Review Article

Effects of antidiabetic drugs on the level of serum uric acid in patients who have type 2 diabetes

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ABSTRACT

إن فرط حمض يوريك الدم ومرض السكري من النوع الثاني (T2DM) مترابطان، حيث أن كل اضطراب يزيد من خطر الإصابة بالآخر. بعض الأدوية المضادة لمرض السكر قد تقلل من مستوى حمض اليوريك في الدم (SUA). تصف هذه المراجعة السردية تأثيرات الأدوية المضادة لمرض السكر المتعددة على مستوى SUA وآليات عملها المحتملة في المرضى الذين يعانون من T2DM. أظهرت النتائج أن مثبطات ناقل جلوكوز الصوديوم 2- (SGLT2is)، والثيازوليدين ديون، والميتفورمين، والليناجليبتين قللت من مستوى الـ SUA؛ أدى الأنسولين وسيتاجليبتين والألوجليبتين إلى زيادة الـ SUA؛ ولم يكن لمنبهات مستقبلات الببتيد 1- الشبيهة بالجلوكاجون (GLP-1 RAs) والسلفونيل يوريا ومثبطات ألفا جلوكوزيداز تأثير يذكر على SUA. يبدو أن SGLT2is له التأثير الأكبر على خفض SUA، ربما لأنه يقلل من استقلاب مسار فوسفات البنتوز ويزيد من إفراز الكلى لليورات عن طريق تغيير ناقلات حمض اليوريك الأنبوبي الكلوي. من بين جميع الأدوية المضادة لمرض السكر المستخدمة حاليًا، يبدو أن SGLT2is هو الخيار العلاجي الواعد لمرضى T2DM الذين يعانون من فرط حمض يوريك الدم.

Hyperuricemia and type 2 diabetes mellitus (T2DM) are interconnected, in that each disorder increases risk for the other. Some antidiabetic drugs may decrease the level of serum uric acid (SUA). This narrative review describes the effects of multiple antidiabetic drugs on the SUA level and their possible mechanisms of action in patients with T2DM. The results showed that sodium glucose contransporter-2 inhibitors (SGLT2is), thiazolidinediones, metformin, and linagliptin decreased the SUA; insulin, sitagliptin, and alogliptin increased the SUA; and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sulfonylureas, and alpha-glucosidase inhibitors had little effect on the SUA. Sodium glucose contransporter-2 inhibitors appeared to have the greatest effect on lowering SUA, possibly because they reduce pentose phosphate pathway metabolism and increase the renal excretion of urate by altering renal tubular uric acid transporters. Among all antidiabetic drugs currently used, SGTL2is appeared to be the most promising therapeutic option for T2DM patients with hyperuricemia.

Keywords: serum uric acid, hyperuricemia, type 2 diabetes mellitus, antidiabetic drugs, cardiovascular disease

Saudi Med J 2025; Vol. 46 (3): 213-225
doi: 10.15537/smj.2025.46.3.20240920

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The ultimate step of purine catabolism is the xanthine oxidoreductase-mediated oxidation of hypoxanthine to uric acid (UA). The kidneys clear approximately 60-70% of serum UA from the body, and intestinal enterocytes clear the other 30-40%.[1] Hyperuricemia, which is conventionally considered to be a serum UA (SUA) level over 420 µmol/L (the solubility limit of monosodium urate [MSU] crystals in plasma) can be caused by the decreased excretion of UA, and less commonly by the increased production of UA.[2] Specific polymorphisms in genes that control UA production and the urinary or intestinal elimination of UA can cause hyperuricemia.[3,4] Obesity, metabolic syndrome, and consumption of excessive sugars or purines can also cause hyperuricemia.[5]

Numerous large epidemiological studies and meta-analyses have consistently shown a strong association between serum urate level and several cardiovascular and metabolic disorders and risk factors.[6,7] For example, hyperuricemia increases the risk for hypertension, diabetes, heart disease, atrial fibrillation, myocardial infarction, heart failure, cerebrovascular events, and chronic kidney disease (CKD).[8,9] The 2021 CARDIA study demonstrated that males and females whose SUA levels increased the most over a 10-year period had a 2.89-fold increased risk of heart disease, heart failure, or a cerebrovascular event relative to a group whose UA level remained stable.[10]

The prevalences of hyperuricemia and type 2 diabetes mellitus (T2DM) have increased globally during recent

decades, and many studies have shown that these 2 metabolic diseases are interconnected. Thus, diabetes and obesity increase the risk for hyperuricemia, because they can cause renal lesions and the overproduction of UA due to the increased activity of xanthine oxidase and increased lipid peroxidation.[11,12] On the other hand, hyperuricemia is accompanied by decreased glucose tolerance, and this increases the risk for diabetes.[13] A meta-analysis by Kodama et al[14] examined genetic studies that assessed the association between SUA level and diabetes, and identified several genetic variants that were associated with increased UA level, thus establishing a possible causal link of an increased UA level and diabetes. Hyperuricemia in patients who have T2DM also increases the risk of major heart failure and nephropathy.[15,16]

A 2024 meta-analysis examined 31,535 patients (76% with T2DM) and evaluated the effect of a decreased SUA level on cardiovascular outcomes and mortality in patients receiving a sodium-glucose cotransporter 2 inhibitor (SGLT2i). The results showed that a 1 mg/dL decrease of SUA was significantly associated with a decreased risk of the composite of cardiovascular death and hospitalization for heart failure (hazard ratio [HR]=0.64, 95% confidence interval [95% CI]: [0.46-0.88]).[17] Thus, because hyperuricemia is associated with multiple detrimental complications, lowering the SUA is considered essential for T2DM patients because of their increased risk of microvascular and macrovascular diseases.

A healthy lifestyle, with an emphasis on diet, exercise, and weight control, is also beneficial to patients with hyperuricemia and T2DM. For example, SGLT2is, a relatively new class of oral antidiabetics, can also increase weight loss, decrease blood pressure, and possibly lower the serum level of UA.[18] Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) can also regulate hyperglycemia, increase weight loss, and decrease the risk of cardiovascular disease.[19] Antidiabetic drugs that also decrease the level of SUA can be especially advantageous for patients with T2DM and hyperuricemia, because these drugs may eliminate the need for or decrease the necessary dose of traditional UA-lowering drugs and these traditional UA-lowering drugs can cause adverse reactions. It must also be considered that some antidiabetic drugs may increase the level of SUA. Overall, an increased understanding of the effects of antidiabetic drugs on the SUA level in patients with T2DM may help physicians to improve their selection of medications and allow the more effective prevention and treatment of these 2 conditions.

Disclosure. This study was supported by grants from the Department of Science and Technology of Jilin Province (20210303001SF, 20190901006JC, and YDZJ202202CXJD042), and the First Hospital of Jilin University (JDYYZH-2102030), Changchun, China.

The aim of this review was to describe recent research and developments in the use of antidiabetic drugs, especially SGLT2is and GLP-1 RAs, on the SUA level of T2DM patients, and to describe the possible mechanisms of different treatments. We therefore searched PubMed using the terms "uric acid", "hyperuricemia", and "diabetes", along with specific drugs and drug classes. We examined all clinical studies (prospective clinical trials, observational studies, post-hoc analyses, and meta-analyses) that were published prior to April 2024. We ultimately included original studies whose primary or secondary purpose was to examine the effects of different antidiabetic drugs on the SUA level in T2DM patients.

We summarized the clinical responses to different antidiabetic drugs on the SUA levels in patients with T2DM (**Table 1**) and also described the main features of the major studies that examined this effect (**Table 2**). The text below provides more detailed information regarding the effects of specific drugs and drug classes.

Metformin. Metformin is the most commonly administered anti-diabetic drug, although very few studies have examined its effects on the SUA level in patients with T2DM. However, there is some evidence that metformin decreases the SUA level of these patients. For example, Gregorio et al[20] assessed the effect of the addition of metformin to 76 elderly patients with T2DM (31 men, 45 women; mean age: 76.44±1.03 years) that was poorly controlled by sulfonylurea for a one-year period. Their results showed that metformin decreased the SUA level from 5.88±0.25 to 5.02±0.28 mg/dL ($p<0.05$). Another controlled study examined the effect of metformin in patients with gout and insulin resistance (IR; 28 men and 2 women; mean age: 51 years). Their results showed that it lowered the SUA concentration from 9.57±1.84 to 7.44±1.81 mg/dL ($p<0.01$), and that 11 patients developed normouricemia (<6.0 mg/dL) after 12 months of metformin therapy.[21] Notably, the authors of this study found that the normouricemic effect of metformin was unrelated to the renal excretion of UA or decreased body weight, and they hypothesized that metformin decreased UA production in these patients due to metformin-mediated decrease in the synthesis of free fatty acids.[21] Another study that examined 50 obese females (mean age: 43.58±1.40 years)

reported that the SUA level decreased from 5.52±0.20 to 4.78±0.12 mg/dL (p<0.0001) after 6 months of metformin treatment.[22] Krzystek-Korpacka et al[23] implemented a one-year weight reduction program for children and adolescents who were overweight or obese, and examined its effect on the SUA level. They reported that the efficacy of metformin in decreasing the SUA level was apparently independent of weight loss.

