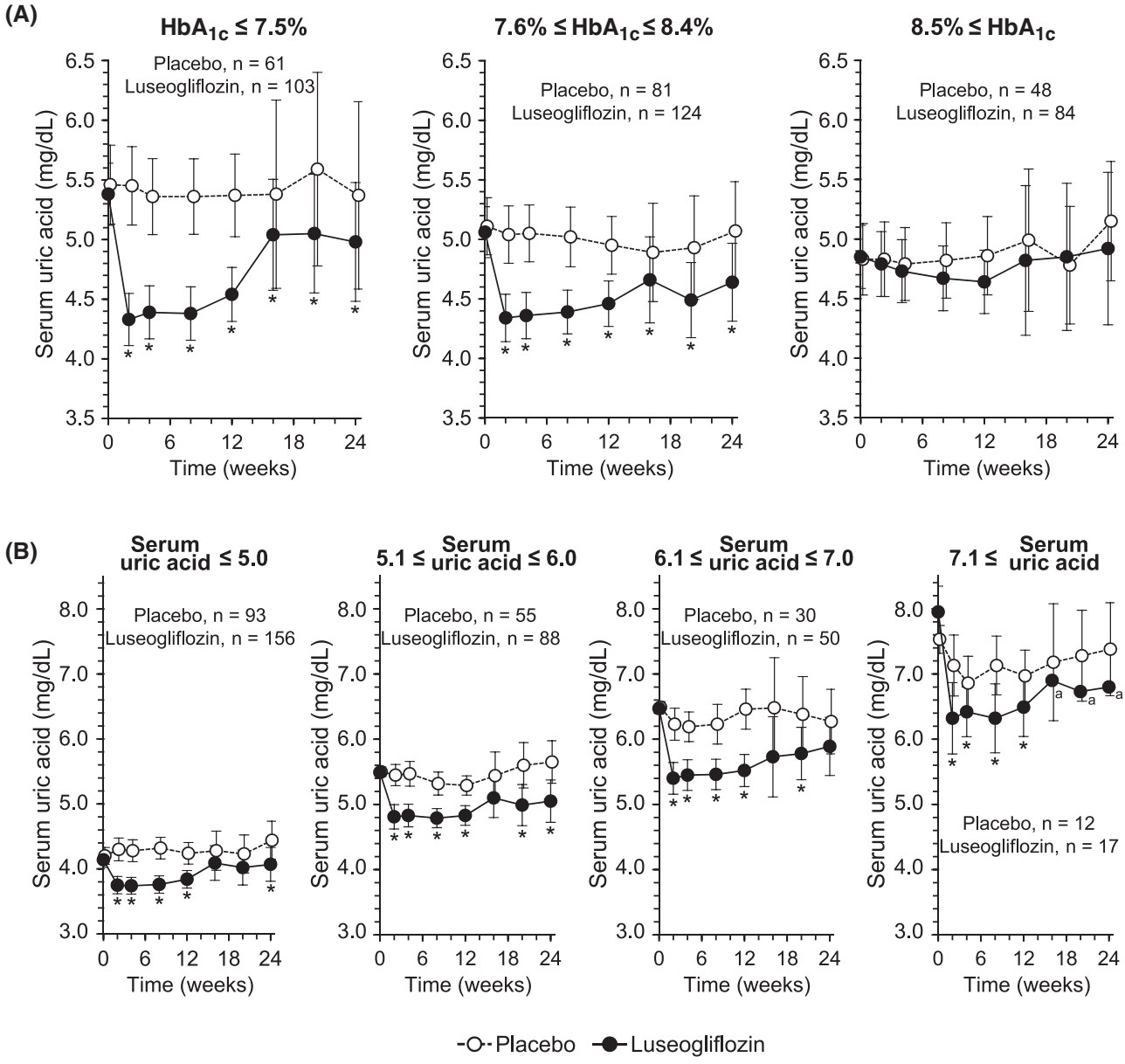

Figure 2. Change in serum uric acid levels after treatment with luseogliflozin or placebo. Change in serum uric acid stratified by baseline HbA_{1c} (a) or serum uric acid levels (b). HbA_{1c}, glycated hemoglobin. Data are expressed as mean ± 95% confidence interval. Differences between the changes from baseline in the luseogliflozin and placebo groups were analyzed using an unpaired *t*-test. *$P < .05$. [a]Data are expressed as mean without 95% confidence interval; n = 3.

