EnM
ENDOCRINOLOGY AND METABOLISM

Brief Report

Endocrinol Metab 2024;39:653-658
https://doi.org/10.3803/EnM.2024.1919
pISSN 2093-596X · eISSN 2093-5978

Ketonuria as an Indicator of Improvement of Renal Function in Patients with Type 2 Diabetes Receiving SGLT2 Inhibitor Treatment

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We investigated the potential association between ketonuria during treatment with sodium-glucose cotransporter-2 (SGLT2) inhibitors and its renoprotective effect in patients with type 2 diabetes. We included 192 patients who had received SGLT2 inhibitors for more than 6 months. After propensity score matching, 52 patients each were allocated into groups with or without ketonuria, respectively. The estimated glomerular filtration rate exhibited a significant improvement only in subjects with ketonuria (without ketonuria: mean difference, –0.02 mL/min/1.73 m^2 [95% confidence interval (CI), –3.87 to 3.83 mL/min/1.73 m^2] vs. with ketonuria: mean difference, 6.81 mL/min/1.73 m^2 [95% CI, 3.16 to 10.46 mL/min/1.73 m^2]; $P<0.001$). Improvement in estimated glomerular filtration rate at 6 months was associated with female sex and lower baseline body weight, blood pressure, and triglyceride levels in patients with ketonuria. In conclusion, the presence of ketonuria was associated with the renoprotective effect of SGLT2 inhibitors, and female sex and the absence of metabolic syndrome components may serve as additional indicators of these medications' substantial renoprotective effects in individuals with ketonuria.

Keywords: Diabetes mellitus, type 2; Sodium-glucose transporter 2 inhibitors; Ketosis; Renal protection

INTRODUCTION

Diabetes is the leading cause of end-stage renal-disease, accounting for 40% to 50% of patients requiring renal replacement therapy [1,2]. Among anti-diabetic medications, sodium-glucose cotransporter-2 (SGLT2) inhibitors are the drug of choice to attenuate the progression of chronic kidney disease, including diabetic kidney disease (DKD) [3,4]. However, there is a lack of reliable indicators for the therapeutic efficacy of SGLT2 inhibitors in patients with DKD.

In both clinical studies and real-world situations, low-grade ketonemia has been observed after SGLT2 inhibitor treatment

Received: 27 December 2023, **Revised:** 9 March 2024,
Accepted: 26 March 2024

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[5]. Ketone bodies, which serve as an important energy source, are produced in the liver when glucose is scarce, such as during fasting, after alcohol intake, and following prolonged exercise [6,7]. Studies have suggested that ketone bodies, mainly β-hydroxybutyrate, may function as signaling metabolites that mitigate cellular senescence and injury [6,8,9]. However, the relevance of ketone bodies in monitoring and predicting the response to therapy with SGLT2 inhibitors remains incompletely understood.

This study aimed to investigate the potential association between the presence of ketonuria and the renoprotective effects of SGLT2 inhibitors in patients with type 2 diabetes.

METHODS

Data sources and patients

Electronic medical records housed in the Clinical Data Warehouse of Seoul National University Bundang Hospital (SNUBH) were used. The study was approved by the SNUBH Institutional Review Board (IRB No. B-2208-775-105) and written informed consent by the patients was waived due to a retrospective nature of our study. A total of 192 patients older than 18 years of age with type 2 diabetes who had been treated with SGLT2 inhibitors for more than 6 months were collected from January 2014 to January 2022. These patients were required to have consecutive urinalyses from the initiation of SGLT2 inhibitor treatment to the 6-month follow-up. Patients with a baseline hemoglobin A1c (HbA1c) below 6.5% (48 mmol/mol), an HbA1c of 10% (86 mmol/mol) or higher, and a baseline estimated glomerular filtration rate (eGFR) below 45 mL/min/1.73 m^2 were excluded. Additionally, patients with history of organ transplantation or chemotherapy, those lost to follow-up, and those living in nursing hospitals were excluded.

Study design

Patients were classified into two groups: those with and without ketonuria. The group with ketonuria included subjects who had no previous history of ketonuria prior to starting SGLT2 inhibitor treatment and those who developed ketonuria coinciding with the treatment period. Only these patients were selected for inclusion in the study. Patients who had ketonuria before beginning SGLT2 inhibitor therapy were excluded. Additionally, those who developed ketonuria during the treatment period but did not have persistent ketonuria throughout were also excluded (Supplemental Fig. S1). Ketone bodies were detected using the sodium nitroprusside reaction (UC-3500, Sysmex Corporation, Kobe, Japan).