There is also evidence that a high SUA level is linked with IR. For example, the decreased renal clearance of UA in patients with hyperinsulinemia is related to IR, and other evidence suggested that IR led to increased synthesis of free fatty acids, and that these were eventually metabolized into UA.[24-26] Metformin treatment of patients with T2DM leads to decreased IR and hyperinsulinemia, and this may lead to increased urinary clearance of UA, decreased synthesis of free fatty acids, and a decreased level of SUA.[27] There is also evidence that metformin can lead to weight reduction and appetite suppression. Taken together, normouricemia appears to be one of the many beneficial effects of metformin.

Sulfonylureas. The sulfonylureas have uricosuric effects, but they differ in the strength of this effect.[28] However, none of the sulfonylureas have known normouricemic effects.[29-31] A study of 29 patients with T2DM (19 men, 10 women; mean age: 56.1 years) showed that 12 months of gliclazide treatment did not alter the SUA level.[30] Another study of T2DM patients (17 men, 3 women; mean age: 65 years) showed that a 12-week regimen of gliclazide led to a slightly increased level of plasma UA in the fasting state (5.2±0.9 to 5.6±0.9 mg/dL; p=0.02), but the UA level was unchanged during hyperglycemic conditions.[32] Hussain et al[31] carried out a case-control study of 40 patients with T2DM and showed that glibenclamide did not have normouricemic effects. Kitazawa et al[33] carried out a prospective randomized controlled trial (RCT)

Table 1 - Effects of different antidiabetic drugs on the serum uric acid level in patients with type-2 diabetes mellitus.

Drugs class	Serum UA levels	Mechanisms
Metformin	↓	Ameliorates insulin resistance and hyperinsulinemia, which increases urinary clearance of UA and reduces UA production.
Sulfonylureas		
Glibenclamide	NS	NA
Gliclazide	NS	
Glimepiride	NS	
Dipeptidyl peptidase 4 inhibitors		
Sitagliptin	↑	Unknown
Alogliptin	↑	
Linagliptin	↓	Decreases UA production by suppressing xanthine oxidase activity
Vildagliptin	↓	Unknown
Alpha-glucosidase inhibitors		
Acarbose	No data	NA
Voglibose	NS	NA
Thiazolidinediones		
Troglitazone	↓	Ameliorates insulin resistance and hyperinsulinemia; increases urine pH, which enhances urinary excretion of UA
Rosiglitazone	↓	
Pioglitazone	↓	
Insulin	↑	Increases urate reabsorption via URAT1 or sodium-dependent anion cotransporter in renal proximal tubules
Glucagon-like peptide-1 receptor agonists		
Exenatide	NS	NA
Liraglutide	NS	
Lixisenatide	NS	
Dulaglutide	NS	
Sodium-glucose cotransporter 2 inhibitors		
Empagliflozin	↓	Increases renal excretion of urate by altering renal tubular UA transporters (GLUT9 and URAT1); decreases flux through the pentose phosphate pathway via indirect activation of sirtuin-1, which can inhibit xanthine oxidase
Dapagliflozin	↓	
Canagliflozin	↓	
Luseogliflozin	↓	
Tofogliflozin	↓	
Ipragliflozin	↓	

GLUT9: glucose transporter 9, NA: not applicable, NS: not significant, UA: uric acid, URAT1: urate transporter 1

Table 2 - Studies that evaluated the effects of different antidiabetic drugs on the serum level of uric acid in patients with type-2 diabetes.

Drug classification	References	Study location	Study design	Patients (N)	Age (years)	Gender (M/F)
Metformin* (-)	Gregorio et al[20]	Italy	Before-after study	76	76.44±1.03	31/45
Gliclazide (sulfonylurea)	Kilo et al[30]	USA	Before-after study	29	56.1	19/10
	Suijk et al[32]	Netherlands	Randomized, double-blind, comparator-controlled, intervention trial	44 (gliclazide, n=20; dapagliflozin, n=24)	65 (8)	17/3
Glimepiride (suilfonylurea)	Kitazawa et al[33]	Japan	Multicenter, randomized, open-label, parallel-group trial	64 (glimepiride, n=31; tofogliflozin, n=33)	57.6±9.3	19/12
Sitagliptin (DDP4i)	Matsushima et al[34]	Japan	Multicenter, randomized, open-label, parallel-group trial	241 (sitagliptin, n=120; voglibose, n=121)	63.2±13.8	72/48
	Kutoh et al[35]	Japan	Prospective, nonrandomized, observational study	64	56.0±12.3	50/14
	Tojikubo et al[36]	Japan	Before-after study	73	66±13	41/32
	Fuchigami et al[37]	Japan	Prospective, randomized, open-label, blinded-endpoint, parallel-group trial	331 (sitagliptin, n=163; dapagliflozin, n=168)	57.9±12.1	95/68
Alogliptin (DDP4i)	Kutoh et al[35]	Japan	Prospective, nonrandomized, observational study	55	52.4±13.2	46/9
Linagliptin* (DDP4i)	Tojikubo et al[36]	Japan	Before-after study	73	66±13	41/32
	Yamagishi et al[38]	Japan	Prospective trial	26	69.4±12.4	18/8
Vildagliptin* (DDP4i)	Shimodaira et al[39]	Japan	Retrospective study	62	67.2±12.2	42/20
Voglibose (alpha-glucosidase inhibitor)	Matsushima et al[34]	Japan	Multicenter, randomized, open-label, parallel-group trial	241 (voglibose, n=121; sitagliptin, n=120)	63.2±11.6	71/50
Troglitazone* (thiazolidinedione)	Iwatani et al[42]	Japan	Before-after study	95	61.1±10.3	61/34
Rosiglitazone* (thiazolidinedione)	Seber et al[43]	Turkey	Prospective trial	40	NR	NR
	Macić-Dzanković et al[44]	Sarajevo	Before-after study	21	NR	NR
Pioglitazone* (thiazolidinedione)	Kutoh et al[45]	Japan	Cohort study	19	53.6±12.6	NR
Insulin (-)	MacFarlane et al[47]	USA	Matched cohort study	23	57 (47,64)	11/12
Exenatide (GLP-1 RA)	Dutour et al[51]	France	Prospective randomized clinical trial	44 (exenatide, n=22; reference, n=22)	51±2	13/9
	Muskiet et al[52]	Sweden, Finland, Netherlands	Post-hoc analysis of a randomized, open-label, active-comparator, parallel-group trial	54 (exenatide, n=26; insulin glargine, n=28)	59.7±8.1	16/10
Liraglutide (GLP-1 RA)	Tonneijck et al[53]	Netherlands	Randomized, double-blind, placebo-controlled trial	36 (liraglutide, n=19; placebo, n=17)	63.0±7.0	27/9
	Nakaguchi et al[54]	Japan	Open-label, parallel-group, randomized controlled trial	61 (liraglutide, n=30; empagliflozin, n=31)	67.2±9.0	21/9
	Kurir et al[55]	Croatia	Non-randomized, controlled, interventional study	15	60 (55,68)	all male
	Liakos et al[56]	Greece	Randomized, double blind, placebo-controlled trial	62 (liraglutide, n=31; placebo, n=31)	60.5±12.0	19/12
Lixisenatide (GLP-1 RA)	Tonneijck et al[53]	Netherlands	Randomized, open-label, comparator-controlled trial	35 (lixisenatide, n=17; insulin glulisine, n=18)	61.7±6.6	23/12
Dulaglutide (GLP-1 RA)	Kuchay et al[57]	India	Open-label, parallel-group, randomized controlled trial	64 (dulaglutide,n=32; control,n=32)	46.6±9.1	23/9
	Hirai et al[58]	Japan	Retrospective comparative study	20 (dulaglutide, n=10; liraglutide, n=10)	67.6±9.9	6/4
	Iwasaki et al[59]	Japan	Single-center, open-label, single-arm, pilot study	36	66.7±11.1	15/21
Empagliflozin* (SGLT2i)	You Y et al[61]	NA	Meta-analysis	7801	51–78.4	NR
	Hao Z et al[62]	China	Randomized controlled trial	59 (dapagliflozin, n=29; control,n=30)	57.77±12.29	20/9
Dapagliflozin* (SGLT2i)	Fuchigami et al[37]	Japan	Prospective, randomized, open-label, blinded-endpoint, parallel-group trial	331 (dapagliflozin, n=168; sitagliptin, n=163)	58.3±12.4	104/64
	Suijk et al[32]	Netherlands	Randomized, double-blind, comparator-controlled intervention trial	44 (dapagliflozin, n=24; gliclazide, n=20)	63±7	17/7
Canagliflozin* (SGLT2i)	Davies et al[63]	NR	Post-hoc analysis of pooled data from four randomized placebo-controlled phase III multinational studies	2313 (canagliflozin, n=1667; placebo, n=646)	59.1±9.6	812/855
Luseogliflozin* (SGLT2i)	Seino et al[64]	Japan	Phase II, randomized, placebo-controlled, double-blind, parallel-group study	236 (luseogliflozin,n=182; placebo,n=54)	58.3±9.4	35/26
	Chino et al[65]	Japan	Retrospective study	480 (luseogliflozin, n=297; placebo, n=183)	58±10	207/90
Tofogliflozin* (SGLT2i)	Terauchi et al[66]	Japan	Randomized, double-blind, placebo-controlled multicentre trial	211 (tofogliflozin, n=141; placebo, n=70)	59.1±10.8	90/51
Ipragliflozin* (SGLT2i)	Tanaka et al[67]	Japan	Randomized, open-label, active-controlled, blinded-endpoint trial	30 (ipragliflozin,n=15; control,n=15)	59.1±11.2	8/7
	Tsukagoshi-Yamaguchi et al[68]	Japan	Prospective, multicenter, open-label, blinded-end point, randomized, controlled study	30 (ipragliflozin,n=15; metformin,n=15)	57.8±13.3	9/6
	Nagao et al[69]	Japan	Multicenter, open-label, randomized controlled trial	160 (ipragliflozin,n=77; sitagliptin,n=83)	62(53–67)	44/33