To determine the changes in uric acid metabolism and glucose metabolism in the luseogliflozin group, changes in respective representative variables at week 12 were compared between the luseogliflozin and placebo groups (Figure 3). The luseogliflozin group had a significantly reduced serum uric acid and a significantly increased C_{UA}/C_{Cr} ratio compared with the placebo group ($P < .05$ for both), but the urinary uric acid/Cr ratio was not significantly different (Figure 3). In the luseogliflozin group, HbA_{1c} and HOMA-R were significantly reduced compared with the placebo group ($P < .05$ for both), and the urinary glucose/Cr ratio was significantly increased ($P < .05$).

To determine the relationship of luseogliflozin-induced change in serum uric acid with baseline value and change at week 12 for clinical variables, a single regression analysis between change in serum uric acid at week 12 and baseline value or change at week 12 for other variables in the pooled analysis set 2 was performed (Table 1). A highly positive correlation was observed between change in serum uric acid and baseline HbA_{1c}, fasting plasma glucose, urinary

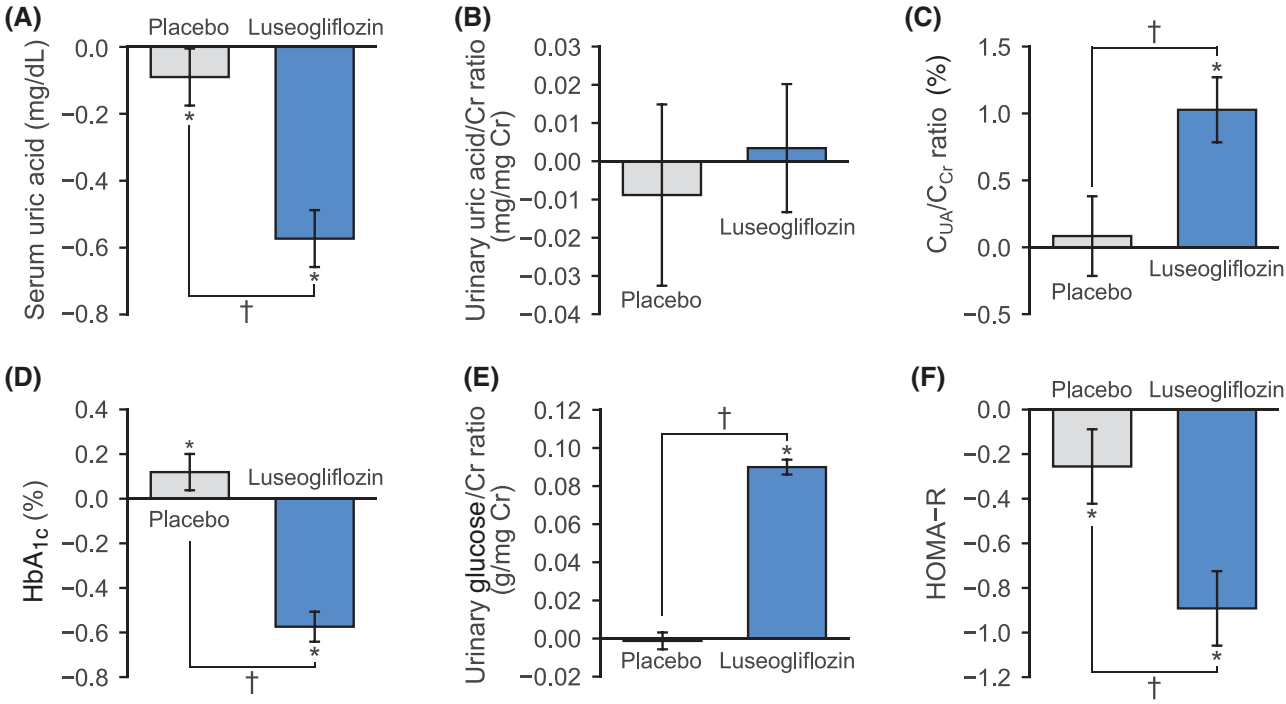

Figure 3. Changes in metabolic variables of uric acid and glucose after 12 weeks of treatment with luseogliflozin or placebo. C_{Cr}, urinary creatinine clearance; Cr, creatinine; C_{UA}, urinary uric acid clearance; HbA_{1c}, glycated hemoglobin; HOMA-R, homeostasis model assessment-insulin resistance. Data are expressed as mean ± 95% confidence interval (placebo, n = 183; luseogliflozin, n = 297). Differences between the changes from baseline were analyzed using a paired *t*-test. Differences between the changes from baseline in the luseogliflozin and placebo groups were analyzed using an unpaired *t*-test or Aspin-Welch's *t*-test. $^{*}P < .05$ versus baseline. $^{\dagger}P < .05$ versus the placebo group in the change from baseline.

glucose excretion, urinary glucose/Cr ratio, C_{UA}, or C_{UA}/C_{Cr} ratio, and a highly negative correlation was noted between baseline levels and change in serum uric acid ($P < .001$ for all). Moreover, a highly negative correlation was observed between change in fasting plasma glucose, C_{UA}, C_{UA}/C_{Cr} ratio, or eGFR at week 12 and change in serum uric acid ($P < .001$ for all). No significant correlation was noted between baseline HOMA-R and change in serum uric acid, but a weak negative correlation was observed between change in HOMA-R at week 12 and change in serum uric acid ($P < .05$; Table 1).

