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# Effect of baseline urinary glucose levels on the relationship between sodium-glucose cotransporter 2 inhibitors and serum uric acid in Japanese patients with type 2 diabetes mellitus

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In patients with type 2 diabetes mellitus (T2DM), controlling serum uric acid (SUA) and blood glucose levels is important. Moreover, sodium-glucose cotransporter 2 (SGLT2) inhibitors decrease SUA levels by accelerating urinary uric acid excretion. We investigated the effect of baseline urinary glucose levels on the relationship between SGLT2 inhibitors and SUA levels. We conducted a retrospective observational study using the electronic medical records of patients with T2DM of Kindai University Nara Hospital (April 2013 to March 2022). We divided the patients into two groups according to their baseline urinary glucose levels: the N-UG group, which included patients with negative urinary glucose strip test results (-), and the P-UG group, which included patients with positive urinary glucose strip test results (± or more). The changes in SUA levels before and after SGLT2 inhibitor administration were investigated. For comparison, the changes in SUA levels before and after the prescription of antidiabetic agents, excluding SGLT2 inhibitors, were also investigated. Our results revealed that SGLT2 inhibitors significantly decreased the SUA levels in patients in the N-UG group but tended to decrease its levels in those in the P-UG group. Regardless of the urinary glucose status at baseline, the administration of SGLT2 inhibitors may be useful for patients with T2DM to prevent the complications of hyperuricemia.

## 1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic disease and one of the most common metabolic disorders worldwide. Furthermore, its prevalence has increased significantly during the past decades (Lovic et al. 2020). Controlling blood glucose levels and improving insulin resistance are the main therapeutic approaches for T2DM (Czech 2017). Temporal and mechanistic connections exist between insulin resistance and hyperinsulinemia, with the latter reducing the excretion of serum uric acid (SUA) in the proximal convoluted tubules of the kidney and leading to hyperuricemia (Li et al. 2013). Moreover, T2DM and hyperuricemia are closely related, and hyperuricemia has also been associated with gout (Jiang et al. 2023). Recently, hyperuricemia has been reported to be strongly associated with metabolic, renal, and cardiovascular diseases (Sharaf et al. 2017). As such, it is important to control SUA and blood glucose levels in patients with T2DM.

The first sodium-glucose cotransporter 2 (SGLT2) inhibitor was launched in Japan in April 2014. SGLT2 inhibitors improve blood glucose levels by blocking urinary glucose reabsorption in the proximal convoluted tubules of the kidney nephrons, thereby increasing urinary glucose excretion (Scheen 2015). In contrast, SGLT2 inhibitors decrease SUA levels by accelerating urinary uric acid excretion, which is linked to the urinary excretion of glucose (Suijk et al. 2022). Currently, six types of SGLT2 inhibitors are used in Japan, and have been reported to decrease SUA levels in Japanese patients with T2DM (Kutoh et al. 2019; Kitazawa et al. 2020; Kusunoki et al. 2020; Koshizaka et al. 2021). Elevated SUA levels are independent predictors of vascular complications and mortality (Xu et al. 2013). Lowering SUA levels using SGLT2 inhibitors is expected to prevent the complications of hyperuricemia and improve the prognosis of patients with T2DM.

After four weeks of SGLT2 inhibitor administration, urinary glucose levels increase significantly (Jinnouchi et al. 2021). The basic research by Chino et al. (2014) revealed that uric acid is linearly excreted into the urine via glucose transporter 9 (GLUT9), depending on the glucose concentration. In clinical practice, the urinary glucose levels of some patients with T2DM are measured before the prescription of SGLT2 inhibitors. If urinary glucose is negative before the administration of SGLT2 inhibitors, their administration is assumed to lead to decreased SUA levels through urinary glucose excretion. However, if urinary glucose were positive, SUA levels would already be excreted, and administering SGLT2 inhibitors would further reduce its levels. As no studies have explored it previously, the relationship between SUA and urinary glucose levels needs to be clarified. In this study, we investigated the effect of baseline urinary glucose levels on the relationship between SGLT2 inhibitors and SUA levels.

## 2. Investigations and results

### *2.1. Study patients*

As shown in the flowchart in Fig. 1, we identified 1,632 patients with their first prescription of antidiabetic agents in the electronic medical records. Of these, patients who were <18 years of age (n=1), prescribed with two or more antidiabetic agents at the same time on the Cohort Entry Date (CED) (n=157), with <180 days of washout period (n=265), with a follow-up period ≤14 days (n=319), prescribed hypouricemic agents during washout period (n=191), or with no laboratory data on SUA, urinary glucose, and hemoglobin A1c (HbA1c) at baseline or in outcome (n=261) were excluded. Finally, a total of 438 patients were enrolled in the study. SGLT2 inhibitors are administered to patients with and without diabetes; however, those without diabetes were not included in this study.

Of the enrolled patients, 90 were newly prescribed SGLT2 inhibitors and included in the SGLT2i group, while the remaining 348