*Drugs that decreased serum uric acid. NA: not applicable, NR: not reported, SMD: standardized mean difference, F: female, M: male, N: number, SGLT2i: sodium-glucose cotransporter 2 inhibitors, GLP-RA: glucagon-like peptide-1 receptor agonists, DDP4i: dipeptidyl peptidase 4 inhibitor

Table 2 - Studies that evaluated the effects of different antidiabetic drugs on the serum level of uric acid in patients with type-2 diabetes (continuation).

Drug classification	References	Study location	BMI (kg/m²)	eGFR (mL/min/ 1.73 m²)	Baseline Serum UA (mg/dL)	HbA1c (%)	Duration of diabetes (years)
Metformin* (-)	Gregorio et al[20]	Italy	NR	NR	5.88±0.25	>9	15.08±1.27
Gliclazide (Sulfonylurea)	Kilo et al[30]	USA	42.8% overweight	NR	NR	10.1±0.44	8.03
	Suijk et al[32]	Netherlands	32±4	89 (22)	5.2±0.9	7.4±0.6	NR
Glimepiride (Suilfonylurea)	Kitazawa et al[33]	Japan	25.4±3.8	88.5±16.2	5.5±1.6	7.5±0.4	7.7±6.7
Sitagliptin (DDP4i)	Matsushima et al[34]	Japan	25.0±4.5	88.0±23.3	5.08±1.14	7.9±1.0	NR
	Kutoh et al[35]	Japan	24.58±4.35	NR	4.91±1.28	10.14±2.19	NR
	Tojikubo et al[36]	Japan	24.6±5.0	78.0±24.4	5.10±1.13	8.19±1.07	15.3±7.8
	Fuchigami et al[37]	Japan	27.9±4.2	78.9±16.9	5.4±1.4	7.8±0.8	5.6±5.8
Alogliptin (DDP4i)	Kutoh et al[35]	Japan	25.69±5.21	NR	4.69±1.60	10.60±2.24	NR
Linagliptin* (DDP4i)	Tojikubo et al[36]	Japan	24.6±4.1	71.8±23.3	5.63±1.24	7.32±1.05	15.3±7.8
	Yamagishi et al[38]	Japan	24.7±3.6	NR	5.5±1.2	7.4±1.4	NR
Vildagliptin* (DDP4i)	Shimodaira et al[39]	Japan	24.7±3.8	71.7±26.8	6.0±1.6	7.7±1.0	NR
Voglibose (alpha-glucosidase inhibitor)	Matsushima et al[34]	Japan	25.1±4.5	83.7±22.2	5.13±1.40	7.8±0.8	NR
Troglitazone* (Thiazolidinedione)	Iwatani et al[42]	Japan	25.4±3.0	NR	5.5±1.2	8.4±1.3	NR
Rosiglitazone* (Thiazolidinedione)	Seber et al[43]	Turkey	30.31±5.3	NR	4.78±1.1	9.95±9.7	NR
	Macić-Dzanković et al[44]	Sarajevo	NR	NR	6.22±1.31	8.55±1.9	NR
Pioglitazone* (Thiazolidinedione)	Kutoh et al[45]	Japan	27.82±6.32	NR	6.87±0.73	8.63±1.74	Newly Diagnosed
Insulin (-)	MacFarlane et al[47]	USA	38.1 (32.8,39.1)	NR	6.4 (4.6, 8.2)	8.9 (7.5, 10.9)	NR
Exenatide (GLP-1 RA)	Dutour et al[51]	France	37.2±1.8	NR	6.3±1.5	NR	4 (2, 8)
	Muskiet et al[52]	Sweden, Finland, Netherlands	30.4±4.1	84.7±17.0	NR	7.53±0.98	NR
Liraglutide (GLP-1 RA)	Tonneijck et al[53]	Netherlands	31.2 (29.2,33.3)	79±3	5.39±1.07	7.4±0.7	8 (4–12)
	Nakaguchi et al[54]	Japan	26.4±4.6	63.3±18.9	5.3±1.3	8.04±0.75	18.8±9.9
	Kurir et al[55]	Croatia	40.9±7.3	NR	6.69±1.21	7.98±0.70	NR
	Liakos et al[56]	Greece	33.6 (7.9)	82.3 (30.3)	NR	7.8 (1.7)	8.0 (6.0)
Lixisenatide (GLP-1 RA)	Tonneijck et al[53]	Netherlands	31.5±4.0	93±3	5.68±1.19	8.0±0.9	13±7
Dulaglutide (GLP-1 RA)	Kuchay et al[57]	India	29.6±3.6	NR	5.0±1.7	8.4±1.0	4.9±3.1
	Hirai et al[58]	Japan	25.7±3.2	20.3±10.4	6.3±0.8	7.2±0.8	NR
	Iwasaki et al[59]	Japan	28.7±5.3	NR	4.93±1.35	7.80±0.99	17.9±9.1
Empagliflozin* (SGLT2i)	You Y et al[61]	NA	NR	NR	NR	NR	NR
Dapagliflozin* (SGLT2i)	Hao Z et al[62]	China	27.34±3.88	NR	5.86±1.72	9.89±1.24	12.20±6.59
	Fuchigami et al[37]	Japan	27.8±4.0	79.0±18.5	5.4±1.3	7.8±0.8	6.0±6.4
	Suijk et al[32]	Netherlands	31±4	84 (24)	5.5±1.2	7.3 (0.8)	NR
Canagliflozin* (SGLT2i)	Davies et al[63]	NR	32.0±6.5	88.8±18.9	5.3–5.4	8.0±0.9	NR
Luseogliflozin* (SGLT2i)	Seino et al[64]	Japan	24.8±3.56	NR	5.09±1.49	8.07±0.90	6.15±6.50
	Chino et al[65]	Japan	NR	85±18	5.1±1.3	8.1±0.9	NR
Tofogliflozin* (SGLT2i)	Terauchi et al[66]	Japan	25.8±3.5	79.7±19.8	5.05±1.25	8.53±0.75	15.02±9.36
Ipragliflozin* (SGLT2i)	Tanaka et al[67]	Japan	30.5±7.0	67.3±18.2	5.7±1.4	7.0±0.5	NR
	Tsukagoshi-Yamaguchi et al[68]	Japan	29.0±5.7	NR	5.1±1.4	8.1±0.7	4.4±4.9
	Nagao et al[69]	Japan	NR	NR	5.5 (4.5–6.2)	7.5 (7.1–7.9)	NR

*Drugs that decreased serum uric acid. NA: not applicable, NR: not reported, SMD: standardized mean difference, F: female, M: male, N: number, SGLT2i: sodium-glucose cotransporter 2 inhibitors, GLP-RA: glucagon-like peptide-1 receptor agonists, DDP4i: dipeptidyl peptidase 4 inhibitor

Table 2 - Studies that evaluated the effects of different antidiabetic drugs on the serum level of uric acid in patients with type-2 diabetes (continuation).

