Hematocrit elevation after SGLT2 inhibitor administration may be associated with the degree of proximal tubular damage

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1. Introduction

SGLT2 inhibitors are drugs that increase urine glucose excretion and lower blood glucose levels by inhibiting the action of SGLT2 in the proximal tubules. The drug attracted attention with data reported to have not only a strong hypoglycemic effect but also reduce the incidence of cardiovascular disease 3POINT MACE (cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction).[1] In addition, the following year, SGLT2 inhibitors were reported to reduce the incidence of renal complex end-points (progression to overt albuminuria, doubling of serum creatinine levels, initiation of renal replacement therapies (such as dialysis), and death from kidney disease) and to minimize the estimated glomerular filtration rate (eGFR) decline postadministration.[2] Although many unclear points have been reported about these mechanisms, the nephroprotective effect is used to eliminate glomerular hypertension by improving the tubular glomerular feedback mechanism and hypoxia and oxidative stress in the proximal tubules.[3,4] Although administration of SGLT2 inhibitors increases the hematocrit level by approximately 2% to 4%, a post hoc analysis of EMPA-REG OUTCOME trials reports that this increase was most commonly associated with reduced cardiovascular death.[5] Increased hematocrit (ΔHct) level is not caused by hemoconcentration due to the diuretic action of SGLT2 inhibitors but by erythropoiesis that increases erythropoietin concentration due to the administration of SGLT2 inhibitors.[6] Fibroblasts around the proximal tubule express erythropoietin production ability when normal, their ability to produce erythropoietin is lost when impaired.[6a] In chronic

Abstract

The renal protective effects of SGLT2 inhibitors are known to be due to the elimination of glomerular hypertension and improvement of hypoxia and oxidative stress in the proximal tubule. Therefore, this increased hematocrit (ΔHct) level has been hypothesized to indicate restored tubular function and improved renal prognosis. To analyze the relationship between ΔHct and decreased estimated glomerular filtration rate (eGFR) after SGLT2 inhibitor administration backward from medical record data. Data from 206 patients who continued SGLT2 inhibitors for >3 years were analyzed. The decreased eGFR after administration of SGLT2 inhibitors was defined as Slope B. Factors statistically significantly associated with Slope B in multiple regression analysis were systolic blood pressure (sBP) ($\beta$ = −.211, $P = .003$), short-term decreased eGFR after SGLT2 inhibitor administration (initial dip) ($\beta$ = −.235, $P = .003$), ΔHct ($\beta$ = −.185, $P = .015$). These findings were the opposite of our hypothesis. ΔHct was not a marker indicating improved renal prognosis and may reflect the extent of the proximal tubular disorder before administering SGLT2 inhibitors.

Abbreviations: CKD = chronic kidney disease, dBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, sBP = systolic blood pressure, ΔHct = increased hematocrit.

Keywords: erythropoietin, estimated glomerular filtration rate, hematocrit, proximal tubular disorder, SGLT2 inhibitor

OUTCOME trials reports that this increase was most commonly associated with reduced cardiovascular death.[5] Increased hematocrit (ΔHct) level is not caused by hemoconcentration due to the diuretic action of SGLT2 inhibitors but by erythropoiesis that increases erythropoietin concentration due to the administration of SGLT2 inhibitors.[6] Fibroblasts around the proximal tubule express erythropoietin production ability when normal, their ability to produce erythropoietin is lost when impaired.[6a] In chronic

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Keywords: CKD = chronic kidney disease, dBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, sBP = systolic blood pressure, ΔHct = increased hematocrit.
hyperglycemic conditions, proximal tubules become hypoxic, and fibroblasts are damaged. Improved hypoxia state of the proximal tubules by administering SGLT2 inhibitors restored the erythropoietin production ability and elevated the hematocrit level. Therefore, elevated hematocrit levels after administering SGLT2 inhibitors may be a surrogate marker of improved renal prognosis.[7] However, no study has verified the relationship between elevated hematocrit levels and renal prognosis after administering SGLT2 inhibitors. In this study, we retrospectively analyzed medical record data and how hematocrit changes after administration of SGLT2 inhibitors were associated with kidney prognosis.

2. Materials and Methods

This retrospective study was conducted by correcting the data from medical records. The study participants were patients with type 2 diabetes who had been attending Tokyo Medical University hospital and had continued SGLT2 inhibitors for >3 years. Data from January 1, 2011, to October 31, 2020, were excluded. Exclusion criteria included patients who added or discontinued GLP1 receptor agonists and RAS inhibitors. Analyzed data are collected every 3 months for 36 months before and after the administration of SGLT2 inhibitors.