Furthermore, because serum uric acid was increased after luseogliflozin treatment in some patients, patients in the pooled analysis set 2 were stratified into a serum uric acid increase group, a low-responder group, and a high-responder group according to the change in serum uric acid at week 12. Clinical variables in these groups are presented in Table 2. The serum uric acid increase group comprised 55 patients (19%), with a mean change of +0.4 mg/dL and a maximum change of +1.0 mg/dL; the low-responder group comprised 159 patients (54%), with a mean change of −0.4 mg/dL; and the high-responder group comprised 83 patients (28%), with a mean change of −1.5 mg/dL and a maximum change of −3.2 mg/dL. Although no significant difference in change in HbA_{1c} or urinary glucose/Cr ratio at week 12 was observed among the 3 groups, the C_{UA}/C_{Cr} ratio at week 12 was increased in the 2 responder groups but decreased in the serum uric acid increase group ($P < .05$ versus the responder groups). In addition, the eGFR at week 12 was unchanged in the low-responder group and increased in the high-responder group but was significantly reduced in the serum uric acid increase group ($P < .05$ versus the responder groups).

With baseline HbA_{1c}, baseline serum uric acid, and changes in HOMA-R and eGFR at week 12 as covariates, the effects of these covariates on covariate-adjusted change in serum uric acid were evaluated using multiple regression analysis. Notably, baseline HbA_{1c}, baseline serum uric acid, and change in eGFR significantly contributed to the covariate-adjusted change in serum uric acid. No correlation was noted between the change in HOMA-R and covariate-adjusted change in serum uric acid (Table S2).

Discussion

While it is well known that SGLT2 inhibitors reduce serum uric acid, only a few reports have thoroughly analyzed the clinical efficacy based on the mechanism of action. The lowering effect of SGLT2 inhibitors on serum uric acid has been reported to be due to a short-term mechanism via the transport protein

Table 1. Association Between Clinical Parameters and Changes in Serum Uric Acid at Week 12 After Administration of Luseogliflozin