**Table 1: Characteristics of patients before and after propensity score matching**

| Variables | Before propensity score matching | | | After propensity score matching | | |
|---|---|---|---|---|---|---|
| | SGLT2i group (n=90) | Non-SGLT2i group (n=348) | Standardized difference | SGLT2i group (n=62) | Non-SGLT2i group (n=62) | Standardized difference |
| Demographics | | | | | | |
| Sex male, n (%) | 61 (67.8) | 228 (65.5) | 0.05 | 40 (64.5) | 43 (69.4) | 0.10 |
| Age, mean ± SD | 63.3 ± 11.3 | 70.4 ± 11.4 | 0.62 | 65.4 ± 11.4 | 65.9 ± 13.3 | 0.04 |
| HbA1c, mean ± SD | 7.7 ± 1.0 | 7.4 ± 1.4 | 0.25 | 7.6 ± 1.0 | 7.7 ± 1.6 | 0.04 |
| SUA, mean ± SD | 5.3 ± 1.2 | 5.2 ± 1.5 | 0.04 | 5.4 ± 1.2 | 5.3 ± 1.3 | 0.09 |
| Urinary glucose (-), n (%) | 49 (54.4) | 200 (57.5) | 0.06 | 36 (58.1) | 36 (58.1) | 0.00 |
| Comorbidities | | | | | | |
| Diabetic nephropathy, n (%) | 21 (23.3) | 52 (14.9) | 0.22 | 13 (21.0) | 9 (14.5) | 0.17 |
| Diabetic neuropathy, n (%) | 30 (33.3) | 87 (25.0) | 0.18 | 20 (32.3) | 16 (25.8) | 0.14 |
| Diabetic retinopathy, n (%) | 12 (13.3) | 24 (6.9) | 0.22 | 9 (14.5) | 10 (16.1) | 0.05 |
| Disorders of lipoprotein metabolism, n (%) | 77 (85.6) | 234 (67.2) | 0.44 | 49 (79.0) | 50 (80.6) | 0.04 |
| Hypertensive diseases, n (%) | 58 (64.4) | 207 (59.5) | 0.10 | 39 (62.9) | 38 (61.3) | 0.03 |
| Ischemic heart diseases, n (%) | 33 (36.7) | 116 (33.3) | 0.07 | 23 (37.1) | 23 (37.1) | 0.00 |
| Disorders of thyroid gland, n (%) | 21 (23.3) | 61 (17.5) | 0.14 | 14 (22.6) | 16 (25.8) | 0.08 |
| Heart failure, n (%) | 18 (20.0) | 62 (17.8) | 0.06 | 13 (21.0) | 16 (25.8) | 0.11 |
| Chronic liver diseases, n (%) | 18 (20.0) | 63 (18.1) | 0.05 | 12 (19.4) | 6 (9.7) | 0.28 |
| Cerebrovascular diseases, n (%) | 16 (17.8) | 77 (22.1) | 0.11 | 11 (17.7) | 12 (19.4) | 0.04 |
| Atherosclerosis, n (%) | 10 (11.1) | 24 (6.9) | 0.15 | 6 (9.7) | 3 (4.8) | 0.19 |
| Kidney diseases, n (%) | 9 (10.0) | 23 (6.6) | 0.12 | 8 (12.9) | 8 (12.9) | 0.00 |
| COPD, n (%) | 4 (4.4) | 24 (6.9) | 0.11 | 3 (4.8) | 4 (6.5) | 0.07 |
| Medications | | | | | | |
| Antidiabetic agents, excluding SGLT2i | | | | | | |
| DPP-4 inhibitors, n (%) | 54 (60.0) | 110 (31.6) | 0.59 | 32 (51.6) | 33 (53.2) | 0.03 |
| Biguanides, n (%) | 43 (47.8) | 35 (10.1) | 0.92 | 20 (32.3) | 15 (24.2) | 0.18 |
| Human insulin and analogs, n (%) | 35 (38.9) | 70 (20.1) | 0.42 | 24 (38.7) | 22 (35.5) | 0.07 |
| Alpha-glucosidase inhibitors, n (%) | 30 (33.3) | 55 (15.8) | 0.42 | 14 (22.6) | 16 (25.8) | 0.08 |
| Glinides, n (%) | 25 (27.8) | 65 (18.7) | 0.22 | 18 (29.0) | 20 (32.3) | 0.07 |
| Sulfonylureas, n (%) | 22 (24.4) | 40 (11.5) | 0.34 | 10 (16.1) | 12 (19.4) | 0.09 |
| Glitazones, n (%) | 6 (6.7) | 22 (6.3) | 0.01 | 4 (6.5) | 7 (11.3) | 0.17 |
| GLP-1 agonists, n (%) | 2 (2.2) | 0 (0.0) | 0.21 | 0 (0.0) | 0 (0.0) | - |
| Other agents | | | | | | |
| Lipid modifying agents, n (%) | 70 (77.8) | 168 (48.3) | 0.64 | 43 (69.4) | 38 (61.3) | 0.17 |
| ACE inhibitors and ARBs, n (%) | 44 (48.9) | 114 (32.8) | 0.33 | 27 (43.5) | 24 (38.7) | 0.10 |
| Calcium channel blockers, n (%) | 24 (26.7) | 94 (27.0) | 0.01 | 18 (29.0) | 18 (29.0) | 0.00 |
| Beta-blocking agents, n (%) | 13 (14.4) | 34 (9.8) | 0.14 | 9 (14.5) | 9 (14.5) | 0.00 |
| Diuretics, n (%) | 13 (14.4) | 26 (7.5) | 0.23 | 7 (11.3) | 10 (16.1) | 0.14 |
| NSAIDs for systemic use, n (%) | 5 (5.6) | 22 (6.3) | 0.03 | 4 (6.5) | 4 (6.5) | 0.00 |
| Corticosteroids for systemic use, n (%) | 4 (4.4) | 24 (6.9) | 0.11 | 4 (6.5) | 6 (9.7) | 0.12 |
| Thyroid and anti-thyroid preparations, n (%) | 1 (1.1) | 10 (2.9) | 0.13 | 1 (1.6) | 0 (0.0) | 0.18 |

SGLT2i, sodium-glucose cotransporter 2 inhibitor; SD, standard deviation; HbA1c, Hemoglobin A1c; SUA, serum uric acid; COPD, chronic obstructive pulmonary disease; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; NSAID, non-steroidal anti-inflammatory drug; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1.

patients were prescribed antidiabetic agents other than SGLT2 inhibitors, and were non-SGLT2i group. The SGLT2i group included patients who received an SGLT2 inhibitor as an antidiabetic agent for the first time, those who had already received antidiabetic agents other than SGLT2 inhibitors before April 2015, and those who received an SGLT2 inhibitor after April 2015. In contrast, the non-SGLT2i group comprised patients who received an antidiabetic agent other than SGLT2 inhibitors for the first time, those who had already received antidiabetic agents other than SGLT2 inhibitors, and those who received their first antidiabetic agent other than SGLT2 inhibitors after April 2015. The demographic and clinical characteristics of the patients are shown in Table 1. Patients in the SGLT2i group were younger compared to those in the non-SGLT2i group (mean age at baseline: 63.3 vs. 70.4 years, $p<0.01$). The prevalence of comorbidities, such as diabetic retinopathy and disorders of lipoprotein metabolism, was significantly higher in the SGLT2i group than that in the non-SGLT2i group. In the SGLT2i group, a significantly higher proportion of patients were prescribed dipeptidyl peptidase-4 (DPP-4) inhibitors, biguanides, human insulin and analogs, alpha-glucosidase inhibitors, sulfonylureas, and glucagon-like peptide-1 (GLP-1) agonists than that in the non-SGLT2i group, before propensity score matching. After propensity score matching, 62 patients were included in each group (Fig. 1).