Drug classification	Reference, year	Study location	Drug dose	Drug duration	Serum urate change (mg/dL)	*P*-value
Metformin* (-)	Gregorio et al[20]	Italy	1000 mg/day progressively increased to 1500 mg/day	1 year	From 5.88±0.25 to 5.02±0.28	$p<0.05$ vs. baseline
Gliclazide (Sulfonylurea)	Kilo et al[30]	USA	80-320 mg/day	1 year	No significant change	$p>0.05$ vs. baseline
	Suijk et al[32]	Netherlands	30 mg/day	12 weeks	No significant change during hyperglycemic conditions	$p=0.07$ vs. baseline
Glimepiride (Suilfonylurea)	Kitazawa et al[33]	Japan	0.5 mg/day	24 weeks	No significant change	$p=0.773$ vs. baseline
Sitagliptin (DDP4i)	Matsushima et al[34]	Japan	50 mg/day	12 weeks	From 5.08±1.14 to 5.30±1.24	$p=0.001$ vs. baseline
	Kutoh et al[35]	Japan	25 mg/day for females (n=14), 50 mg/day for males (n=50)	3 months	From 4.91±1.28 to 5.42±1.43	$p<0.00001$ vs. baseline
	Tojikubo et al[36]	Japan	50 mg/day	at least 1 year	From 5.10±1.13 to 5.63±1.24	$p<0.001$ vs. baseline
	Fuchigami et al[37]	Japan	50–100 mg/day	24 weeks	From 5.4±1.4 to 5.6±1.3	$p=0.004$ vs. baseline
Alogliptin (DDP4i)	Kutoh et al[35]	Japan	12.5 mg/day for females (n=9), 5 mg/day for males (n=46)	3 months	From 4.69±1.60 to 5.24±1.61	$p<0.00001$ vs. baseline
Linagliptin* (DDP4i)	Tojikubo et al[36]	Japan	5 mg/day	1 year	From 5.63±1.24 to 5.24±1.10	$p<0.001$ vs. baseline
	Yamagishi et al[38]	Japan	5 mg/day	24 weeks	From 5.5±1.2 to 5.1±1.2	$p<0.05$ vs. baseline
Vildagliptin* (DDP4i)	Shimodaira et al[39]	Japan	100 mg/day	1 year	From 6.0 ± 1.6 to 5.3±1.3	$p<0.05$ vs. baseline
Voglibose (alpha-glucosidase inhibitor)	Matsushima et al[34]	Japan	0.6 mg/day	12 weeks	No significant change	$p=0.073$ vs. baseline
Troglitazone* (Thiazolidinedione)	Iwatani et al[42]	Japan	400 mg/day	9.7±7.6 months	From 5.5±1.2 to 5.0±1.2	$p<0.0001$ vs. baseline
Rosiglitazone* (Thiazolidinedione)	Seber et al[43]	Turkey	4 mg/day	12weeks	From 4.78±1.1 to 4.41±1.1	$p=0.001$ vs. baseline
	Macić-Dzanković et al[44]	Sarajevo	4 mg/day	12 weeks	From 6.22±1.31 to 6.02±1.27	$p<0.015$ vs. baseline
Pioglitazone* (Thiazolidinedione)	Kutoh et al[45]	Japan	7.5–30 mg/day	12 weeks	From 6.87±0.73 to 5.90±0.77	$p<0.00001$ vs. baseline
Insulin (-)	MacFarlane et al[47]	USA	NA	Mean of 2.9 years	+1.25	$p=0.02$
Exenatide (GLP-1 RA)	Dutour et al[51]	France	10–20 µg/day	26 weeks	No significant change	$p=0.79$ vs. reference
	Muskiet et al[52]	Sweden, Finland, Netherlands	20 µg/day	52 weeks	No significant change	$p>0.05$ vs. baseline
Liraglutide (GLP-1 RA)	Tonneijck et al[53]	Netherlands	1.8 mg/day	12 weeks	No significant change	$p=0.8$ vs. placebo
	Nakaguchi et al[54]	Japan	0.9 mg/day	24 weeks	No significant change	NR
	Kurir et al[55]	Croatia	1.2 mg/day	3 months	No significant change	$p=0.104$ vs. baseline
	Liakos et al[56]	Greece	1.2 mg/day	5 weeks	No significant change	$p=0.23$ vs. placebo
Lixisenatide (GLP-1 RA)	Tonneijck et al[53]	Netherlands	20 µg/day	8 weeks	No significant change	*p>0.1* vs. baseline
Dulaglutide (GLP-1 RA)	Kuchay et al[57]	India	1.5 mg/week	24 weeks	No significant change	$p=0.11$ vs. control
	Hirai et al[58]	Japan	0.75 mg/week	1 year	No significant change	$p>0.05$ vs. baseline
	Iwasaki et al[59]	Japan	0.75 mg/week	24 weeks	No significant change	$p=0.0818$ vs. baseline
Empagliflozin* (SGLT2i)	You Y et al[61]	NA	10 or 25 mg/day	5 days to 164 weeks	SMD: -1.34	$p<0.001$ vs. placebo
Dapagliflozin* (SGLT2i)	Hao Z et al[62]	China	10 mg/day	NR	From 5.86±1.72 to 4.71±1.20	$p<0.001$ vs. baseline
	Fuchigami et al[37]	Japan	5-10 mg/day	24 weeks	From 5.4±1.3 to 4.9 ± 1.1	$p<0.001$ vs. baseline
	Suijk et al[32]	Netherlands	10 mg/day	12 weeks	From 5.5±1.1 to 4.6±1.0	$p<0.001$ vs. baseline
Canagliflozin* (SGLT2i)	Davies et al[63]	NR	100 or 300 mg/day	26 weeks	–0.7	NR
Luseogliflozin* (SGLT2i)	Seino et al[64]	Japan	2.5 mg/day	12 weeks	–0.63	$p<0.05$ vs. placebo
	Chino et al[65]	Japan	2.5 or 5 mg/day	12 weeks	–0.6	$p<0.05$ vs. baseline
Tofogliflozin* (SGLT2i)	Terauchi et al[66]	Japan	20 mg/day	16 weeks	–0.18	$p=0.0062$ vs. placebo
Ipragliflozin* (SGLT2i)	Tanaka et al[67]	Japan	50 mg/day	12 weeks	From 5.7±1.4 to 5.0±1.3	$p<0.05$ vs. baseline
	Tsukagoshi-Yamaguchi et al[68]	Japan	50 mg/day	24 weeks	–11.3%	$p=0.012$ vs. control
	Nagao et al[69]	Japan	50 mg/day	6 months	–0.41	$p<0.05$ vs. baseline

*Drugs that decreased serum uric acid. NA: not applicable, NR: not reported, SMD: standardized mean difference, SGLT2i: sodium-glucose cotransporter 2 inhibitors, GLP-RA: glucagon-like peptide-1 receptor agonists, DDP4i: dipeptidyl peptidase 4 inhibitor

of Japanese patients with T2DM (19 men, 12 women; mean age: 57.6±9.3 years) to compare glimepiride with tofogliflozin as the third oral agent added to a regimen consisting of metformin with a dipeptidyl peptidase 4 inhibitor (DPP4i). They found that the 24-week glimepiride regimen did not significantly alter the SUA level. Skillman et al[29] hypothesized that sulfonylureas did not have uricosuric or normouricemic effects because these agents simply lacked this activity or because the serum concentrations were too low. It is also possible sulfonylureas may initially decrease the SUA level, but that this effect decreases over time.

Dipeptidyl peptidase 4 inhibitors. A study of 120 patients with T2DM (72 men, 48 women; mean age: 63.2±13.8 years) reported that sitagliptin significantly increased the SUA level after 12 weeks (5.08±1.14 to 5.30±1.24 mg/dL; p=0.001).[34] Another study of 64 drug-naïve patients with T2DM (50 men; 14 women; mean age: 56.0±12.3 years) found that 3 months of sitagliptin increased the SUA level 4.91±1.28 to 5.42±1.43 mg/dL (p<0.00001).[35] Tojikubo et al[36] studied the effect of sitagliptin in 73 patients with T2DM and found that it led to a significant increase in the SUA level (5.10±1.13 to 5.63±1.24 mg/dL; p<0.001) and significant decrease in the estimated glomerular filtration rate (eGFR: 78.0±24.4 to 71.8±23.3 mL/min/1.73 m^2; p<0.001) after at least one year of treatment. A RCT of 163 patients with T2DM found that the SUA increased 5.4±1.4 to 5.6±1.3 mg/dL (p=0.004) after 24 weeks.[37] Another study of alogliptin therapy in 55 drug-naïve individuals with T2DM (46 men, 9 women; mean age: 52.4±13.2 years) reported an increased SUA level from 4.69±1.60 to 5.24±1.61 mg/dL (p<0.00001) after 3 months of treatment.[35]

In contrast, a study that assessed the effect of changing from sitagliptin to linagliptin in 73 subjects who had T2DM (41 men, 32 women; mean age: 66±13 years) showed that linagliptin lowered the SUA concentration after one year (5.63±1.24 to 5.24±1.10 mg/dL; p<0.001) and led to no significant decrease in the eGFR.[36] Yamagishi et al[38] examined 26 patients with T2DM (18 men, 8 women; mean age: 69.4±12.4 years) and reported that linagliptin decreased the SUA level after 24 weeks (5.5±1.2 to 5.1±1.2 mg/dL; p<0.05). These same researchers also confirmed that linagliptin inhibited xanthine oxidase activity in vitro, and suggested that this effect was partly responsible for the UA-lowering effect of linagliptin.[38] Another retrospective study of T2DM patients found that switching from sitagliptin to vildagliptin led to a decreased serum level of UA.[39]

The precise mechanism by which DPP4is alter the SUA level remains unknown, and it is also unknown why some of these drugs increase the UA level but others decrease the UA level. One suggestion is that the inconsistent effects of different DPP4is may be attributed to their different chemical structures and pharmacological properties.[36,38] Regardless of the mechanisms of the different drugs and the reasons for their differences, it seems that linagliptin is more effective than other DDP4is for controlling hyperuricemia in patients with T2DM.