		Single Regression				Single Regression		
Factors	Baseline	Slope	*r*	*P*	Change at Week 12	Slope	*r*	*P*
Age, y	58 ± 10	−0.002	−0.020	.725				
Male, n (%)	207 (70)	0.161	0.100	.086				
Female, n (%)	90 (30)							
HbA_{1c}, 4.6%-6.2%	8.1 ± 0.9	0.297	0.346	<.001	−0.6 ± 0.6[a]	−0.179	−0.142	.015
Fasting plasma glucose, 70-109 mg/dL	157 ± 29	0.008	0.297	<.001	−24 ± 26[a]	−0.007	−0.240	< .001
Urinary glucose, g/2 h	2.9 ± 3.0	0.067	0.273	<.001	8.7 ± 4.8[a]	−0.024	−0.155	.007
Urinary glucose/Cr ratio, g/mg Cr	0.02 ± 0.02	9.551	0.305	<.001	0.09 ± 0.03[a]	−3.467	−0.159	.006
HOMA-R	2.8 ± 2.3	0.030	0.091	.117	−0.9 ± 1.5[a]	−0.075	−0.147	.011
HOMA-β, %	29 ± 21	−0.004	−0.110	.059	2 ± 12[a]	0.003	0.057	.331
Adiponectin, ≥4.0 μg/mL[b]	6.2 ± 2.7	0.002	0.008	.945	0.6 ± 0.8[a]	−0.163	−0.216	.058
Serum uric acid, male, 3.8-7.0; female, 2.5-7.0 mg/dL	5.1 ± 1.3	−0.282	−0.475	<.001	−0.6 ± 0.7[a]	1.000	1.000	…
Urinary uric acid, mg/2 h	68 ± 29	0.000	−0.018	.758	−9 ± 24[a]	0.001	0.043	.459
Urinary uric acid/Cr ratio, g/g Cr	0.6 ± 0.2	−0.056	−0.012	.832	0.0 ± 0.1; n.s.	0.283	0.056	.339
C_{UA}, mL/min	11.8 ± 6.0	0.026	0.213	<.001	−0.3 ± 4.8; n.s.	−0.047	−0.304	< .001
C_{UA}/C_{Cr} ratio, %	8.2 ± 3.0	0.067	0.271	<.001	1.0 ± 2.1[a]	−0.132	−0.378	< .001
Serum Cr, male, 0.61-1.04; female, 0.47-0.79 mg/dL	0.7 ± 0.2	−0.250	−0.051	.383	0.0 ± 0.1; n.s.	3.953	0.315	< .001
Urinary Cr, mg/2 h	121 ± 47	0.000	0.007	.902	−15 ± 38[a]	0.000	−0.017	.772
eGFR, mL/min/1.73 m^2	85 ± 18	0.006	0.141	.015	−1 ± 8; n.s.	−0.026	−0.277	<.001
Urinary Na/Cr ratio, g/g Cr	3.2 ± 1.7	0.041	0.092	.114	0.8 ± 1.9[a]	−0.046	−0.119	.041
Urine pH, 5.0-7.5	6.1 ± 0.7	0.071	0.065	.262	−0.5 ± 0.7[a]	−0.070	−0.062	.291
Urine volume, mL/2 h	219 ± 161	0.001	0.136	.019	78 ± 162[a]	−0.001	−0.130	.026
Body weight, kg	68 ± 13	0.001	0.021	.719	−2 ± 1[a]	−0.053	−0.096	.099
Hematocrit, male 39.7-52.4%; female, 34.8-45.0%	42 ± 3	−0.004	−0.017	.776	2 ± 2[a]	0.022	0.063	.278
Uric acid–lowering drugs, n (%)[c]	7 (2)	−0.086	−0.018	.763				
Antihypertensive drugs, n (%)	112 (38)	0.239	0.156	.007				
Angiotensin receptor blockers, n (%)	73 (25)	0.170	0.098	.091				
Diuretics, n (%)	9 (3)	−0.016	−0.004	.948				
Lipid-lowering drugs, n (%)	87 (29)	0.012	0.008	.897				

C_{Cr}, urinary creatinine clearance; Cr, creatinine; C_{UA}, urinary uric acid clearance; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HOMA-R, homeostasis model assessment-insulin resistance; HOMA-β, homeostasis model assessment-beta cell function; n.s., not significant; *r*, regression coefficient.
Data are expressed as mean ± standard deviation (n = 297).
[a] Statistically significant difference versus baseline, based on a paired *t*-test.
[b] n = 78.
[c] Allopurinol was used in all cases, and K^+, Na^+-citrate was used in 2.