**Tabel 2: Characteristics of patients based on the results of urinary glucose test strips before and after propensity score matching**

| Variables | N-UG group | | | | | | P-UG group | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Before propensity score matching | | | After propensity score matching | | | Before propensity score matching | | | After propensity score matching | | |
| | SGLT2i group (n=49) | Non-SGLT2i group (n=200) | Stan-dardized difference | SGLT2i group (n=34) | Non-SGLT2i group (n=34) | Stan-dardized difference | SGLT2i group (n=41) | Non-SGLT2i group (n=148) | Stan-dardized differ-ence | SGLT2i group (n=20) | Non-SGLT2i group (n=20) | Stan-dardized differ-ence |
| Demographics | | | | | | | | | | | | |
| Sex male, n (%) | 27 (55.1) | 122 (61.0) | 0.12 | 17 (50.0) | 17 (50.0) | 0.00 | 34 (82.9) | 106 (71.6) | 0.27 | 16 (80.0) | 14 (70.0) | 0.23 |
| Age, mean ± SD | 62.0 ± 12.5 | 71.1 ± 10.0 | 0.80 | 62.9 ± 11.4 | 64.9 ± 10.6 | 0.18 | 65.0 ± 9.7 | 69.5 ± 13.0 | 0.39 | 67.3 ± 9.9 | 72.4 ± 12.2 | 0.46 |
| HbA1c, mean ± SD | 7.4 ± 0.9 | 7.1 ± 1.0 | 0.34 | 7.4 ± 0.9 | 7.1 ± 1.2 | 0.23 | 8.1 ± 1.1 | 7.9 ± 1.7 | 0.17 | 8.1 ± 1.1 | 7.7 ± 1.4 | 0.27 |
| SUA, mean ± SD | 5.6 ± 1.2 | 5.3 ± 1.4 | 0.21 | 5.5 ± 1.2 | 5.7 ± 1.5 | 0.14 | 4.9 ± 1.2 | 5.1 ± 1.5 | 0.14 | 4.8 ± 1.2 | 4.8 ± 1.1 | 0.00 |
| Comorbidities | | | | | | | | | | | | |
| Diabetic nephropathy, n (%) | 13 (26.5) | 28 (14.0) | 0.32 | 8 (23.5) | 6 (17.6) | 0.15 | 8 (19.5) | 24 (16.2) | 0.09 | 2 (10.0) | 3 (15.0) | 0.15 |
| Diabetic neuropathy, n (%) | 17 (34.7) | 47 (23.5) | 0.25 | 9 (26.5) | 8 (23.5) | 0.07 | 13 (31.7) | 40 (27.0) | 0.10 | 7 (35.0) | 8 (40.0) | 0.10 |
| Diabetic retinopathy, n (%) | 7 (14.3) | 13 (6.5) | 0.26 | 5 (14.7) | 6 (17.6) | 0.08 | 5 (12.2) | 11 (7.4) | 0.16 | 2 (10.0) | 2 (10.0) | 0.00 |
| Disorders of lipoprotein metab-olism, n (%) | 39 (79.6) | 137 (68.5) | 0.26 | 29 (85.3) | 26 (76.5) | 0.23 | 38 (92.7) | 97 (65.5) | 0.71 | 17 (85.0) | 18 (90.0) | 0.15 |
| Hypertensive diseases, n (%) | 31 (63.3) | 117 (58.5) | 0.10 | 24 (70.6) | 21 (61.8) | 0.19 | 27 (65.9) | 90 (60.8) | 0.11 | 14 (70.0) | 14 (70.0) | 0.00 |
| Ischemic heart diseases, n (%) | 13 (26.5) | 69 (34.5) | 0.17 | 10 (29.4) | 9 (26.5) | 0.07 | 20 (48.8) | 47 (31.8) | 0.35 | 9 (45.0) | 8 (40.0) | 0.10 |
| Disorders of thyroid gland, n (%) | 11 (22.4) | 39 (19.5) | 0.07 | 7 (20.6) | 9 (26.5) | 0.14 | 10 (24.4) | 22 (14.9) | 0.24 | 6 (30.0) | 5 (25.0) | 0.11 |
| Heart failure, n (%) | 10 (20.4) | 35 (17.5) | 0.07 | 7 (20.6) | 9 (26.5) | 0.14 | 8 (19.5) | 27 (18.2) | 0.03 | 5 (25.0) | 4 (20.0) | 0.12 |
| Chronic liver diseases, n (%) | 13 (26.5) | 36 (18.0) | 0.21 | 6 (17.6) | 8 (23.5) | 0.15 | 5 (12.2) | 27 (18.2) | 0.17 | 2 (10.0) | 3 (15.0) | 0.15 |
| Cerebrovascular diseases, n (%) | 9 (18.4) | 43 (21.5) | 0.08 | 5 (14.7) | 6 (17.6) | 0.08 | 7 (17.1) | 34 (23.0) | 0.15 | 4 (20.0) | 2 (10.0) | 0.28 |
| Atherosclerosis, n (%) | 6 (12.2) | 15 (7.5) | 0.16 | 5 (14.7) | 3 (8.8) | 0.18 | 4 (9.8) | 9 (6.1) | 0.14 | 1 (5.0) | 0 (0.0) | 0.32 |
| Kidney diseases, n (%) | 7 (14.3) | 11 (5.5) | 0.30 | 5 (14.7) | 6 (17.6) | 0.08 | 2 (4.9) | 12 (8.1) | 0.13 | 1 (5.0) | 1 (5.0) | 0.00 |
| COPD, n (%) | 1 (2.0) | 15 (7.5) | 0.26 | 1 (2.9) | 1 (2.9) | 0.00 | 3 (7.3) | 9 (6.1) | 0.05 | 1 (5.0) | 2 (10.0) | 0.19 |
| Medications | | | | | | | | | | | | |
| Antidiabetic agents, excluding SGLT2i | | | | | | | | | | | | |
| DPP-4 inhibitors, n (%) | 28 (57.1) | 61 (30.5) | 0.56 | 18 (52.9) | 17 (50.0) | 0.06 | 26 (63.4) | 49 (33.1) | 0.64 | 11 (55.0) | 13 (65.0) | 0.21 |
| Biguanides, n (%) | 23 (46.9) | 21 (10.5) | 0.88 | 11 (32.4) | 9 (26.5) | 0.13 | 20 (48.8) | 14 (9.5) | 0.96 | 3 (15.0) | 6 (30.0) | 0.37 |
| Human insulin and analogs, n (%) | 19 (38.8) | 42 (21.0) | 0.40 | 11 (32.4) | 10 (29.4) | 0.06 | 16 (39.0) | 28 (18.9) | 0.46 | 6 (30.0) | 6 (30.0) | 0.00 |
| Alpha-glucosidase inhibitors, n (%) | 14 (28.6) | 40 (20.0) | 0.20 | 11 (32.4) | 6 (17.6) | 0.35 | 16 (39.0) | 15 (10.1) | 0.71 | 5 (25.0) | 6 (30.0) | 0.11 |
| Glinides, n (%) | 12 (24.5) | 39 (19.5) | 0.12 | 7 (20.6) | 6 (17.6) | 0.08 | 13 (31.7) | 26 (17.6) | 0.33 | 6 (30.0) | 6 (30.0) | 0.00 |
| Sulfonylureas, n (%) | 13 (26.5) | 26 (13.0) | 0.35 | 7 (20.6) | 7 (20.6) | 0.00 | 9 (22.0) | 14 (9.5) | 0.35 | 2 (10.0) | 3 (15.0) | 0.15 |
| Glitazones, n (%) | 4 (8.2) | 15 (7.5) | 0.03 | 4 (11.8) | 3 (8.8) | 0.10 | 2 (4.9) | 7 (4.7) | 0.01 | 1 (5.0) | 0 (0.0) | 0.32 |
| GLP-1 agonists, n (%) | 1 (2.0) | 0 (0.0) | 0.20 | 0 (0.0) | 0 (0.0) | - | 1 (2.4) | 0 (0.0) | 0.22 | 0 (0.0) | 0 (0.0) | - |
| Other agents | | | | | | | | | | | | |
| Lipid modifying agents, n (%) | 34 (69.4) | 104 (52.0) | 0.36 | 25 (73.5) | 19 (55.9) | 0.38 | 36 (87.8) | 64 (43.2) | 1.06 | 15 (75.0) | 16 (80.0) | 0.12 |
| ACE inhibitors and ARBs, n (%) | 22 (44.9) | 72 (36.0) | 0.18 | 16 (47.1) | 11 (32.4) | 0.30 | 22 (53.7) | 42 (28.4) | 0.53 | 10 (50.0) | 11 (55.0) | 0.10 |
| Calcium channel blockers, n (%) | 13 (26.5) | 57 (28.5) | 0.04 | 10 (29.4) | 6 (17.6) | 0.28 | 11 (26.8) | 37 (25.0) | 0.04 | 7 (35.0) | 8 (40.0) | 0.10 |
| Beta-blocking agents, n (%) | 5 (10.2) | 22 (11.0) | 0.03 | 4 (11.8) | 6 (17.6) | 0.17 | 8 (19.5) | 12 (8.1) | 0.34 | 3 (15.0) | 1 (5.0) | 0.34 |
| Diuretics, n (%) | 6 (12.2) | 17 (8.5) | 0.12 | 5 (14.7) | 4 (11.8) | 0.09 | 7 (17.1) | 9 (6.1) | 0.35 | 3 (15.0) | 1 (5.0) | 0.34 |
| NSAIDs for systemic use, n (%) | 1 (2.0) | 13 (6.5) | 0.22 | 1 (2.9) | 0 (0.0) | 0.25 | 4 (9.8) | 9 (6.1) | 0.14 | 2 (10.0) | 1 (5.0) | 0.19 |
| Corticosteroids for systemic use, n (%) | 2 (4.1) | 19 (9.5) | 0.22 | 1 (2.9) | 1 (2.9) | 0.00 | 2 (4.9) | 5 (3.4) | 0.08 | 2 (10.0) | 1 (5.0) | 0.19 |
| Thyroid and anti-thyroid preparations, n (%) | 0 (0.0) | 8 (4.0) | 0.29 | 0 (0.0) | 0 (0.0) | - | 1 (2.4) | 2 (1.4) | 0.08 | 1 (5.0) | 0 (0.0) | 0.32 |