Clinical and biochemical data were collected for analysis from the initial period and at 6 months following the initiation of SGLT2 inhibitor treatment. The degree of improvement in eGFR after 6 months and 1 year of SGLT2 inhibitor treatment was evaluated and compared with baseline values.

Statistical analysis

The patients who initially were positive and negative for ketonuria were matched using propensity score matching for the following variables: sex, age, duration of diabetes, baseline HbA1c, and baseline eGFR. Propensity score matching was performed using 1:1 nearest neighbor matching with a caliper width of 0.15, utilizing the "MatchIt" package version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Data are presented as mean±standard deviation or as number and percentage. Continuous variables were analyzed using the Student *t* test, while categorical data were evaluated using the chi-square test and Fisher exact test. The change in each parameter was calculated as the value at the 6-month period minus the value at baseline. Linear regression analysis was conducted for the individual biomarkers believed to be associated with the change in eGFR. Statistical analyses were performed using R software version 3.6.1. All comparisons were two-sided, and a *P* value of less than 0.05 was considered statistically significant.

RESULTS

Study population

We initially identified a total of 192 patients: 107 who were negative for ketonuria and 85 who were positive for ketonuria. The patients with ketonuria were predominantly male, younger, and had a shorter duration of diabetes compared to those without ketonuria (Table 1). The baseline body weight and eGFR were higher, while HbA1c was lower in patients with ketonuria. There were no differences in the use of concomitant diabetic medications, renin-angiotensin-aldosterone system (RAAS) blockade, or the presence of diabetes complications between the two groups. After propensity score matching, 52 subjects from each group—ketonuria-negative and ketonuria-positive, were matched. The baseline characteristics were similar between the matched groups.

Prespecified outcomes

Statistically significant improvements in glycemic control were observed in both ketonuria-negative and ketonuria-positive pa-

Table 1. Baseline Clinical Characteristics of Patients with or without Ketonuria before and after Propensity Score Matching

Characteristic	Before matching				After matching			
	Ketonuria (–) (*n*=107)	Ketonuria (+) (*n*=85)	SMD	*P* value	Ketonuria (–) (*n*=52)	Ketonuria (+) (*n*=52)	SMD	*P* value
Male sex	50 (46.7)	58 (68.2)	0.446	0.005	32 (61.5)	34 (65.4)	0.080	0.839
Age, yr	56.9±9.3	47.3±11.7	0.913	<0.001	51.9±8.4	52.4±9.6	0.055	0.781
Diabetes duration, yr	10.9±7.0	8.3±7.0	0.373	0.011	8.7±6.2	9.2±7.3	0.068	0.729
Body weight, kg	72.2±12.7	77.9±14.7	0.414	0.009	77.0±13.1	74.9±13.0	0.165	0.449
BMI, kg/m^2	27.1±3.8	27.5±4.0	0.122	0.439	27.8±3.6	26.9±3.7	0.228	0.296
SBP, mm Hg	131.7±13.4	133.4±15.9	0.117	0.442	131.6±13.0	132.5±16.7	0.059	0.780
DBP, mm Hg	76.8±9.1	80.4±12.3	0.328	0.037	77.8±10.2	78.7±12.4	0.085	0.688
FPG, mg/dL	172.9±48.1	178.6±58.7	0.106	0.460	167.9±47.8	182.9±50.4	0.306	0.122
HbA1c, %	8.7±1.3	8.2±1.0	0.394	0.007	8.4±1.1	8.4±1.1	0.005	0.979
C-peptide, ng/mL	3.0±1.9	3.1±1.9	0.045	0.785	3.1±2.3	3.1±1.7	0.002	0.993
BUN, mg/dL	14.5±3.8	13.9±4.0	0.149	0.303	13.9±3.6	14.3±4.5	0.114	0.561
Creatinine, mg/dL	0.77±0.19	0.77±0.17	0.011	0.938	0.79±0.18	0.78±0.18	0.077	0.697
eGFR, mL/min/1.73 m^2	94.7±21.6	105.4±23.7	0.476	0.001	96.7±19.8	100.5±23.2	0.176	0.372
Uric acid, mg/dL	5.3±1.3	5.2±1.3	0.077	0.598	5.5±1.2	5.2±1.2	0.236	0.232
AST, IU/L	30.7±16.4	35.5±26.7	0.214	0.153	30.9±13.6	31.6±21.2	0.036	0.856
ALT, IU/L	34.7±22.0	44.2±39.9	0.296	0.050	39.4±24.7	36.2±27.2	0.121	0.537
Total cholesterol, mg/dL	164.4±35.6	169.8±49.1	0.125	0.403	166.0±36.1	166.6±50.9	0.014	0.945
TG, mg/dL	160.9±98.5	160.6±143.1	0.003	0.986	165.8±101.7	161.9±150.2	0.030	0.879
HDL-cholesterol, mg/dL	47.6±10.0	47.9±12.2	0.025	0.862	47.1±9.7	48.2±12.2	0.102	0.606
LDL-cholesterol, mg/dL	92.3±26.8	99.4±35.7	0.228	0.133	92.2±29.0	95.1±37.1	0.088	0.657
ACR ≥30 mg/g	28 (31.1)	16 (22.2)	0.202	0.277	15 (31.2)	8 (17.8)	0.317	0.206
Hypertension	59 (55.1)	26 (30.6)	0.512	0.001	27 (51.9)	14 (26.9)	0.529	0.016
Dyslipidemia	70 (65.4)	44 (51.8)	0.280	0.077	31 (59.6)	25 (48.1)	0.233	0.325
Concomitant medications								
Metformin	107 (100.0)	84 (98.8)	0.154	0.443	52 (100.0)	52 (100.0)	<0.001	1.000
Sulfonylurea	48 (44.9)	34 (40.0)	0.098	0.597	18 (34.6)	25 (48.1)	0.276	0.232
DPP-4 inhibitor	28 (26.2)	27 (31.8)	0.124	0.489	15 (28.8)	19 (36.5)	0.165	0.531
Insulin	21 (19.6)	9 (10.6)	0.259	0.130	9 (17.3)	6 (11.5)	0.214	0.577
RAAS blockade	58 (54.2)	38 (44.7)	0.191	0.245	28 (53.8)	24 (46.2)	0.154	0.556
Diabetic complications								
Diabetic retinopathy	23 (21.5)	9 (10.6)	0.301	0.069	11 (21.2)	6 (11.5)	0.262	0.289
Diabetic nephropathy	33 (30.8)	17 (20.0)	0.251	0.125	16 (30.8)	9 (17.3)	0.319	0.169
Diabetic polyneuropathy	14 (13.1)	8 (9.4)	0.116	0.572	6 (11.5)	6 (11.5)	<0.001	1.000
Family history								
Type 2 diabetes	51 (47.7)	31 (36.5)	0.228	0.158	30 (57.7)	18 (34.6)	0.476	0.030
Social history								
Alcohol	41 (38.3)	17 (20.0)	0.411	0.010	18 (34.6)	12 (23.1)	0.257	0.279
Smoking	39 (36.4)	17 (20.0)	0.372	0.020	19 (36.5)	11 (21.2)	0.345	0.130