GLUT9[13] and also appears to be mediated by improvement in insulin resistance over a longer duration.[12,20,21] Ouchi et al[6] performed a pooled analysis of patients with T2DM treated with tofogliflozin and reported that the effect appeared during the early stage of treatment, with the greatest reduction in serum uric acid observed in patients with the lowest baseline HbA_{1c}. Kuriyama et al[22] retrospectively analyzed spot

Table 2. Clinical Parameters at Baseline and Week 12 in 3 Groups Stratified by Change in Serum Uric Acid After Administration of Luseogliflozin

	Increase Group, ΔSerum Uric Acid ≥ 0.1 mg/dL (n = 55)			Low-Responder Group, 0 ≥ ΔSerum Uric Acid ≥ −0.9 mg/dL (n = 159)			High-Responder Group, −1.0 mg/dL ≥ ΔSerum Uric Acid (n = 83)		
Factors	Baseline	Week 12	Change at Week 12	Baseline	Week 12	Change at Week 12	Baseline	Week 12	Change at Week 12
Age, y	56 ± 11			58 ± 10			59 ± 9		
Male, n (%)	45 (82)			108 (68)			54 (65)		
Female, n (%)	10 (18)			51 (32)			29 (35)		
HbA_{1c}, %	8.5 ± 1.0[a,b]	7.8 ± 0.8[a,b,c]	−0.7 ± 0.7	8.1 ± 0.8[b]	7.5 ± 0.6[b,c]	−0.6 ± 0.6	7.7 ± 0.7	7.2 ± 0.5[c]	−0.5 ± 0.4
Fasting plasma glucose, mg/dL	171 ± 35[a,b]	139 ± 22[b,c]	−32 ± 30[b]	157 ± 27[b]	133 ± 20[c]	−24 ± 25	146 ± 24	130 ± 15[c]	−16 ± 21
Urinary glucose, g/2 h	4.1 ± 3.8[b]	12.6 ± 4.9[c]	8.5 ± 4.5	3.0 ± 2.6[b]	11.4 ± 5.7[c]	8.3 ± 4.9	2.0 ± 2.9	11.6 ± 5.9[c]	9.6 ± 4.8
Urinary glucose/Cr ratio, g/mg Cr	0.03 ± 0.03[b]	0.12 ± 0.05[c]	0.08± 0.04	0.03 ± 0.02[b]	0.11 ± 0.04[c]	0.09 ± 0.03	0.02 ± 0.02	0.11 ± 0.04[c]	0.10 ± 0.03
HOMA-R	3.1 ± 2.5	1.9 ± 1.4[c]	−1.1 ± 1.5	2.8 ± 2.5	1.9 ± 1.6[c]	−0.9 ± 1.6	2.5 ± 1.5	1.8 ± 1.2[c]	−0.6 ± 1.1
HOMA-β, %	25.9 ± 19.1	28.5 ± 19.9[c]	2.6 ± 8.3	28.3 ± 20.9	30.8 ± 24.7[c]	2.5 ± 12.5	32.0 ± 20.9	32.4 ± 20.7	0.4 ± 13.6
Adiponectin, μg/mL	5.8 ± 2.9[d]	6.0 ± 3.0[d]	0.2 ± 0.8[b,d]	6.3 ± 2.8[e]	6.9 ± 3.2[c,e]	0.6 ± 0.8[e]	6.2 ± 2.2[f]	7.1 ± 2.8[c,f]	0.9 ± 0.9[f]