SGLT2i, sodium-glucose cotransporter 2 inhibitor; SD, standard deviation; HbA1c, Hemoglobin A1c; SUA, serum uric acid; COPD, chronic obstructive pulmonary disease; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; NSAID, non-steroidal anti-inflammatory drug; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1.

Based on the results of urinary glucose strip tests, the enrolled patients (n=438) were divided into two groups (Fig. 2). The N-UG and P-UG groups included 249 (56.8 %) and 189 (43.2 %) patients, respectively. Baseline $HbA_{1c}$ levels in the P-UG group were significantly higher than those in N-UG group (7.9 ± 1.6 vs. 7.1 ± 1.0, $p<0.01$). Of the patients in the N-UG group, 49 were newly prescribed SGLT2 inhibitors. The remaining 200 patients were prescribed antidiabetic agents, excluding SGLT2 inhibitors. After propensity score matching, 34 patients were included in each group. Among the patients in the P-UG group, 41 were newly prescribed SGLT2 inhibitors. The remaining 148 patients were prescribed antidiabetic agents, excluding SGLT2 inhibitors. After propensity score matching, 20 patients were included in each group. Patient characteristics are shown in Table 2.

### *2.2. Changes of SUA levels before and after treatment*

Regarding the treatment effect on SUA levels, Fig. 3 shows the changes in SUA levels before and after treatment. Before propensity score matching, SUA levels significantly decreased in the SGLT2i group (5.28 ± 1.23 to 4.82 ± 1.18 mg/dL, $p<0.01$), while significantly increasing in the non-SGLT2i groups (5.23 ± 1.45 to 5.39 ± 1.40 mg/dL, $p<0.01$). Similar trends were observed after propensity score matching (5.36 ± 1.21 to 4.81 ± 1.15 mg/dL in the SGLT2i group, $p<0.01$; 5.25 ± 1.35 to 5.56 ± 1.59 mg/dL in the non-SGLT2i group, $p<0.05$).