Alpha-glucosidase inhibitors. Moriwaki et al[40] provided evidence that acarbose can attenuate the increase of plasma UA induced by sucrose ingestion. More specifically, these authors examined 6 healthy subjects and reported that the pre-administration of acarbose attenuated the increase of plasma UA that occurred after sucrose ingestion, although this treatment did not alter the urinary excretion or fractional clearance of UA. These authors hypothesized that this effect may be due to the inhibition of intestinal sucrose absorption, which delayed its conversion into fructos.[40] One study of 121 T2DM patients reported that voglibose had no effect on the SUA level.[34] Based on the mechanism and site of action of these drugs, we speculate that they probably do not have a clinically significant impact on the SUA concentration. However, further studies of the mechanisms of these drugs and their effects on the SUA level are warranted.

Thiazolidinediones. A review article that analyzed the pleiotropic effects of thiazolidinediones reported that these drugs had urate-lowering effects.[41] More specifically, a study of 95 T2DM patients (61 men, 34 women; mean age: 61.1±10.3 years) found that troglitazone significantly decreased the SUA level (5.5±1.2 to 5.0±1.2 mg/dL; p<0.0001) after 9.7±7.6 months of treatment.[42] Similarly, a study of 40 T2DM patients reported that a 12 week regimen of rosiglitazone decreased the SUA level from 4.78±1.1 to 4.41±1.1 mg/dL (p=0.001).[43] Another study of 21 T2DM patients with metabolic syndrome found that a 12-week regimen of rosiglitazone decreased the SUA level from 6.22±1.31 to 6.02±1.27 mg/dL (p<0.015).[44] Kutoh et al[45] examined 19 drug-naïve patients with newly diagnosed T2DM whose baseline SUA levels were above 6.0 mg/dL. They reported that a 12-week regimen of pioglitazone significantly lowered the UA level (6.87±0.73 to 5.90±0.77 mg/dL; p<0.00001).[45]

It is possible that thiazolidinediones decrease the SUA level due to their attenuation of IR, because IR is associated with an elevated level of SUA.[45] An alternative mechanism was suggested in a study of UA

stone formers.[46] This study showed that pioglitazone therapy increased urine pH, and the authors suggested that the resulting increased solubility of UA led to enhanced urinary excretion of UA and a lower serum level of UA.

Insulin. A matched cohort study reported that insulin significantly increased the SUA level by 1.25 mg/dL (p=0.02).[47] This effect is likely because insulin increases the renal reabsorption of urate due to its activation of urate transporter-1 (URAT-1) or the sodium-dependent organic anion co-transporter (SOAT) in the renal proximal tubules.[47] Another study of healthy individuals found that exogenous insulin led to an acute decrease of fractional renal urate excretion in a euglycemic clamp experiment.[48] Other studies reported that the insulin-induced increase of SUA may increase the risk of gout.[49,50]

Glucagon-like peptide-1 receptor agonists. A study of T2DM patients with obesity (13 men, 9 women; mean age: 51±2 years) showed that a 26-week regimen of exenatide had no significant effect on the SUA level.[51] Similarly, Muskiet et al[52] determined the effect of a 52-week regimen of twice-daily exenatide in T2DM patients (16 men and 10 women; mean age: 59.7±8.1 years) and found no effect on the SUA level. Tonneijck et al[53] carried out a post-hoc analysis of 4 previous clinical trials and examined the short-term response to exenatide. The acute effect was a mild elevation of SUA in healthy individuals, although there was no effect in patients with T2DM.[53] This post-hoc analysis also examined the effect of a 12-week liraglutide regimen in T2DM subjects (27 men, 9 women; mean age: 63±7years) and found no significant changes relative to placebo.[53] A RCT by Nakaguchi et al[54] evaluated the effect of a 24-week liraglutide regimen on the SUA level of patients with T2DM (21 men, 9 women; mean age: 67.2±9.0 years) and reported no significant effect. In agreement, Kurir et al[55] and Liakos et al[56] carried out before-after studies in populations of T2DM patients and reported that liraglutide had no significant effect on the SUA level.

A randomized, open-label, comparator-controlled trial of T2DM patients that examined an 8-week regimen of lixisenatide injections showed that this treatment had no effect on the SUA level.[53] Several before-after studies of patients with T2DM reported that dulaglutide had no effect on the SUA level. In particular, Kuchay et al[57] investigated the effect of dulaglutide on the SUA level of patients who had T2DM and nonalcoholic fatty liver disease (NAFLD) and found it had no significant effect. Hirai et al[58] and Iwasaki et al[59] reported similar findings. However, an animal study that examined a rat model of diabetes showed that rats receiving GLP-1 RAs had lower SUA levels than untreated rats.[60] Taken together, the current data provide no support for the view that GLP-1 RAs can lower the SUA level. However, very few studies were specifically designed to examine the effects of GLP-1 RAs on the SUA level, not all GLP-1 RAs have yet been studied, many of the available studies had limited durations, and different GLP-1 RAs may have different effects on SUA. Further studies that examine multiple variables, including different GLP-1 RAs, treatment duration, and dosage, are required to ascertain the impact of individual GLP-1 RAs on the SUA level.

Sodium-glucose cotransporter 2 inhibitors. There is evidence that multiple drugs in the class of sodium-glucose cotransporter 2 inhibitors (SGLT2is) can promote normouricemia. For example, a meta-analysis that examined 10 RCTs and 2 observational studies of T2DM patients (n=7801) found that empagliflozin significantly decreased the SUA level compared with placebo (standardized mean difference [SMD]: -1.34 mg/dL, 95% CI: [-2.05, -0.63]).[61] A RCT that assessed the effect of dapagliflozin in patients with T2DM (20 men, 9 women; mean age: 57.77±12.29 years) showed that this drug significantly lowered the SUA level (5.86±1.72 to 4.71±1.20 mg/dL; p<0.001).[62] Similarly, Fuchigami et al[37] carried out a prospective randomized trial of 168 patients with T2DM and showed that a 24-week dapagliflozin regimen significantly decreased the SUA level (5.4±1.3 to 4.9±1.1 mg/dL; p<0.001). A 2022 RCT of 24 patients with T2DM measured the plasma UA level, fractional UA excretion, and hemodynamic function of the kidneys during fasting state and during clamped euglycemia or hyperglycemia before and after a 12-week dapagliflozin regimen.[32] The results showed that dapagliflozin decreased the plasma UA level by 0.8±0.8 mg/dL during fasting, by 1.0±1.0 mg/dL during hyperinsulinemia-euglycemia, and by 08±0.7 mg/dL during the hyperglycemia (all p<0.001). This study also showed that the fractional daily UA excretion increased by 3.0±2.1% (p<0.001) and by 2.6±4.5% during hyperinsulinemia-euglycemia (p=0.003).[32]

A post-hoc study of data from 4 placebo-controlled phase III trials of 2313 patients with T2DM found that canagliflozin decreased the SUA level by ~13% (0.7 mg/dL) relative to placebo at week 26.[63] Similarly, Seino et al[64] reported decreases in the SUA after luseogliflozin administration in T2DM subjects. Chino et al[65] stratified T2DM patients into 3 groups according to baseline level of glycosylated hemoglobin (HbA1c) and into 4 groups according to baseline level

of SUA. Their multivariate analysis showed that the luseogliflizin-mediated decline of SUA was associated with a higher baseline SUA level and a lower HbA1c level.[65] One RCT of Japanese subjects who had T2DM showed that tofogliflozin decreased the SUA level.[66] Similarly, 3 other studies in Japan also found that ipragliflozin had significant SUA-lowering effects compared with controls.[67-69]

Several meta-analyses also examined the results of administering drugs in this class on the SUA level. For example, Zhao et al[70] reviewed 62 RCTs (34,941 patients) that examined patients with T2DM, and found that multiple SGLT2is (empagliflozin, canagliflozin, dapagliflozin, ipragliflozin, luseogliflozin, and tofogliflozin) significantly decreased the SUA level relative to controls (range: -0.29 to -0.77 mg/dL, total weighted mean difference [WMD]: -0.63 mg/dL). Among these many SGLT2is, Zhao et al[70] reported that empagliflozin had the strongest effect (WMD: -0.77 mg/dL). A different systematic review and meta-analysis that included 19 RCTs (4218 patients) examined the response to SGLT2is in Asian T2DM patients. This study showed that SGLT2is significantly decreased the SUA concentration compared with the control treatment (total SMD: -0.965; 95% CI: [-1.029, -0.901]; $p<0.001$; I2=98.7%).[71] Furthermore, a network meta-analysis by these researchers that compared different specific drugs with placebo showed that the UA-lowering effects of these drugs were as follows: luseogliflozin (SMD: -1.28, 95% credible interval [CrI]: [-1.70, -0.86]), dapagliflozin (SMD: -0.97, 95% CrI: [-1.40, -0.55]), empagliflozin (SMD: -0.67, 95% CrI: [-1.10, -0.24]), tofogliflozin (SMD: -0.59, 95% CrI: [-1.02, -0.16]), ipragliflozin (SMD: -0.57, 95% CrI: [-0.99, -0.14]), and canagliflozin (SMD: -0.51, 95% CrI: -0.95, -0.07]). Their further analysis showed that luseogliflozin at 1 or 10 mg/day and dapagliflozin at 5 mg/day had superior effects.