The eGFR decline at 36 months before the SGLT2 inhibitor administration was defined as Slope A and that after the SGLT2 inhibitor administration was defined as Slope B. The short-term eGFR decline before and after SGLT2 inhibitor administration was defined as the initial dip (at 3 months postadministration and just before administration). The short-term hematocrit level increases before and after SGLT2 inhibitor administration was defined as ΔHct (at 3 months postadministration and just before administration). We analyzed the relationships between Slope B and age, diabetes duration, systolic blood pressure (SBP), diastolic blood pressure (DBP), hemoglobin A1c (HbA1c), eGFR, urinary protein qualitative (before the SGLT2 inhibitor administration), ΔHct, Slope A, and initial dip. The amount of urine protein by urine qualitative was converted to a rank scale of -r, ±, 30, 100, >300, to 0, 1, 2, 3, 4. This study was conducted with the approval of the medical ethical review board of Tokyo Medical University (approval code T2020-0397). The need for informed consent was waived as this study was retrospective. Instead, we provided opt-out on our website.

2.1. Statistical analysis

All analyses were performed using the IBM SPSS version 28 (IBM, Chicago). Variables were expressed as mean ± standard deviation. A comparison of data just before and after 36 months of SGLT2 inhibitor administration was analyzed using paired t test. The relationship between Slope B and various data was evaluated using multiple regression analysis by the forced input method with Slope B as the objective variable and age, diabetes duration, SBP, DBP, HbA1c, eGFR, urinary protein qualitative (before SGLT2 inhibitor administration), ΔHct, Slope A, and initial dip as the explanatory variable. Significance was defined as P < .05 Analysis was performed ignoring missing data due to occurrence mechanism of missing data.

2.2. Baseline characteristics and laboratory parameters

A total of 206 (151 males and 55 females) were included with a mean age of 60.9 years, average diabetes duration of 13.5 years, average body mass index of 28.8 kg/m², mean HbA1c of 8.5%, and mean eGFR of 80.4 mL/min/1.73 m² (Table 1).

| Table 1 Baseline characteristics and laboratory parameters. |
|---------------------|---------------------|---------------------|
| Sex, n (%)          | Male                | Female              |
|                     | 151 (73.3)          | 55 (26.7)           |
| Age (yr)            | 60.9 ± 10.5         |
| Diabetes duration (yr)| 13.5 ± 6.0         |
| BMI                 | 28.8 ± 4.6          |
| dBP (mm Hg)         | 135.5 ± 17.0        |
| dBP (mm Hg)         | 79 ± 12.4           |
| Hemoglobin (g/dL)   | 14.5 ± 1.5          |
| Hematocrit (%)      | 42.8 ± 3.8          |
| ALT (U/L)           | 42.8 ± 34.6         |
| AST (U/L)           | 33.9 ± 24.8         |
| HDL-Chol (mg/dL)    | 45.6 ± 11.3         |
| LDL-Chol (mg/dL)    | 99.4 ± 22.9         |
| Triglyceride (mg/dL)| 196.1 ± 141.9       |
| Uric acid (mg/dL)   | 5.5 ± 1.3           |
| BUN (mg/dL)         | 14.4 ± 4.3          |
| Creatinine (mg/dL)  | 7.8 ± 23.2          |
| eGFR (mL/min/1.73 m²)| 80.4 ± 22.3       |
| Glucose (mg/dL)     | 171.7 ± 59.9        |
| HbA1c (%)           | 8.5 ± 1.2           |
| Urine protein (%)   | −/+30/100/>300       |
| Medications that affect renal function |
| ACE inhibitor/ARB (%)| 49                  |
| Statin (%)          | 31.6                |
| GLP-1 RA (%)        | 47.6                |
| MRA (%)             | 2.4                 |

ACE inhibitor = angiotensin-converting enzyme inhibitor, ALT = alanine transaminase, ARB = angiotensin II receptor blocker, AST = aspartate transaminase, BMI = body mass index, BUN = blood urea nitrogen, dBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, GLP-1 RA = glucagon-like peptide-1 receptor agonist, HbA1c, hemoglobin A1c, HDL-Chol = high density cholesterol, LDL-Chol = low density cholesterol, MRA = mineral corticoid receptor antagonist, SBP = systolic blood pressure.