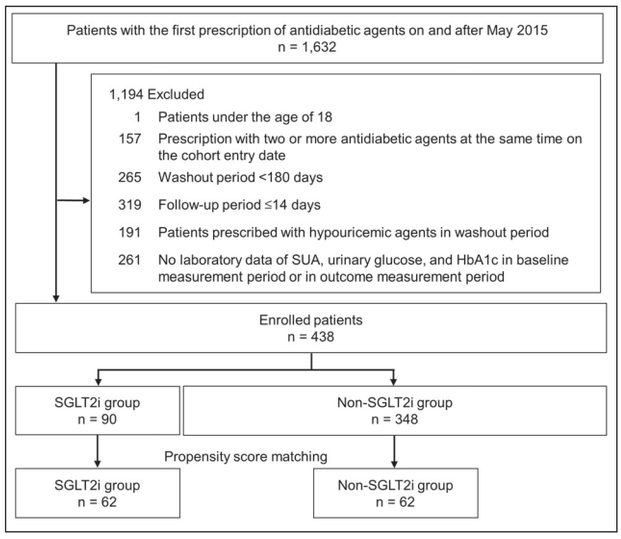


Fig. 1: Patient selection flowchart. The SGLT2i group included patients newly prescribed SGLT2 inhibitors. The non-SGLT2i group included patients newly prescribed antidiabetic agents, excluding SGLT2 inhibitors. Abbreviations: SUA, serum uric acid; HbA1c, hemoglobin A1c; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

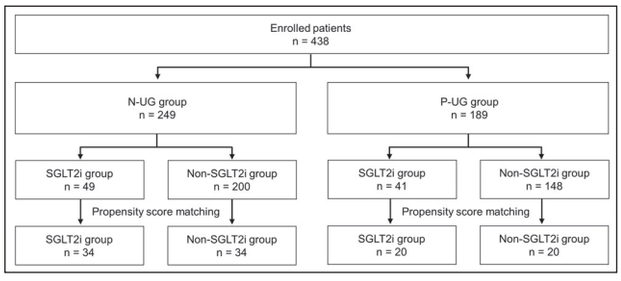


Fig. 2: Patient selection flowchart according to the results of urinary glucose strip tests. The N-UG group included patients with negative urinary glucose strip test results (-), and the P-UG group included patients with positive urinary glucose strip test results (± or more) in baseline measurements. The SGLT2i group included patients newly prescribed SGLT2 inhibitors. The non-SGLT2i group included patients newly prescribed antidiabetic agents, excluding SGLT2 inhibitors.
Abbreviation: SGLT2i, sodium-glucose cotransporter 2 inhibitor.

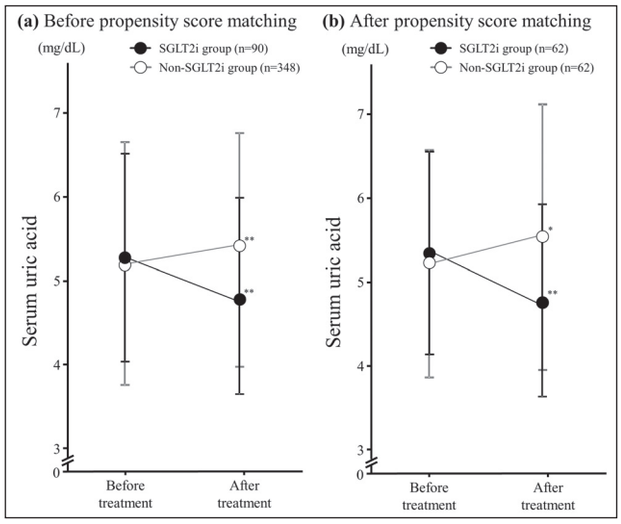


Fig. 3: Changes in serum uric acid levels before and after treatment in the SGLT2i and non-SGLT2i groups. (a) Before and (b) after propensity score matching. Data are expressed as mean ± SD. Paired *t*-test was used to compare between serum uric acid levels before and after treatment. $*p < 0.05$, $**p < 0.01$. Abbreviations: SGLT2i, sodium-glucose cotransporter 2 inhibitor; SD, standard deviation.

### *2.3. Changes of SUA levels before and after treatment based on urinary glucose status*

Fig. 4A shows the SUA levels changes in the N-UG group. Before propensity score matching, SUA levels in the SGLT2i group significantly decreased (5.57 ± 1.19 to 4.90 ± 1.25 mg/dL, $p<0.01$), while there were the non-SGLT2i group showed no significant differences in SUA levels (5.30 ± 1.41 to 5.41 ± 1.37 mg/dL, $p=0.12$) before and after treatment. Similar trends were observed after propensity score matching (5.50 ± 1.21 to 4.68 ± 1.09 mg/dL in the SGLT2i group, $p<0.01$; 5.69 ± 1.46 to 5.67 ± 1.51 mg/dL in the non-SGLT2i group, $p=0.90$).
Fig. 4B shows the changes in SUA levels of the P-UG group. Before propensity score matching, there were no significant differences in SUA levels before and after treatment in the SGLT2i group (4.93 ± 1.21 to 4.74 ± 1.11 mg/dL, $p=0.12$), while the SUA levels in the non-SGLT2i group significantly increased (5.12 ± 1.51 to 5.35 ± 1.44 mg/dL, $p<0.05$). Similar trends were observed after propensity score matching (4.83 ± 1.24 to 4.64 ± 1.18 mg/dL in the SGLT2i group, $p=0.15$; 4.82 ± 1.14 to 5.24 ± 1.46 mg/dL in the non-SGLT2i group, $p<0.05$).