Serum uric acid, mg/dL	4.5 ± 1.0[b]	4.9 ± 1.1[a,b,c]	0.4 ± 0.3[a,b]	4.9 ± 1.2[b]	4.5 ± 1.2[c]	−0.4 ± 0.3[b]	5.9 ± 1.2	4.4 ± 1.0[c]	−1.5 ± 0.5
Urinary uric acid, mg/2 h	70 ± 23	64 ± 24[c]	−7 ± 23	66 ± 27	58 ± 26[c]	−8 ± 24	71 ± 37	58 ± 27[c]	−13 ± 24
Urinary uric acid /Cr ratio, g/g Cr	0.6 ± 0.1	0.6 ± 0.2	0.0 ± 0.1	0.6 ± 0.2	0.6 ± 0.1	0.0 ± 0.1	0.6 ± 0.2	0.6 ± 0.1	0.0 ± 0.2
C_{UA}, mL/min	13.8 ± 7.6[b]	11.3 ± 5.7[c]	−2.5 ± 4.9[a,b]	11.9 ± 5.6	11.6 ± 5.6	−0.3 ± 4.8	10.3 ± 5.3	11.6 ± 5.2[c]	1.3 ± 4.0
C_{UA}/C_{Cr} ratio, %	9.0 ± 3.3[b]	8.7 ± 2.6	−0.3 ± 1.9[a,b]	8.5 ± 3.2[b]	9.5 ± 2.8[c]	1.0 ± 2.0[b]	7.1 ± 2.1	9.0 ± 2.2[c]	1.9 ± 2.1
Serum Cr, mg/dL	0.7 ± 0.2	0.7 ± 0.2[c]	0.0 ± 0.1[a,b]	0.7 ± 0.2	0.7 ± 0.2	0.0 ± 0.1	0.7 ± 0.1	0.7 ± 0.1[c]	0.0 ± 0.1
Urinary Cr, mg/2 h	128 ± 44	113 ± 43[c]	−15 ± 40	118 ± 45	103 ± 48[c]	−15 ± 39	121 ± 54	106 ± 50[c]	−15 ± 34
eGFR, mL/min/ 1.73 m^2	90 ± 21[b]	87 ± 23[c]	−4 ± 9[a,b]	85 ± 17	85 ± 17	−1 ± 8	82 ± 16	84 ± 17[c]	2 ± 6
Urinary Na/Cr ratio, g/g Cr	3.3 ± 1.6	3.7 ± 2.2	0.3 ± 2.0	3.2 ± 1.7	4.0 ± 1.9[c]	0.8 ± 1.9	3.0 ± 1.7	4.0 ± 1.9[c]	0.9 ± 1.8
Urine pH	6.2 ± 0.6	5.6 ± 0.6[c]	−0.5 ± 0.6	6.1 ± 0.7	5.7 ± 0.5[c]	−0.5 ± 0.6	6.1 ± 0.7	5.6 ± 0.6[c]	−0.4 ± 0.7
Urine volume, mL/2 h	259 ± 193	316 ± 198[c]	57 ± 134	212 ± 137	292 ± 163[c]	80 ± 157	209 ± 179	295 ± 180[c]	87 ± 187
Body weight, kg	71 ± 13	69 ± 13[c]	−2 ± 1	68 ± 13	66 ± 13[c]	−2 ± 1	67 ± 13	66 ± 13[c]	−2 ± 1
Hematocrit, %	43 ± 3	45 ± 3[c]	3 ± 2	42 ± 4	45 ± 4[c]	2 ± 2	42 ± 4[g]	45 ± 4[c]	2 ± 2[g]
Uric acid–lowering drugs, n (%)	1 (2)[h]			4 (3)[i]			2 (2)[h]		
Antihypertensive drugs, n (%)	29 (53)[b]			58 (36)			25 (30)		
Angiotensin receptor blockers, n (%)	20 (36)			37 (23)			16 (19)		
Diuretics, n (%)	2 (4)			4 (3)			3 (4)		
Lipid-lowering drugs, n (%)	16 (29)			47 (30)			24 (29)		