HbA1c was reduced significantly (just before vs 36 months after: 8.5 ± 1.2 vs 7.9 ± 1.2, P < .001). Body weight (kg) also reduced significantly (79.3 ± 14.9 vs 76.4 ± 14.8, P < .001). Both systolic and dBP (mm Hg) were reduced significantly. (Systolic: 135.4 ± 17.0 vs 129.8 ± 16.2, P < .001, Diastolic: 79.0 ± 12.5 vs 75.7 ± 11.2, P < .001) Aspartate transaminase (AST) and alanine transaminase (ALT), liver function data were improved significantly. (AST: 34.1 ± 24.8 vs 27.6 ± 16.2, P < .001, ALT: 43.1 ± 34.6 vs 33.1 ± 25.4, P < .001). In lipid data, HDL cholesterol (mg/dL) was significantly elevated. (45.4 ± 10.7 vs 48.5 ± 11.8, P < .001) Uric acid was reduced significantly. (5.6 ± 1.3 vs 5.3 ± 1.2, P < .001) eGFR declined significantly, but eGFR decline rate per year was significantly slow. (eGFR: 80.3 ± 22.3 vs 78.6 ± 24.1, P < .001, eGFR decline rate per year: −1.6 ± 4.3 vs 0.2 ± 3.1, P < .001) Hemoglobin and Hematocrit elevated significantly. (Hemoglobin: 14.5 ± 1.5 vs was15.2 ± 1.6, P < .001, Hematocrit: 42.8 ± 3.8 vs 44.8 ± 4.3, P < .001) (Table 2).

Factors statistically significantly associated with Slope B in multiple regression analysis were SBP (β = −211, P = .03), initial dip (β = −235, P = .003), ΔHct (β = −185, P = .026), and urine protein (β = −204, P = .015) (Table 3).

4. Discussion

In this study, four factors were detected to be associated with the eGFR decline after SGLT2 inhibitor administration, such as SBP initial dip, urine protein, and ΔHct. For SBP, the higher the SBP before the SGLT2 inhibitor administration, the steeper the eGFR decline after the SGLT2 inhibitor administration. It is widely known that blood pressure is associated with the onset of chronic kidney disease (CKD), and when the normal
blood pressure group (<120/80 mmHg) is set to 1, the incidence of CKD has been reportedly increased by 1.49 times in the normal hypertension group (120–139/80–89 mmHg), 1.83 times in the degree I hypertension (140–159/90–99 mmHg), and 2.55 times in the degree II hypertension (≥160/100 mmHg),[8] indicating kidney damage due to hypertension. For initial dips, the larger the initial dip, the slower the eGFR decline after SGLT2 inhibitor administration. The initial dip indicates the degree of recovery from glomerular hypertension occurring due to the breakdown of the tubular glomerular feedback mechanism.[9] However, in real-world data, regarding the relationship between the initial dip and renal composite end-point, decreased risk of the renal composite end-point has been reported regardless of the degree of the initial dip.[10] Conversely, reports have demonstrated the risk of newly developed AF and MACE/HF, and renal combined end-points were increased in the group with an initial dip of ≥30% compared to the group without eGFR reduction, and the significance of the initial dip remains largely unknown.[11] As for the amount of urine protein, the eGFR decline was steeper as the urine protein amount increased. The amount of urine protein reflects the degree of glomerular disorder and is related to the eGFR decline.[12] The last is the relationship between ΔHct and renal prognosis. The results showed that the higher the ΔHct, the steeper the eGFR decline. The hypothesis is that ΔHct after the SGLT2 inhibitor administration indicates an improvement in the proximal tubule environment and becomes a marker of improved renal prognosis. The results of this study differed from the hypothesis. Patients with diabetes are more prone to anemia, and anemia is known to be associated with diabetic complications.[13,14] In patients with diabetes mellitus and anemia, a relative erythropoietin deficiency is observed in approximately 60% even in those without CKD. Furthermore, the erythropoietin value is independently related to the subsequent eGFR decline and has been reported that the lower the erythropoietin, the steeper the eGFR decline.[15] To date, diabetic nephropathy has been considered a glomerular and podocyte disorders; however, in recent years, tubular disorders precede podocyte disorders. Hasegawa et al proved the mechanism of ultraearly renal impairment before presenting albuminuria may begin with a tubular disorder.[16] In a 3-year follow-up study of 470 patients with type 2 diabetes without albuminuria, hemoglobin levels were reported to predict the albuminuria progression.[17] From these, ultraearly renal impairment can be inferred to begin in the renal tubules and causes anemia due to a decreased erythropoietin level. Moreover, renal tubular disorders lead to glomerular disorders. In this study, many patients without CKD were included, 83% had eGFR of