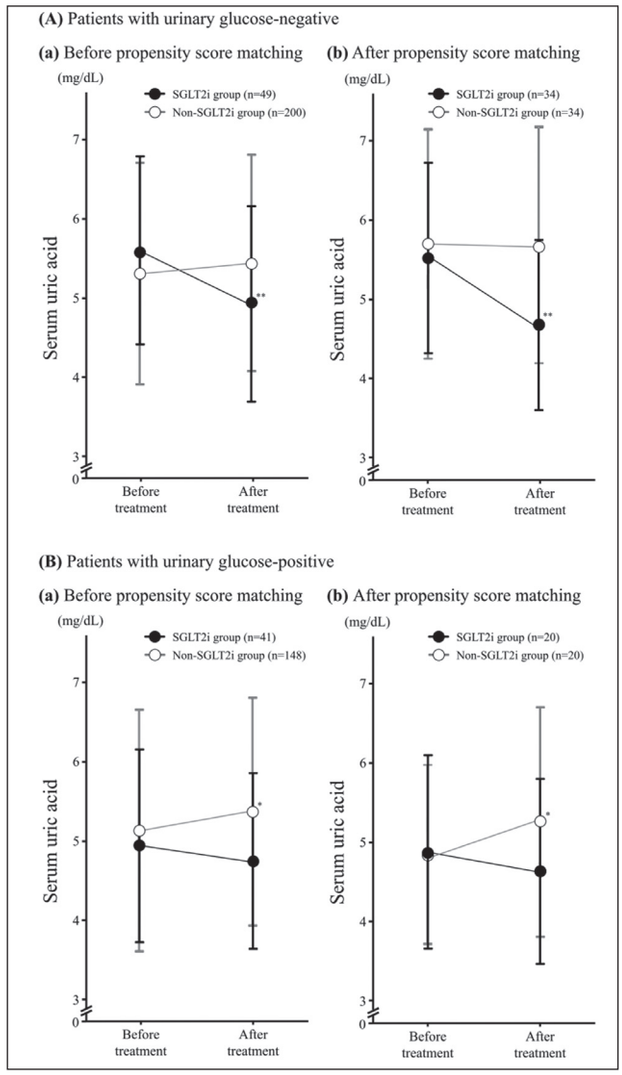


Fig. 4: Changes in serum uric acid levels before and after treatment in the SGLT2i and non-SGLT2i groups in patients with urinary glucose-negative (A) and -positive (B). (a) Before and (b) after propensity score matching. Data are expressed as mean ± SD. Paired *t*-test was used to compare between serum uric acid levels before and after treatment. $*p < 0.05$, $**p < 0.01$. A urinary glucose-negative status was defined as a negative urinary glucose strip test result (-).
Urinary glucose-positive was defined as a positive urinary glucose strip test result (± or more).
Abbreviations: SGLT2i, sodium-glucose cotransporter 2 inhibitor; SD, standard deviation.

## 3. Discussion

This retrospective observational study clarified the effects of baseline urinary glucose levels on the relationship between SGLT2 inhibitors and SUA levels. SGLT2 inhibitors significantly decreased the SUA levels in patients with baseline urinary glucose negativity but tended to decrease its levels in those with baseline urinary glucose positivity. Interestingly, the administration of antidiabetic agents, other than SGLT2 inhibitors, increased SUA levels in patients with baseline urinary glucose positivity. Similar results were obtained after propensity score matching. These results suggest the importance of SGLT2 inhibitor administration for prevention of complications of hyperuricemia in Japanese patients with T2DM.

In this study, approximately 35% of the patients enrolled at a single hospital were female, and their mean age was approximately 65 years. When compared to research data from the Japanese administrative claims database (2012–2020) (Iketani and Imai 2023), the male-to-female ratio of patients with T2DM was similar, but the mean age in our study was higher. The reason for this was considered to be the difference in the timing of age calculation. The patients in the SGLT2i group were significantly younger than those in the non-SGLT2i group, as SGLT2 inhibitors should be administered with utmost caution in elderly patients (Committee on the Proper Use of SGLT2 Inhibitors. 2020). The proportion of patients who were prescribed DPP-4 inhibitors and biguanides was higher in the SGLT2i group than in the non-SGLT2i group. Two antidiabetic agents, biguanides and DPP-4 inhibitors, were reported to be the most prevalent first prescriptions in Japanese patients with T2DM (Tanabe et al. 2017). Furthermore, the proportion of patients prescribed lipid-modifying agents, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or diuretics was higher in the SGLT2i group. These results suggest that the 438 patients enrolled in this study had profiles similar to those of general Japanese patients with T2DM, and the SGLT2i group consisted of patients whose blood glucose levels could not be controlled by lifestyle modification and who had hyperlipidemia and cardiovascular problems.

To the best of our knowledge, there are few reports on the relationship between baseline urinary glucose and changes in SUA levels induced by SGLT2 inhibitors. Administration of SGLT2 inhibitors for at least one week can significantly decrease SUA levels (Yuan et al. 2020). Changes in SUA and urinary glucose levels before and after the administration of luseogliflozin were investigated in patients with T2DM, and 85% of patients had negative urinary glucose levels at baseline (Jinnouchi et al. 2021). SUA levels decreased significantly after four weeks of treatment with luseogliflozin, and all patients had urinary glucose positivity (4+). As the majority of patients were urinary glucose-negative at baseline, changes in SUA levels in patients with urinary glucose positivity were not clear. In our study, SUA levels decreased significantly in the N-UG group but tended to decrease in the P-UG group without significant differences. $HbA_{1c}$ levels at baseline were significantly higher in the P-UG group than those in the N-UG group. As such, the P-UG group seems to have a high proportion of patients with poor glycemic control. Regarding the association between HbA1c at baseline and changes in SUA levels after SGLT2 inhibitor administration, SUA levels were reported to be decreased to a greater degree in patients with lower baseline $HbA_{1c}$ levels (Ouchi et al, 2018). Several studies showed that the difference in SUA levels in patients with lower $HbA_{1c}$ at baseline was approximately -0.8 to -0.6 mg/dL and that in patients with higher HbA1c at baseline was approximately -0.5 to -0.3 mg/dL (Fuchigami et al. 2020; Jinnouchi et al. 2021; Kario et al. 2020; Koshizaka et al. 2021; Okada et al. 2021; Ouchi et al. 2018). Even if SGLT2 inhibitors are administered to patients with poor glycemic control, such as those with urinary glucose-positive or higher $HbA_{1c}$ levels, the difference in SUA levels may be lower than that in patients with good glycemic control. This our study also showed a similar trend. Although SGLT2 inhibitors administration increased urinary glucose concentration when urinary glucose was positive before SGLT2 inhibitors administration, GLUT9-mediated SUA excretion may reach a plateau. Specifically, SGLT2 inhibitors may not cause excessively low SUA levels.

This study had some limitations. First, this was a single-center study with a small sample size and limited to Japanese patients. Second, the treatment duration in this study was, at most, 90 days after SGLT2 inhibitors administration, and the dosage of SGLT2 inhibitors was not considered. Third, lifestyle habits, such as diet, were not considered. SUA levels are increased by high purine diets and excessive fructose-containing diets (Choi et al. 2004). Furthermore, SUA levels have seasonal and diurnal variations (Kanabrocki et al. 2000), that have not been previously considered. Fourth, the qualitative urinary glucose test is affected by ascorbic acid (Mayson et al. 1972); however, ascorbic acid intake before the test could not be considered. Fifth, propensity score matching was used to account for covariate effects; however, the retrospective, nonrandomized nature of the design made it difficult to completely eliminate selection bias and residual confounding.