Values are expressed as number (%) or mean±standard deviation. *P* values represent the results of the Student *t* test or chi-square test.
SMD, standardized mean difference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACR, albumin-creatinine ratio; DPP-4, dipeptidyl peptidase-4; RAAS, renin-angiotensin-aldosterone system.

Table 2. Changes in Glycemic and Non-Glycemic Parameters in the Propensity Score–Matched Cohort (6 Months Follow-up)

Variable	Ketonuria (–)				Ketonuria (+)				*P* value[a]
	Baseline	Follow-up	Change (95% CI)	*P* value	Baseline	Follow-up	Change (95% CI)	*P* value	
Body weight, kg	76.6±13.0	73.6±12.4	–2.6 (–3.7 to –1.5)	<0.001	74.9±13.0	71.9±13.8	–2.6 (–3.2 to –1.9)	<0.001	0.922
BMI, kg/m^2	27.7±3.7	26.7±3.3	–1.0 (–1.4 to –0.6)	<0.001	26.9±3.7	25.9±3.8	–1.0 (–1.2 to –0.7)	<0.001	0.977
SBP, mm Hg	131.6±13.0	128.2±14.3	–3.6 (–8.0 to 0.9)	0.114	132.5±16.7	127.2±16.8	–5.5 (–10.3 to –0.7)	0.026	0.550
DBP, mm Hg	77.8±10.2	75.9±9.5	–1.8 (–5.0 to 1.5)	0.279	78.7±12.4	77.6±11.4	–0.8 (–3.9 to 2.3)	0.600	0.674
FPG, mg/dL	167.9±47.8	136.0±30.1	–31.9 (–45.2 to –18.6)	<0.001	182.9±50.4	141.3±38.6	–41.6 (–53.8 to –29.4)	<0.001	0.282
HbA1c, %	8.4±1.1	7.5±0.9	–0.9 (–1.2 to –0.6)	<0.001	8.4±1.1	7.6±1.0	–0.8 (–1.1 to –0.5)	<0.001	0.534
BUN, mg/dL	13.9±3.6	16.2±3.9	2.3 (1.4 to 3.2)	<0.001	14.3±4.5	16.5±4.4	2.2 (1.1 to 3.2)	<0.001	0.847
Creatinine, mg/dL	0.79±0.18	0.80±0.19	0.0 (–0.0 to 0.0)	0.873	0.78±0.18	0.74±0.19	–0.0 (–0.1 to –0.0)	0.001	0.015
eGFR, mL/min/1.73 m^2	96.7±19.8	96.7±21.2	–0.0 (–3.9 to 3.8)	0.993	100.5±23.2	107.3±25.2	6.8 (3.2 to 10.5)	<0.001	0.011
Total cholesterol, mg/dL	166.0±36.1	166.3±37.1	0.3 (–7.4 to 8.0)	0.937	166.6±50.9	157.5±44.9	–9.1 (–21.9 to 3.7)	0.160	0.210
TG, mg/dL	165.8±101.7	152.1±100.8	–13.1 (–31.8 to 5.6)	0.165	161.9±150.2	136.1±70.8	–23.1 (–58.8 to 12.6)	0.200	0.621
HDL-cholesterol, mg/dL	47.1±9.7	48.9±9.1	1.8 (–0.4 to 4.0)	0.110	48.2±12.2	50.8±14.1	2.3 (–0.2 to 4.8)	0.065	0.737
LDL-cholesterol, mg/dL	92.2±29.0	92.7±27.7	0.5 (–5.6 to 6.6)	0.862	95.1±37.1	89.4±34.3	–5.5 (–14.6 to 3.6)	0.228	0.269