C_{Cr}, urinary creatinine clearance; Cr, creatinine; C_{UA}, urinary uric acid clearance; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HOMA-R, homeostasis model assessment-insulin resistance; HOMA-β, homeostasis model assessment-beta cell function.

Data are expressed as mean ± standard deviation (n = 297).

[a] Statistically significant difference versus the low-responder group, based on the Bonferroni test for continuous variables or Steel-Dwass test for discrete variables.

[b] Statistically significant difference versus the high-responder group, based on the Bonferroni test for continuous variables or Steel-Dwass test for discrete variables.

[c] Statistically significant difference versus baseline, based on a paired *t*-test.

[d] n = 15.

[e] n = 49.

[f] n = 14.

[g] n = 82.

[h] Allopurinol was used.

[i] Allopurinol was used in all cases, and K^+, Na^+-citrate was used in 2.

urine data from 90 patients treated with an SGLT2 inhibitor and showed that the reduced serum uric acid was associated with increased urine glucose and increased C_{UA}/C_{Cr} ratio. These reports support the short-term urine glucose–induced, GLUT9-mediated mechanism.[13]

The present pooled analysis of luseogliflozin also showed that the reduction in serum uric acid in the luseogliflozin group was significant from week 2 onward, with a greater reduction in serum uric acid noted in patients with a lower baseline HbA_{1c}, consistent with previous reports. In addition, this analysis showed for the first time that the reduction in serum uric acid was greater in the group with higher serum uric acid at baseline. While Zhao et al[8] performed a meta-analysis of 6 SGLT2 inhibitors in 34 941 patients from 62 studies and showed that the mean reduction in serum uric acid was ≈0.6 mg/dL; our analysis showed that the reduction in the luseogliflozin group was 1.6 mg/dL in the subgroup with a serum uric acid of ≥7.1 mg/dL—a definition of hyperuricemia in Japan[17]—at week 2 (0.4 mg/dL reduction in the placebo group; Figure 2B). This finding suggests that SGLT2 inhibitors reduce serum uric acid more markedly in patients requiring serum uric acid correction. At week 12, a significant reduction in serum uric acid and a significant increase in the C_{UA}/C_{Cr} ratio from baseline were observed without a change in urinary uric acid/Cr ratio in the luseogliflozin group (Figure 3). While continued treatment with luseogliflozin results in reduced serum uric acid, which may in turn result in reduced uric acid excretion to the amount produced, the C_{UA}/C_{Cr} ratio—a parameter not affected by substrate concentration—accurately reflects the progress of urinary uric acid excretion. In the present analysis, the C_{UA}/C_{Cr} ratio calculated from 2-hour pooled urine samples in the luseogliflozin group versus the placebo group strongly supported the urine glucose–induced mechanism of urinary uric acid excretion. On the other hand, the uric acid/Cr ratio in urine, which is the major route of excretion, was not significantly changed in the luseogliflozin group, indicating that the effect of luseogliflozin on uric acid production may be limited.

SGLT2 inhibitors, which reduce blood glucose through an insulin-independent mechanism, reduce serum insulin and improve insulin resistance.[14–16] Therefore, a long-term reduction in serum uric acid mediated by improvement in insulin resistance is expected.[12,20,21] In the present pooled analysis, HOMA-R, which reflects insulin resistance, was significantly reduced at week 12 in the luseogliflozin group ($P < .05$; Table 1). However, the reduction in HOMA-R tended to be greater in the serum uric acid increase group than in the responder groups (Table 2), showing a weak negative correlation between change in HOMA-R and change in serum uric acid ($P < .05$; Table 1), contrary to the assumption. Adiponectin, which is associated with insulin resistance, was also significantly increased at week 12 in the luseogliflozin group ($P < .05$; Table 1), but there was no correlation between the baseline value or change at week 12 for adiponectin and change in serum uric acid (Table 1). A multiple regression analysis adjusted for confounding factors showed no significant correlation between change in HOMA-R and change in serum uric acid (Table S2). Based on the above, it is unlikely that serum uric acid is reduced because of an improvement in insulin resistance, at least as early as week 12.

When patients in the luseogliflozin group were stratified into a serum uric acid increase group, a low-responder group, and a high-responder group according to the change in serum uric acid at week 12, 28% of patients were included in the high-responder group with a mean change of −1.5 mg/dL and a maximum change of −3.2 mg/dL (Table 2). On the other hand, 19% of patients were included in the serum uric acid increase group, with a significantly higher HbA_{1c} ($P < .05$ versus the responder groups) and significantly lower serum uric acid ($P < .05$ versus the high-responder group) than in the other groups at baseline, consistent with the trends mentioned above. In the serum uric acid increase group, the C_{UA}/C_{Cr} ratio was not increased and the eGFR was significantly reduced in contrast to the responder groups ($P < .05$; Table 2), without any difference in the increase in urinary glucose excretion. Because luseogliflozin reduces glomerular filtration through the tubuloglomerular feedback mechanism, serum uric acid may have been increased.[23] The eGFR in the serum uric acid increase group tended to be higher at baseline ($P < .05$ versus the high-responder group), suggesting glomerular hyperfiltration because of DM. Thus, the increase in serum uric acid may have been due to luseogliflozin-induced improvement in hyperfiltration. The mean level of serum uric acid in the serum uric acid increase group at week 12 was 4.9 mg/dL, which did not appear to increase to a diagnostically high level.