In conclusion, SGLT2 inhibitors significantly decreased the SUA levels in patients with baseline urinary glucose negativity and tended to decrease its levels in those with urinary glucose positivity. Similar results were obtained after adjusting for patient backgrounds with propensity score matching. Regardless of the urinary glucose status at baseline, the administration of SGLT2 inhibitors may be useful for patients with T2DM to prevent complications of hyperuricemia. Studies with larger sample sizes, long-term follow-ups, and various ethnic backgrounds are warranted to confirm our results.

## 4. Experimental

### *4.1. Study design and data source*

We conducted a retrospective observational study using the electronic medical records of patients with T2DM of Kindai University Nara Hospital (April 2013 to March 2022). It is an academic hospital with 518 beds and is located in Ikoma, Nara, Japan. From the electronic medical records, we obtained disease records using the International Classification of Diseases tenth revision (ICD-10) codes, hospital visit dates, admission dates, discharge dates, patient characteristics, laboratory data, and prescription data. After data collection, personal data were anonymized so that specific individuals could not be identified.

### *4.2. Ethics*

This study was conducted in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Health, Labor, and Welfare in Japan. This study was approved by the Ethics Committee of Kindai University Nara Hospital on Jan 23, 2023 (approval number: 688), and the Ethics Committee of Kindai University School of Pharmacy on April 8, 2023 (approval number, 22-223). The requirement for informed consent was waived due to the use of anonymized data.

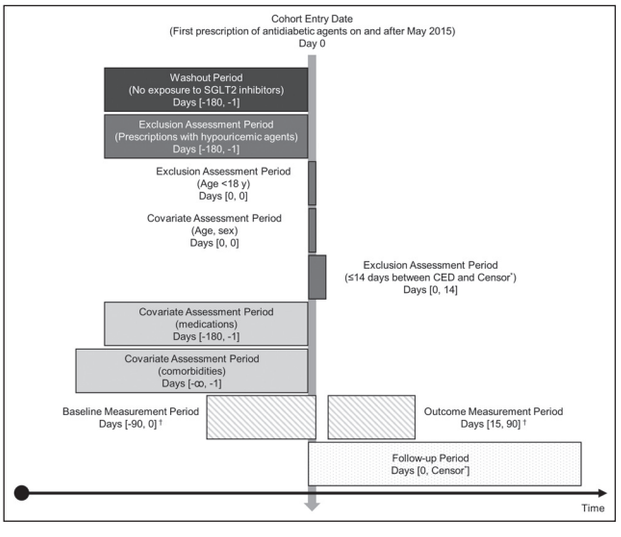


Fig. 5: Study design. *The censor was defined as the discontinuation of the antidiabetic agent started at the CED, prescription of an antidiabetic agent of the other group, or initiation of hypouricemic agents, whichever came first.
†Laboratory data for each patient were collected at the date closest to the CED for the baseline measurement and closest to 90 days after CED for the outcome measurement.
Abbreviation: CED, cohort entry date.

### 4.3. Study patients

SGLT2 inhibitors started being prescribed at the Kindai University Nara Hospital on May 1, 2015. Patients who were newly prescribed antidiabetic agents, such as sulfonylureas, biguanides, glitazones, alpha-glucosidase inhibitors, glinides, DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors, at the hospital from May 2015, inclusively, were included in the study. The date of the first prescription of antidiabetic agents from May 2015 onwards was defined as the CED. The washout period was defined as 180 days prior to CED. Fig. 5 illustrates the study design. Patients newly prescribed SGLT2 inhibitors in hospitals were included in the SGLT2i group, while those who were newly prescribed antidiabetic agents (excluding SGLT2 inhibitors) were included in the non-SGLT2i group. The follow-up period was defined as the period from the first prescription of antidiabetic agents to the discontinuation of the agents, prescription of an antidiabetic agent of the other group, or initiation of hypouricemic agents, whichever came first. Patients with 1) age <18 years at CED, 2) two or more antidiabetic agents simultaneously at CED, 3) <180 days of washout, 4) ≤14 days of follow-up, 5) prescription of hypouricemic agents in during washout, and 6) no baseline or outcome laboratory data on SUA, urinary glucose, and $HbA_{1c}$ were excluded from this study.
We used propensity score matching to minimize between-group differences (Austin 2011). Propensity scores were calculated using logistic regression analysis. Propensity score-matched pairs were created by matching the SGLT2i and non-SGLT2i groups based on the nearest neighbor pair-matching algorithm with a 0.2 caliper width.

### 4.4. Comparison of SUA before or after administration of SGLT2 inhibitors

We defined baseline and outcome measurement periods to obtain laboratory data for SUA, urinary glucose, and HbA1c. The baseline measurement period was defined as 90 days prior to CED and during CED. The outcome measurements were defined as those performed between days 15 and 90. Fourteen days after CED, patients were excluded from the outcome measurement period to evaluate the effect of newly prescribed antidiabetic agents on SUA levels. We collected laboratory data from the date closest to the CED in the baseline measurement period. In the outcome measurement period, we collected laboratory data from the date furthest from the CED. First, changes in SUA levels between the baseline and outcome measurement periods were evaluated. Next, based on the results of the urinary glucose strip test in the baseline measurement period, we divided all patients into P-UG and N-UG groups. The P-UG group included patients with positive urinary glucose strip test results (± or more). The N-UG group included patients with negative urinary glucose strip test results (-). The ARKRAY urine strip test, URIFLET™ S (Arkray Inc., Kyoto, Japan), was used for the urinary glucose qualitive test. Subsequently, the patients in each group were divided into SGLT2i and non-SGLT2i groups, and changes in SUA levels were evaluated.