Values are expressed as mean±standard deviation. *P* values within each group represent the results of the paired *t* test.
CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]*P* values represent the results of the Student *t* test or chi-square test for between-group comparisons.

tients from baseline to the follow-up after 6 months of SGLT2 inhibitor treatment (Table 2). HbA1c and fasting plasma glucose significantly improved both in the ketonuria-positive and ketonuria-negative groups. Body weight also improved significantly in both groups. Creatinine and eGFR improved significantly in ketonuria-positive patients: the creatinine level decreased from 0.78 to 0.74 mg/dL, and the eGFR increased from 100.48 to 107.29 mL/min/1.73 m^2. The parameters did not show significant changes in ketonuria-negative patients.

In univariate linear regression analysis to identify clinical parameters associated with the degree of improvement in eGFR from baseline to 6 months in all patients, concomitant ketonuria was identified as the sole significantly relevant clinical parameter (β=6.827, *P*=0.011). Other clinical parameters, such as the duration of diabetes, body weight, body mass index, and HbA1c, did not show significant associations (Supplemental Table S1). In ketonuria-positive patients, female sex (β=8.771, *P*=0.020), lower body weight (β=–0.323, *P*=0.026), lower triglyceride levels (β=–0.032, *P*=0.009), and the absence of hypertension (β=–8.145, *P*=0.046) were significantly associated with eGFR improvement. In multivariate linear regression analysis including these parameters as covariates, ketonuria remained the only significant parameter related to improvement in the eGFR (β=7.838, *P*=0.014). This finding remained stable when excluding patients whose RAAS blockade dosage changed.

The data on changes in the eGFR from baseline to 1 year were further analyzed. The magnitude of eGFR improvement was significantly greater in patients with ketonuria than in those without ketonuria (mean difference, 2.6 mL/min/1.73 m^2; 95% confidence interval [CI], –1.5 to 6.7 mL/min/1.73 m^2 in the ketonuria-positive group vs. –4.1 mL/min/1.73 m^2; 95% CI, –9.3 to 1.1 mL/min/1.73 m^2 in the ketonuria-negative group, *P*=0.026). Regression analysis consistently showed that ketonuria could serve as an indicator of eGFR improvement in patients receiving SGLT2 inhibitor treatment.

DISCUSSION

In this retrospective observational study, treatment with SGLT2 inhibitors demonstrated a renoprotective effect in patients with type 2 diabetes, particularly in those who exhibited concomitant ketonuria during treatment. Additionally, female sex and lower levels of obesity, blood pressure, and triglyceride levels may be associated with a more pronounced renoprotective effect.

Compared to prior studies, the patients included in our study were younger, had shorter durations of diabetes, and had higher

eGFRs at baseline. Therefore, the number of patients with albuminuria was insufficient to demonstrate the beneficial effects of SGLT2 inhibitors. We observed an increase in eGFR after 6 months of treatment; however, this phenomenon may indicate the worsening of hyperfiltration in the early stages of DKD, suggesting that a longer-term observational study is necessary.