Akbari et al[72] carried out a meta-analysis of 55 placebo-controlled clinical trials of 36,215 patients who received SGLT2is (n=23,494) or placebo (n=12,721). In agreement with the other studies, they found that all examined SGLT2is significantly decreased the SUA level compared with placebo. They reported the UA-lowering effects were as follows: empagliflozin (mean difference [MD]: -0.69 mg/dL, 95% CI: [-0.80, -0.58]), dapagliflozin (MD: -0.59 mg/dL, 95% CI: [-0.67, -0.52]), canagliflozin (MD: -0.61 mg/dL, 95% CI: [-0.70, -0.52]), luseogliflozin (MD: -0.41 mg/dL, 95% CI: [-0.56, -0.26]), tofogliflozin (MD: -0.33 mg/dL, 95% CI: [-0.46, -0.19]), and ipragliflozin (MD: -0.32 mg/dL, 95% CI: [-0.46, -0.18]).[72]

A meta-analysis by Yip et al[73] examined 43 RCTs (31,921 subjects) to compare the effect of SGLT2is relative to placebo on the SUA level in patients who did or did not have T2DM. They identified decreases in the SUA level in subjects with diabetes (-0.53 mg/dL; 95% CI: [-0.63, -0.43]) and in those without diabetes (-1.54 mg/dL; 95% CI: [-2.13, -0.95]). Furthermore, a 2024 meta-analysis of 5 trials that had a median follow-up time of 2.2 years examined the effect of SGLT2is in 31,535 patients, 76% with T2DM and 54% with heart failure. Overall, the mean change of SUA was -0.79 mg/dL (95% CI: [-1.03, -0.54]) and each 1 mg/dL decrease of SUA was linked to a lower composite risk of cardiovascular death and hospitalization for heart failure (HR=0.64; 95% CI: [0.46-0.88]).[17] Two recent studies of canagliflozin and erutgliflozin found that the magnitude of the decrease in the SUA level had a negative relationship with adverse kidney outcomes.[74,75] Three other large-scale clinical trials of patients who had diabetes and heart failure reported that SGLT2is decreased the risk for gout by 30-50%.[76-78]

Several studies have examined the possible mechanism by which SGLT2is decrease the SUA level. One study suggested that this effect may be attributable to the induction of decreased flux through the pentose phosphate pathway and increased renal excretion of urate.[79] In particular, because drugs in this class block the reabsorption of glucose by SGLT-2, which has high expression in the apical membranes of renal segments S1 and S2 (regions of the proximal convoluted tubules), this leads to a decreased level of glucose, activation of sirtuin-1, inhibition of xanthine oxidase, and decreased synthesis of UA.[80] Sodium-glucose cotransporter 2 inhibitors may also increase the urinary excretion of urate by altering the function of UA transporters in the renal tubules, such as glucose transporter 9 (GLUT9) and URAT-1. A study of healthy male volunteers in Japan and Xenopus oocytes suggested that the SGLT2i-mediated increase in tubular glucose leads to trans-activation of a GLUT9 isoform, and then to urate efflux in the renal proximal tubules.[81] In addition, the results from clinical trials and animal studies suggest that SGLT2is may increase the excretion of UA due to their blockade of URAT1, which is located on the apical surface of the renal proximal tubules and functions in urate reabsorption after glomerular filtration.[32] Finally, SGLT2is may also upregulate the ATP-binding cassette transporter G-2 (ABCG-2), thus promoting urate secretion.[82] Further studies are needed to examine other potential mechanisms by which drugs in this class decrease the SUA level and compare the effects of different specific drugs.

Conclusion. The pathological processes of T2DM and hyperuricemia are interconnected, and each disorder increases risk for many other diseases, including cardiovascular disease and kidney diseases. Because so many other diseases are associated with hyperuricemia, it is likely that patients with T2DM will benefit by maintaining normouricemia. Fortunately, many of the available antidiabetic drugs also decrease the serum level of UA. Among the various types of antidiabetic drugs, SGTL2is have the best-documented effects on SUA in patients with T2DM. The many studies that support the use of SGTL2is for these patients include well-designed before-after studies, large RCTs, and several meta-analyses. However, for some other classes of antidiabetic drugs, there are relatively few clinical studies that examined SUA as a primary outcome; instead, these studies examined SUA levels as a secondary research objective or using a secondary analysis. Therefore, more well-designed studies are required to assess the effects of these other classes of antidiabetic drugs on the serum level of UA. Moreover, further investigations are needed to examine the underlying mechanisms by which the different antidiabetic drugs decrease SUA.

This review provides strong evidence that administration of SGTL2is to patients with T2DM has an added benefit of decreasing SUA levels. This indicates a significant advantage for this class of drugs when considering treatments for T2DM patients, especially for patients who also have hyperuricemia. Studies of the mechanism of SGLT2is suggest they may lower the SUA by inhibiting the pentose phosphate pathway, and by increasing the excretion of urate by the kidneys due to alteration of renal tubular UA transporters (GLUT9 and URAT1). Overall, the GLP-1 RAs had no significant impact on the SUA level; however, further studies are required to examine the effects of individual GLP-1 RAs on SUA. In addition, thiazolidinediones, metformin, and linagliptin potentially decrease the SUA, whereas insulin, sitagliptin, and alogliptin all appear to increase the SUA. Sulfonylureas and alpha-glucosidase inhibitors appear to have no significant impact on the SUA. We suggest that the results presented here be considered when developing future therapeutic guidelines for patients who have T2DM with hyperuricemia.

Acknowledgment. *The authors gratefully acknowledge Medjaden Inc. for their English language editing.*

References

1. Polito L, Bortolotti M, Battelli MG, Bolognesi A. Chronic kidney disease: which role for xanthine oxidoreductase activity and products? *Pharmacol Res* 2022; 184: 106407.
2. Lin S. Interpretation of Chinese guidelines for the diagnosis and treatment of hyperuricemia and gout (2019). *J Clin Intern Med* 2020; 37: 460-462.
3. Leask MP, Merriman TR. The genetic basis of urate control and gout: insights into molecular pathogenesis from follow-up study of genome-wide association study loci. *Best Pract Res Clin Rheumatol* 2021; 35: 101721.
4. Boocock J, Leask M, Okada Y, Matsuo H, Kawamura Y, Shi Y, et al. Genomic dissection of 43 serum urate-associated loci provides multiple insights into molecular mechanisms of urate control. *Hum Mol Genet* 2020; 29: 923-943.
5. Reynolds RJ, Irvin MR, Bridges SL, Kim H, Merriman TR, Arnett DK, et al. Genetic correlations between traits associated with hyperuricemia, gout, and comorbidities. *Eur J Hum Genet* 2021; 29: 1438-1445.
6. Luo Y, Wu Q, Meng R, Lian F, Jiang C, Hu M, et al. Associations of serum uric acid with cardiovascular disease risk factors: a retrospective cohort study in southeastern China. *BMJ Open* 2023; 13: e073930.
7. Raya-Cano E, Vaquero-Abellán M, Molina-Luque R, De Pedro-Jiménez D, Molina-Recio G, Romero-Saldaña M. Association between metabolic syndrome and uric acid: a systematic review and meta-analysis. *Sci Rep* 2022; 12: 18412.
8. Borghi C, Agabiti-Rosei E, Johnson RJ, Kielstein JT, Lurbe E, Mancia G, et al. Hyperuricaemia and gout in cardiovascular, metabolic and kidney disease. *Eur J Intern Med* 2020; 80: 1-11.
9. Saito Y, Tanaka A, Node K, Kobayashi Y. Uric acid and cardiovascular disease: a clinical review. *J Cardiol* 2021; 78: 51-57.
10. Morikawa N, Bancks MP, Yano Y, Kuwabara M, Gaffo AL, Duprez DA, et al. Serum urate trajectory in young adulthood and incident cardiovascular disease events by middle age: CARDIA study. *Hypertension* 2021; 78: 1211-1218.
11. Mao T, He Q, Yang J, Jia L, Xu G. Relationship between gout, hyperuricemia, and obesity-does central obesity play a significant role?-a study based on the NHANES database. *Diabetol Metab Syndr* 2024; 16: 24.
12. Liu N, Xu H, Sun Q, Yu X, Chen W, Wei H, et al. The role of oxidative stress in hyperuricemia and xanthine oxidoreductase (XOR) inhibitors. *Oxid Med Cell Longev* 2021; 2021: 1470380.
13. Du L, Zong Y, Li H, Wang Q, Xie L, Yang B, et al. Hyperuricemia and its related diseases: mechanisms and advances in therapy. *Signal Transduct Target Ther* 2024; 9: 212.
14. Kodama S, Saito K, Yachi Y, Asumi M, Sugawara A, Totsuka K, et al. Association between serum uric acid and development of type 2 diabetes. *Diabetes Care* 2009; 32: 1737-1742.
15. Verma S, Ji Q, Bhatt DL, Mazer CD, Al-Omran M, Inzucchi SE, et al. Association between uric acid levels and cardio-renal outcomes and death in patients with type 2 diabetes: a subanalysis of EMPA-REG outcome. *Diabetes Obes Metab* 2020; 22: 1207-1214.
16. Zhou Q, Ke S, Yan Y, Guo Y, Liu Q. Serum uric acid is associated with chronic kidney disease in elderly Chinese patients with diabetes. *Ren Fail* 2023; 45: 2238825.
17. Diallo A, Diallo MF, Carlos-Bolumbu M, Galtier F. Uric acid-lowering effects of sodium-glucose cotransporter 2 inhibitors for preventing cardiovascular events and mortality: a systematic review and meta-analysis. *Diabetes Obes Metab* 2024; 26: 1980-1985.
18. Zelniker TA, Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. *J Am Coll Cardiol* 2020; 75: 422-434.