| Table 2 |
|-----------------|-----------------|-----------------|-----------------|
| Characteristics and laboratory parameters just before and 36 months after the SGLT2 inhibitor administration. | | | |
| | Just before administration | SD | 36 mo postadministration | SD | p value |
| Body weight (kg) | 79.3 | 14.9 | 76.4 | 14.8 | <.001 |
| SBP (mm Hg) | 135.4 | 17.0 | 129.8 | 16.2 | <.001 |
| dBP (mm Hg) | 79.0 | 12.5 | 75.7 | 11.2 | <.001 |
| Hemoglobin (g/dL) | 14.5 | 1.5 | 15.2 | 1.6 | <.001 |
| Hematocrit (%) | 42.8 | 3.8 | 44.8 | 4.3 | <.001 |
| ALT (UI/L) | 43.1 | 34.6 | 33.1 | 25.4 | <.001 |
| AST (UI/L) | 34.1 | 24.8 | 27.6 | 16.2 | <.001 |
| HDL-Chol (mg/dL) | 45.4 | 10.7 | 48.5 | 11.8 | <.001 |
| LDL-Chol (mg/dL) | 99.7 | 22.8 | 99.4 | 25.9 | <.001 |
| Triglyceride (mg/dL) | 194.6 | 142.4 | 215.2 | 192.9 | .077 |
| Uric acid (mg/dL) | 5.6 | 1.3 | 5.3 | 1.2 | <.001 |
| BUN (mg/dL) | 14.4 | 4.3 | 16.2 | 6.0 | <.001 |
| Creatinine (mg/dL) | .78 | .23 | .81 | .23 | <.001 |
| eGFR (mL/min/1.73 m²) | 80.3 | 22.3 | 78.6 | 24.1 | .04 |
| eGFR decline/yr | −1.6 (Slope A) | 4.3 | 2.2 (Slope B) | 3.1 | <.001 |
| Glucose (mg/dL) | 172.9 | 60.0 | 149.9 | 45.3 | <.001 |
| HbA1c (%) | 8.5 | 1.2 | 7.9 | 1.2 | <.001 |
| Glycoalbumin (%) | 20.6 | 4.3 | 18.3 | 4.2 | <.001 |

ALT = alanine transaminase, AST = aspartate transaminase, BUN = blood urea nitrogen, dBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, HDL-Chol = high density cholesterol, LDL-Chol = low density cholesterol, sBP = systolic blood pressure.

| Table 3 |
|-----------------|-----------------|-----------------|-----------------|
| Multiple regression analysis by the forced input method. | | | |
| Nonstandardized coefficients | Standardized coefficients | t value | P value |
| B (Const) | 7.661 | 4.114 | 1.862 | .065 |
| Age | −0.024 | 0.029 | −0.084 | −0.826 | .41 |
| Duration | −0.037 | 0.04 | −0.076 | −0.933 | .352 |
| BMI | −0.079 | 0.053 | −0.129 | −1.502 | .135 |
| SBP | −0.038 | .017 | −0.211 | −2.188 | .03 |
| dBP | .034 | .026 | .135 | 1.281 | .202 |
| HbA1c | .097 | .099 | .098 | .843 | .263 |
| ΔHct | −.222 | .099 | −.185 | −2.244 | .026 |
| eGFR | −0.012 | .013 | −0.089 | −0.959 | .339 |
| Slope A | −.053 | .057 | −.075 | −.93 | .354 |
| Initial dip | −.092 | .031 | −.235 | −2.975 | .003 |
| Urine protein | −.661 | .269 | −.204 | −2.457 | .015 |

BMI = body mass index, dBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, ΔHct = hematocrit increase, sBP = systolic blood pressure.
≥60 mL/min/1.73 m², and the qualitative (−) urine protein was 58%. Although the bivariate correlation between ΔHct and Slope B showed a nonstatistically significantly negative association with a correlation coefficient of −.137 and \( P = .05 \); however, when this relationship was analyzed as a quartile at the hematocrit value preadministration, the group with the lowest hematocrit (Hct 31.8%–40.3%), a significant negative correlation was confirmed with a correlation coefficient of −.441 and \( P = .001 \) (Fig. 1). This suggests a clear relationship when targeting a group with a relative erythropoietin deficiency. From these, ΔHct is inferred to reflect the degree of relative erythropoietin deficiency before the SGLT2 inhibitor administration and may indirectly represent the degree of tubular disorder.

4.1. Limitation
First, this was a retrospective, single-site study comprising a small number of cases. Although sBP, initial dips, urine protein qualitative, and ΔHct were statistically related to the eGFR decline after the SGLT2 inhibitor administration, urine protein was not quantified. The association between erythropoietin reduction, tubular disorders, and renal disorders was considered; however, erythropoietin and markers of tubular disorder (KIM1, NAG, NGAL, L-FABP, and \( \beta_2 \) microglobulin) were not measured.

In the future, we would like to measure erythropoietin concentration and tubular disorder markers in patients with type 2 diabetes and anemia before the SGLT2 inhibitor administration and investigate the relationship between these and ΔHct.

5. Conclusion
Changes in the hematocrit levels before and after SGLT2 inhibitor administration (ΔHct) may reflect the degree of the tubular disorder before the SGLT2 inhibitor administration.

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