To the best of our knowledge, this study is the first to investigate the clinical significance of ketonuria and its metabolic effects in relation to the renoprotective effect of SGLT2 inhibitors. Preclinical studies have shown that ketone bodies prevent renal damage in diabetic *db/db* mice [10], and they play a role in mitigating cellular senescence and injury [8]. Ketone bodies may be required to maintain energy homeostasis in damaged kidneys. They also have signaling activities, most notably as an endogenous inhibitor of histone deacetylases, which are linked to the regulation of lifespan and to age-related diseases [6]. Our study contributes to the existing literature by evaluating the renoprotective effects of SGLT2 inhibitors in subjects with type 2 diabetes in relation to concurrent ketonuria. We recommend serial measurements of ketone bodies in large-scale clinical studies to assess their direct renoprotective effects in patients receiving SGLT2 inhibitors.

Nonetheless, our study has some limitations. First, as a retrospective observational study, it did not include senescence-associated β-galactosidase staining or immunohistochemical data, nor were inflammatory markers assessed. Additionally, β-hydroxybutyrate levels were not directly measured in plasma. Investigating these parameters could provide further insight into the potential mechanisms underlying the renoprotective effects of SGLT2 inhibitors in relation to ketonuria. Second, the collection of data on proteinuria was inconsistent due to the guidelines set by the Korean national insurance coverage. For instance, patients without albuminuria did not have follow-up albuminuria measurements within 1 year. In this real-world clinical dataset, patients on SGLT2 inhibitors typically had a relatively normal eGFR, reflecting the previous indications for SGLT2 inhibitor use. Specifically, only 22.9% of the subjects had albuminuria at the outset. This limitation prevented us from capturing a composite renal endpoint that would include renal death, initiation of dialysis, or kidney transplant, or from tracking changes in albuminuria within this population. Lastly, the study did not differentiate between the various types of SGLT2 inhibitors used.

In conclusion, ketonuria can serve as an indicator of improvement of renal function in individuals with type 2 diabetes following relatively short-term treatment with an SGLT2 inhibitor. Furthermore, factors such as female sex and lower levels of obesity, blood pressure, and triglyceride levels may be associated with a significant renoprotective effect in individuals exhibiting ketonuria.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

Tae Jung Oh was supported by an investigator grant from the Seoul National University Bundang Hospital Research Fund (14-2016-0022).

AUTHOR CONTRIBUTIONS

Conception or design: H.N.J., T.J.O. Acquisition, analysis, or interpretation of data: H.A.K., H.N.J., S.H.K., Y.L., S.H.C., Y.M.C., H.C.J., T.J.O. Drafting the work or revising: H.A.K., S.H.C., Y.M.C., H.C.J., T.J.O. Final approval of the manuscript: H.A.K., H.N.J., S.H.K., Y.L., S.H.C., Y.M.C., H.C.J., T.J.O.

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REFERENCES

1. Ghaderian SB, Hayati F, Shayanpour S, Beladi Mousavi SS. Diabetes and end-stage renal disease; a review article on new concepts. J Renal Inj Prev 2015;4:28-33.
2. Kravets I, Mallipattu SK. The role of podocytes and podocyte-associated biomarkers in diagnosis and treatment of diabetic kidney disease. J Endocr Soc 2020;4:bvaa029.
3. The EMPA-KIDNEY Collaborative Group; Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, et al. Empagliflozin in patients with chronic kidney disease. N Engl J Med 2023;388:117-27.
4. Heerspink HJ, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-46.
5. Min SH, Oh TJ, Baek SI, Lee DH, Kim KM, Moon JH, et al. Degree of ketonaemia and its association with insulin resistance after dapagliflozin treatment in type 2 diabetes. Dia-

betes Metab 2018;44:73-6.
6. Newman JC, Verdin E. Ketone bodies as signaling metabolites. Trends Endocrinol Metab 2014;25:42-52.
7. Laffel L. Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. Diabetes Metab Res Rev 1999;15:412-26.
8. Fang Y, Chen B, Gong AY, Malhotra DK, Gupta R, Dworkin LD, et al. The ketone body β-hydroxybutyrate mitigates the senescence response of glomerular podocytes to diabetic insults. Kidney Int 2021;100:1037-53.
9. Rojas-Morales P, Pedraza-Chaverri J, Tapia E. Ketone bodies for kidney injury and disease. Adv Redox Res 2021;2:100009.
10. Tomita I, Kume S, Sugahara S, Osawa N, Yamahara K, Yasuda-Yamahara M, et al. SGLT2 inhibition mediates protection from diabetic kidney disease by promoting ketone body-induced mTORC1 inhibition. Cell Metab 2020;32:404-19.