19. Hamed K, Alosaimi MN, Ali BA, Alghamdi A, Alkhashi T, Alkhaldi SS, et al. Glucagon-like peptide-1 (GLP-1) receptor agonists: exploring their impact on diabetes, obesity, and cardiovascular health through a comprehensive literature review. *Cureus* 2024; 16: e68390.
20. Gregorio F, Manfrini S, Testa I, Filipponi P. Metformin treatment in elderly type II diabetic patients. *Arch Gerontol Geriatr* 1996; 22: 261-270.
21. Barskova VG, Eliseev MS, Kudaeva FM, Aleksandrova EN, Volkov AV, Nasonova VA, et al. [Effect of metformin on the clinical course of gout and insulin resistance]. *Klin Med (Mosk)* 2009; 87: 41-46. [In Russian].
22. Gokcel A, Gumurdulu Y, Karakose H, Melek Ertorer E, Tanaci N, BascilTutuncu N, et al. Evaluation of the safety and efficacy of sibutramine, orlistat and metformin in the treatment of obesity. *Diabetes Obes Metab* 2002; 4: 49-55.
23. Krzystek-Korpacka M, Patryn E, Kustrzeba-Wojcicka I, Chrzanowska J, Gamian A, Noczynska A. The effect of a one-year weight reduction program on serum uric acid in overweight/obese children and adolescents. *Clin Chem Lab Med* 2011; 49: 915-921.
24. Pina AF, Borges DO, Meneses MJ, Branco P, Birne R, Vilasi A, et al. Insulin: trigger and target of renal functions. *Front Cell Dev Biol* 2020; 8: 519.
25. Daza-Arnedo R, Rico-Fontalvo J, Aroca-Martínez G, Rodríguez-Yanez T, Martínez-Ávila MC, Almanza-Hurtado A, et al. Insulin and the kidneys: a contemporary view on the molecular basis. *Front Nephrol* 2023; 3: 1133352.
26. Wang B, Wu L, Chen J, Dong L, Chen C, Wen Z, et al. Metabolism pathways of arachidonic acids: mechanisms and potential therapeutic targets. *Signal Transduct Target Ther* 2021; 6: 94.
27. Herman R, Kravos NA, Jensterle M, Janež A, Dolžan V. Metformin and insulin resistance: a review of the underlying mechanisms behind changes in GLUT4-mediated glucose transport. *Int J Mol Sci* 2022; 23: 1264.
28. Gerdes C, Müller N, Wolf G, Busch M. Nephroprotective properties of antidiabetic drugs. *J Clin Med* 2023; 12: 3377.
29. Skillman TG, Feldman JM. The pharmacology of sulfonylureas. *Am J Med* 1981; 70: 361-372.
30. Kilo C, Dudley J, Kalb B. Evaluation of the efficacy and safety of Diamicron in non-insulin-dependent diabetic patients. *Diabetes Res Clin Pract* 1991; 14: S79-S82.
31. Hussain A, Latiwesh OB, Ali F, Younis MYG, Alammari JA. Effects of body mass index, glycemic control, and hypoglycemic drugs on serum uric acid levels in type 2 diabetic patients. *Cureus* 2018; 10: e3158.
32. Suijk DLS, van Baar MJB, van Bommel EJM, Iqbal Z, Krebber MM, Vallon V, et al. SGLT2 inhibition and uric acid excretion in patients with type 2 diabetes and normal kidney function. *Clin J Am Soc Nephrol* 2022; 17: 663-671.
33. Kitazawa T, Seino H, Ohashi H, Inazawa T, Inoue M, Ai M, et al. Comparison of tofogliflozin versus glimepiride as the third oral agent added to metformin plus a dipeptidyl peptidase-4 inhibitor in Japanese patients with type 2 diabetes: a randomized, 24-week, open-label, controlled trial (STOP-OB). *Diabetes Obes Metab* 2020; 22: 1659-1663.
34. Matsushima Y, Takeshita Y, Kita Y, Otoda T, Kato K, Toyama-Wakakuri H, et al. Pleiotropic effects of sitagliptin versus voglibose in patients with type 2 diabetes inadequately controlled via diet or a single oral antihyperglycemic agent: a multicenter, randomized trial. *BMJ Open Diabetes Res Care* 2016; 4: e000190.
35. Kutoh E, Wada A, Hayashi J. Regulation of free fatty acid by sitagliptin monotherapy in drug-naïve subjects with type 2 diabetes. *Endocr Pract* 2018; 24: 1063-1072.
36. Tojikubo M, Tajiri Y. Different effects of linagliptin and sitagliptin on blood pressure and renal function in Japanese patients with type 2 diabetes mellitus. *Diabetol Int* 2017; 8: 397-401.
37. Fuchigami A, Shigiyama F, Kitazawa T, Okada Y, Ichijo T, Higa M, et al. Efficacy of dapagliflozin versus sitagliptin on cardiometabolic risk factors in Japanese patients with type 2 diabetes: a prospective, randomized study (DIVERSITY-CVR). *Cardiovasc Diabetol* 2020; 19: 1.
38. Yamagishi S, Ishibashi Y, Ojima A, Sugiura T, Matsui T. Linagliptin, a xanthine-based dipeptidyl peptidase-4 inhibitor, decreases serum uric acid levels in type 2 diabetic patients partly by suppressing xanthine oxidase activity. *Int J Cardiol* 2014; 176: 550-552.
39. Shimodaira M, Niwa T, Nakajima K, Kobayashi M. Beneficial effects of vildagliptin on metabolic parameters in patients with type 2 diabetes. *Endocr Metab Immune Disord Drug Targets* 2015; 15: 223-228.
40. Moriwaki Y, Inokuchi T, Ka T, Yamamoto A, Tsutsumi Z, Takahashi S, et al. Effect of acarbose on the increased plasma concentration of uric acid induced by sucrose ingestion. *Nucleosides Nucleotides Nucleic Acids* 2008; 27: 631-633.
41. Giglio RV, Papanas N, Rizvi AA, Ciaccio M, Patti AM, Ilias I, et al. An update on the current and emerging use of thiazolidinediones for type 2 diabetes. *Medicina (Kaunas)* 2022; 58: 1475.
42. Iwatani M, Wasada T, Katsumori K, Watanabe-Takahashi C, Kamatani N, Iwamoto Y. Troglitazone decreases serum uric acid concentrations in type II diabetic patients and non-diabetics. *Diabetologia* 2000; 43: 814-815.
43. Seber S, Ucak S, Basat O, Altuntas Y. The effect of dual PPAR alpha/gamma stimulation with combination of rosiglitazone and fenofibrate on metabolic parameters in type 2 diabetic patients. *Diabetes Res Clin Pract* 2006; 71: 52-58.
44. Macić-Dzanković A, Dzanković F, Pojskić B, Velija-Asimi Z. Evaluation of risk markers fluctuation during an initial therapy with rosiglitazon in patients suffering from metabolic syndrome. *Bosn J Basic Med Sci* 2009; 9: 320-328.
45. Kutoh E, Hori T. Effect of pioglitazone on serum uric acid levels in newly diagnosed, drug-naïve patients with type 2 diabetes. *Endocr Res* 2013; 38: 151-159.
46. Maalouf NM, Poindexter JR, Adams-Huet B, Moe OW, Sakhaee K. Increased production and reduced urinary buffering of acid in uric acid stone formers is ameliorated by pioglitazone. *Kidney Int* 2019; 95: 1262-1268.
47. MacFarlane LA, Liu CC, Solomon DH. The effect of initiating pharmacologic insulin on serum uric acid levels in patients with diabetes: a matched cohort analysis. *Semin Arthritis Rheum* 2015; 44: 592-596.
48. Rosati E, Di Giuseppe G, Mezza T, Ferraro PM. The influence of insulin and incretin-based therapies on renal tubular transport. *J Nephrol* 2024; 37: 2139-2150.