**Table 3: Definition of diseases and medications**

| **Diseases** | **Definition** |
|---|---|
| Atherosclerosis | ICD-10 code: I70 |
| Cerebrovascular diseases | ICD-10 code: I60–I69 |
| Chronic liver diseases | ICD-10 code: K72, K73, K74, K76 |
| COPD | ICD-10 code: J41–J44 |
| Diabetes mellitus | ICD-10 code: E11, E14 |
| Diabetic nephropathy | ICD-10 code: E112, E142 |
| Diabetic neuropathy | ICD-10 code: E114, E115, E144, E145, M142, G590, G632, G730, G990 |
| Diabetic retinopathy | ICD-10 code: E113, E143, H360 |
| Disorders of lipoprotein metabolism | ICD-10 code: E78 |
| Disorders of thyroid gland | ICD-10 code: E00–E07 |
| Heart failure | ICD-10 code: I50 |
| Hypertensive diseases | ICD-10 code: I10–I15 |
| Ischemic heart diseases | ICD-10 code: I20–I25 |
| Kidney diseases | ICD-10 code: N17–N19 |
| | |
| **Medications** | **Definition** |
| ACE inhibitors and ARBs | Aliskiren, Azilsartan, Candesartan, Candesartan and amlodipine, Candesartan and hydrochlorothiazide, Captopril, Enalapril, Imidapril, Irbesartan, Irbesartan and amlodipine, Irbesartan and trichlormethiazide, Losartan, Losartan and hydrochlorothiazide, Olmesartan, Olmesartan and azelnidipine, Perindopril, Telmisartan, Telmisartan and amlodipine, Telmisartan and hydrochlorothiazide, Temocapril, Valsartan, Valsartan and amlodipine, Valsartan and cilnidipine, Valsartan and hydrochlorothiazide, Valsartan and sacubitril |
| Alpha-glucosidase inhibitors | Miglitol, Voglibose |
| Beta-blocking agents | Arotinolol, Atenolol, Bisoprolol, Carteolol, Carvedilol, Celiprolol, Propranolol, Sotalol |
| Biguanides | Metformin, Metoformin and alogliptin, Metformin and anagliptin, Metformin and vildagliptin |
| Calcium channel blockers | Amlodipine, Amlodipine and atorvastatin, Amlodipine and candesartan, Amlodipine and irbesartan, Amlodipine and telmisartan, Amlodipine and valsartan, Azelnidipine, Azelnidipine and olmesartan, Benidipine, Bepridil, Cilnidipine, Cilnidipine and valsartan, Diltiazem, Nicardipine, Nifedipine, Nilvadipine, Verapamil |
| Corticosteroids for systemic use | Betamethasone, Betamethasone and d-chlorpheniramine, Dexamethasone, Fludrocortisone, Hydrocortisone, Prednisolone |
| Diuretics | Azosemide, Furosemide, Hydrochlorothiazide and candesartan, Hydrochlorothiazide and losartan, Hydrochlorothiazide and valsartan, Indapamide, Piretanide, Telmisartan and hydrochlorothiazide, Tolvaptan, Torasemide, Trichlormethiazide, Trichlormethiazide and irbesartan |
| DPP-4 inhibitors | Alogliptin, Alogliptin and metformin, Anagliptin, Anagliptin and metformin, Linagliptin, Linagliptin and empagliflozin, Sitagliptin, Sitagliptin and ipragliflozin, Teneligliptin, Teneligliptin and canagliflozin, Trelagliptin, Vildagliptin, Vildagliptin and metformin |
| Glinides | Mitiglinide, Nateglinide, Repaglinide |
| Glitazones | Pioglitazone |
| GLP-1 agonists | Dulaglutide, Exenatide, Insulin degludec and liraglutide, Insulin glargine and lixisenatide, Liraglutide, Lixisenatide, Semaglutide |
| Human insulin and analogs | Insulin (human), Insulin aspart, Insulin degludec, Insulin degludec and insulin aspart, Insulin degludec and liraglutide, Insulin detemir, Insulin glargine, Insulin glargine and lixisenatide, Insulin glulisine, Insulin lispro |
| Lipid-modifying agents | Atorvastatin, Atorvastatin and amlodipine, Atorvastatin and ezetimibe, Bezafibrate, Colestimide, Ethyl icosapentate, Evolocumab, Ezetimibe, Fenofibrate, Fluvastatin, Omega-3 acid ethyl esters, Pemafibrate, Pitavastatin, Polyenephosphatidylcholine, Pravastatin, Probucol, Rosuvastatin, Simvastatin, Tocopherol |
| NSAIDs for systemic use | Ampiroxicam, Bucolome, Celecoxib, Diclofenac, Emorfazone, Etodolac, Flurbiprofen, Indometacin farnesil, Indometacin, Ketoprofen, Lornoxicam, Loxoprofen, Mefenamic acid, Meloxicam, Nabumetone, Naproxen, Tiaramide |
| SGLT2 inhibitors | Canagliflozin, Canagliflozin and teneligliptin, Dapagliflozin, Empagliflozin, Empagliflozin and linagliptin, Ipragliflozin, Ipragliflozin and sitagliptin, Luseogliflozin, Tofogliflozin |
| Sulfonylureas | Glibenclamide, Gliclazide, Glimepiride |
| Thyroid and anti-thyroid preparations | Levothyroxine sodium, Liothyronine sodium, Potassium iodide, Propylthiouracil, Thiamazole |

Abbreviation: International Classification of Diseases, tenth revision, ICD-10; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; NSAID, non-steroidal anti-inflammatory drug; SGLT2, sodium-glucose cotransporter 2.

### *4.5. Variables*

Baseline characteristics of the study participants were collected as variables. Sex; age at CED; and laboratory data of SUA, urinary glucose, and HbA1c in the baseline measurement period were investigated. Comorbidities and medications used were also assessed. Diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, disorders of lipoprotein metabolism, hypertensive diseases, ischemic heart diseases, disorders of thyroid gland, heart failure, chronic liver diseases, cerebrovascular diseases, atherosclerosis, kidney diseases, and chronic obstructive pulmonary diseases diagnosed before CED were selected as comorbidities. DPP-4 inhibitors, biguanides, human insulin and analogs, alpha-glucosidase inhibitors, glinides, sulfonylureas, glitazones, GLP-1 agonists, lipid-modifying agents, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blocking agents, diuretics, nonsteroidal anti-inflammatory drugs for systemic use, corticosteroids for systemic use, and thyroid and anti-thyroid preparations prescribed 180 days before CED were selected as medications. The ICD-10 codes for comorbidities and the names of therapeutic agents in each therapeutic category are listed in Table 3.

### *4.6. Statistical analysis*

Continuous variables were summarized as mean ± standard deviation. Paired *t*-test were used to compare SUA levels before and after treatment. All reported *p*-values were two-sided, and a *p*-value $<0.05$ was considered statistically significant. Data management was performed using the Visual Mining Studio software (version 8.7; NTT DATA Mathematical Systems Inc., Tokyo, Japan). Statistical analyses were performed using JMP Pro (version 14.2; SAS Institute Inc., Cary, NC, USA).

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Competing interests: The authors declare no competing interests.

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