The present analysis highlighted the importance of both glucose and uric acid metabolism at baseline as well as of posttreatment changes in urinary excretion clearance of uric acid and eGFR in lowering serum uric acid (Figure 4). Regardless of the precise mechanism, the lowering effect on serum uric acid by SGLT2 inhibitors is well established,[3–9] and the long-term uricosuric action may lead to a reduction in the uric acid pool in the body and contribute to the reduced risk of gout reported in other studies.[10,11] In addition, a meta-analysis of placebo- or active comparator–controlled studies with a duration of ≥52 weeks reported that SGLT2 inhibitors were not associated with an increased

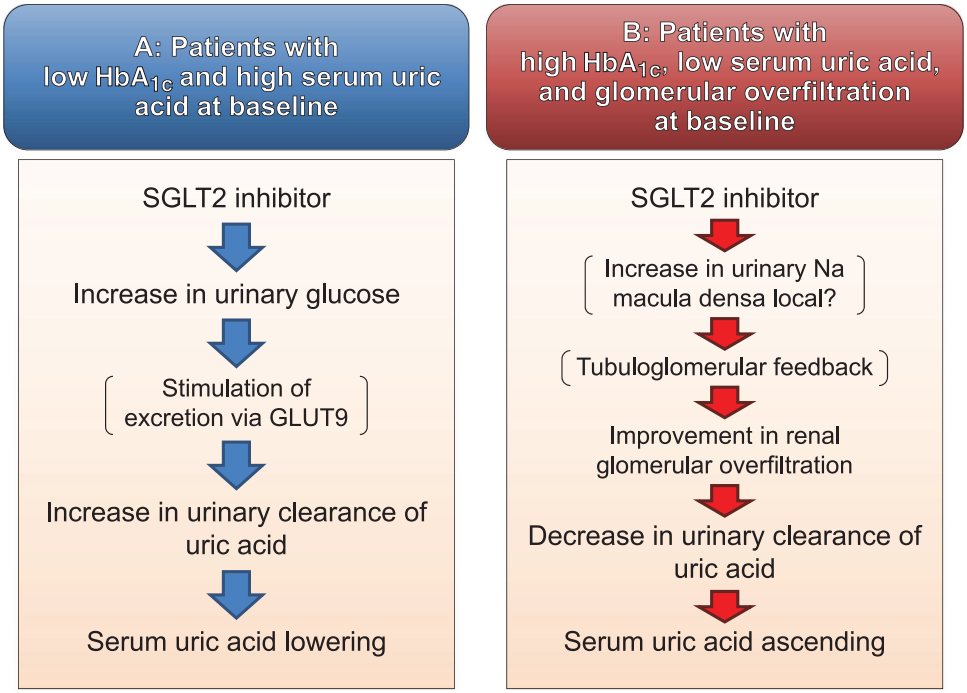

Figure 4. Hypothesis of patient types influencing change in serum uric acid after treatment with an SGLT2 inhibitor in patients with type 2 diabetes mellitus. GLUT9, glucose transporter-9; HbA_{1c}, glycated hemoglobin; SGLT2, sodium-glucose cotransporter-2.

risk of nephrolithiasis.[24] While it is indicated that reduced serum uric acid may contribute to reduced renal and cardiovascular risks,[25–27] further studies are needed to determine whether the lowering effect on serum uric acid by SGLT2 inhibitors contributes to the risk reduction.

Nonetheless, the present analysis had a few limitations. Because the studies were aimed at developing an antidiabetic drug, not many patients with high serum uric acid levels were included in the analysis. Moreover, the number of patients was small after week 12, and the 2-hour pooled urine was collected from all patients only at baseline and week 12.

In conclusion, this analysis thoroughly showed for the first time that the reduction in serum uric acid was greater in patients with higher serum uric acid before SGLT2 inhibitor administration, and that SGLT2 inhibitors reduced serum uric acid by promoting urinary uric acid excretion. Hence, SGLT2 inhibitors are expected to reduce serum uric acid desirably and consistently in patients with T2DM with high serum uric acid requiring reduction.

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Conflicts of Interest

Y.C. is an employee of Taisho Pharmaceutical. M.K. declares no conflicts of interest. I.H. has received scholarship donations from Taisho Pharmaceutical, Mochida Pharmaceutical, Fuji Yakuhin, Teijin Pharma, and Sanwa Kagaku Kenkyusho.

Data-Sharing Statement

The data generated and/or analyzed during the current study that were used to support the findings of the study were supplied by Taisho Pharmaceutical Co., Ltd. under license and, therefore, cannot be made freely available. Requests for access to these data should be made to the corresponding author.

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