49. Asma Sakalli A, Küçükerdem HS, Aygün O. What is the relationship between serum uric acid level and insulin resistance? A case-control study. ***Medicine (Baltimore)*** 2023; 102: e36732.
50. Lee SJ, Oh BK, Sung KC. Uric acid and cardiometabolic diseases. ***Clin Hypertens*** 2020; 26: 13.
51. Dutour A, Abdesselam I, Ancel P, Kober F, Mrad G, Darmon P, et al. Exenatide decreases liver fat content and epicardial adipose tissue in patients with obesity and type 2 diabetes: a prospective randomized clinical trial using magnetic resonance imaging and spectroscopy. ***Diabetes Obes Metab*** 2016; 18: 882-891.
52. Muskiet MHA, Bunck MC, Heine RJ, Cornér A, Yki-Järvinen H, Eliasson B, et al. Exenatide twice-daily does not affect renal function or albuminuria compared to titrated insulin glargine in patients with type 2 diabetes mellitus: a post-hoc analysis of a 52-week randomised trial. ***Diabetes Res Clin Pract*** 2019; 153: 14-22.
53. Tonneijck L, Muskiet MHA, Smits MM, Bjornstad P, Kramer MHH, Diamant M, et al. Effect of immediate and prolonged GLP-1 receptor agonist administration on uric acid and kidney clearance: post-hoc analyses of 4 clinical trials. ***Diabetes Obes Metab*** 2018; 20: 1235-1245.
54. Nakaguchi H, Kondo Y, Kyohara M, Konishi H, Oiwa K, Terauchi Y. Effects of liraglutide and empagliflozin added to insulin therapy in patients with type 2 diabetes: a randomized controlled study. ***J Diabetes Investig*** 2020; 11: 1542-1550.
55. Tičinović Kurir T, Miličević T, Novak A, Vilović M, Božić J. Adropin - potential link in cardiovascular protection for obese male type 2 diabetes mellitus patients treated with liraglutide. ***Acta Clin Croat*** 2020; 59: 344-350.
56. Liakos A, Lambadiari V, Bargiota A, Kitsios K, Avramidis I, Kotsa K, et al. Effect of liraglutide on ambulatory blood pressure in patients with hypertension and type 2 diabetes: a randomized, double-blind, placebo-controlled trial. ***Diabetes Obes Metab*** 2019; 21: 517-524.
57. Kuchay MS, Krishan S, Mishra SK, Choudhary NS, Singh MK, Wasir JS, et al. Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial). ***Diabetologia*** 2020; 63: 2434-2445.
58. Hirai K, Imamura S, Ookawara S, Hirai A, Morishita Y. Effects of once-weekly dulaglutide on glycemic control and renal function in patients with advanced-stage diabetic nephropathy. ***Nephro-Urol Mon*** 2017; 9: e55058.
59. Iwasaki T, Kessoku T, Higurashi T, Taguri M, Yoneda M. Low body mass index and old age are useful in predicting the hemoglobin A1c-lowering effect of switching from sitagliptin to dulaglutide in Japanese patients with type 2 diabetes mellitus: a single-center, open-label, single-arm, pilot study. ***Diabetol Int*** 2018; 9: 189-195.
60. Lotfy M, Singh J, Rashed H, Tariq S, Zilahi E, Adeghate E. The effect of glucagon-like peptide-1 in the management of diabetes mellitus: cellular and molecular mechanisms. ***Cell Tissue Res*** 2014; 358: 343-358.
61. You Y, Zhao Y, Chen M, Pan Y, Luo Z. Effects of empagliflozin on serum uric acid level of patients with type 2 diabetes mellitus: a systematic review and meta-analysis. ***Diabetol Metab Syndr*** 2023; 15: 202.
62. Hao Z, Huang X, Shao H, Tian F. Effects of dapagliflozin on serum uric acid levels in hospitalized type 2 diabetic patients with inadequate glycemic control: a randomized controlled trial. ***Ther Clin Risk Manag*** 2018; 14: 2407-2413.
63. Davies MJ, Trujillo A, Vijapurkar U, Damaraju CV, Meininger G. Effect of canagliflozin on serum uric acid in patients with type 2 diabetes mellitus. ***Diabetes Obes Metab*** 2015; 17: 426-429.
64. Seino Y, Sasaki T, Fukatsu A, Sakai S, Samukawa Y. Efficacy and safety of luseogliflozin monotherapy in Japanese patients with type 2 diabetes mellitus: a 12-week, randomized, placebo-controlled, phase II study. ***Curr Med Res Opin*** 2014; 30: 1219-1230.
65. Chino Y, Kuwabara M, Hisatome I. Factors influencing change in serum uric acid after administration of the sodium-glucose cotransporter 2 inhibitor luseogliflozin in patients with type 2 diabetes mellitus. ***J Clin Pharmacol*** 2022; 62: 366-375.
66. Terauchi Y, Tamura M, Senda M, Gunji R, Kaku K. Efficacy and safety of tofogliflozin in Japanese patients with type 2 diabetes mellitus with inadequate glycaemic control on insulin therapy (J-STEP/INS): results of a 16-week randomized, double-blind, placebo-controlled multicentre trial. ***Diabetes Obes Metab*** 2017; 19: 1397-1407.
67. Tanaka M, Yamakage H, Inoue T, Odori S, Kusakabe T, Shimatsu A, et al. Beneficial effects of ipragliflozin on the renal function and serum uric acid levels in Japanese patients with type 2 diabetes: a randomized, 12-week, open-label, active-controlled trial. ***Intern Med*** 2020; 59: 601-609.
68. Tsukagoshi-Yamaguchi A, Koshizaka M, Ishibashi R, Ishikawa K, Ishikawa T, Shoji M, et al. Metabolomic analysis of serum samples from a clinical study on ipragliflozin and metformin treatment in Japanese patients with type 2 diabetes: Exploring human metabolites associated with visceral fat reduction. ***Pharmacotherapy*** 2023; 43: 1317-1326.
69. Nagao M, Sasaki J, Tanimura-Inagaki K, Sakuma I, Sugihara H, Oikawa S. Ipragliflozin and sitagliptin differentially affect lipid and apolipoprotein profiles in type 2 diabetes: the SUCRE study. ***Cardiovasc Diabetol*** 2024; 23: 56.
70. Zhao Y, Xu L, Tian D, Xia P, Zheng H, Wang L, et al. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: a meta-analysis of randomized controlled trials. ***Diabetes Obes Metab*** 2018; 20: 458-462.
71. Hu X, Yang Y, Hu X, Jia X, Liu H, Wei M, et al. Effects of sodium-glucose cotransporter 2 inhibitors on serum uric acid in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. ***Diabetes Obes Metab*** 2022; 24: 228-238.
72. Akbari A, Rafiee M, Sathyapalan T, Sahebkar A. Impacts of sodium/glucose cotransporter-2 inhibitors on circulating uric acid concentrations: a systematic review and meta-analysis. ***J Diabetes Res*** 2022; 2022: 7520632.
73. Yip ASY, Leong S, Teo YH, Teo YN, Syn NLX, See RM, et al. Effect of sodium-glucose cotransporter-2 (SGLT2) inhibitors on serum urate levels in patients with and without diabetes: a systematic review and meta-regression of 43 randomized controlled trials. ***Ther Adv Chronic Dis*** 2022; 13: 20406223221083509.
74. Li J, Neal B, Perkovic V, de Zeeuw D, Neuen BL, Arnott C, et al. Mediators of the effects of canagliflozin on kidney protection in patients with type 2 diabetes. ***Kidney Int*** 2020; 98: 769-777.
75. Segar MW, Kolkailah AA, Frederich R, Pong A, Cannon CP, Cosentino F, et al. Mediators of ertugliflozin effects on heart failure and kidney outcomes among patients with type 2 diabetes mellitus. ***Diabetes Obes Metab*** 2022; 24: 1829-1839.

76. Doehner W, Anker SD, Butler J, Zannad F, Filippatos G, Ferreira JP, et al. Uric acid and sodium-glucose cotransporter-2 inhibition with empagliflozin in heart failure with reduced ejection fraction: the EMPEROR-reduced trial. ***Eur Heart J*** 2022; 43: 3435-3446.
77. Butt JH, Docherty KF, Claggett BL, Desai AS, Petersson M, Langkilde AM, et al. Association of dapagliflozin use with clinical outcomes and the introduction of uric acid-lowering therapy and colchicine in patients with heart failure with and without gout: a patient-level pooled meta-analysis of DAPA-HF and DELIVER. ***JAMA Cardiol*** 2023; 8: 386-393.
78. Banerjee M, Pal R, Maisnam I, Chowdhury S, Mukhopadhyay S. Serum uric acid lowering and effects of sodium-glucose cotransporter-2 inhibitors on gout: a meta-analysis and meta-regression of randomized controlled trials. ***Diabetes Obes Metab*** 2023; 25: 2697-2703.
79. Packer M. Hyperuricemia and gout reduction by SGLT2 inhibitors in diabetes and heart failure: JACC review topic of the week. ***J Am Coll Cardiol*** 2024; 83: 371-381.
80. Packer M. Uric acid is a biomarker of oxidative stress in the failing heart: lessons learned from trials with allopurinol and SGLT2 inhibitors. ***J Card Fail*** 2020; 26: 977-984.
81. Chino Y, Samukawa Y, Sakai S, Nakai Y, Yamaguchi J, Nakanishi T, 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.
82. Lu YH, Chang YP, Li T, Han F, Li CJ, Li XY, et al. Empagliflozin attenuates hyperuricemia by upregulation of ABCG2 via AMPK/AKT/CREB signaling pathway in type 2 diabetic mice. ***Int J Biol Sci*** 2020; 16: 529-542.