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Original Research

Baseline Sodium-Glucose Cotransporter-2 Inhibitor Use Strongly Attenuates the Uric Acid-Elevating Effect of Thiazide Exposure

Alper Tuna Güven[1], Murat Özdede[2], Yusuf Ziya Şener[3]

[1] Division of General Internal Medicine, Department of Internal Medicine, Faculty of Medicine, Başkent University, Ankara, Turkey
[2] Division of General Internal Medicine, Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Turkey
[3] Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Ankara, Turkey

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Correspondence
Alper Tuna Güven, MD
Address: Division of General Internal Medicine, Department of Internal Medicine, Faculty of Medicine, Başkent University, Ankara, Turkey
E mail: alper.tuna.guven@gmail.com

ABSTRACT

Objective: Thiazide diuretics are among the major anti-hypertensive medications. However, their hyperuricemic effect restricts their use in patients with gout. Sodium glucose co-transporter 2 inhibitor (SGLT-2i) initiation lowers serum uric acid (SUA) levels. It is not known whether existing SGLT-2i use affects the SUA increasing effect of thiazides.

Methods: Post-hoc data analysis of our published study was conducted. Hypertensive patients who were initiated on thiazide diuretics or whose dose escalated were included (thiazide exposure). Demographic, clinical, and laboratory data were acquired via an electronic database. Patients were grouped according to SGLT-2i presence at the time of thiazide exposure. Since the number of SGLT-2i users was low, bootstrapping via simple random sampling was performed.

Results: 144 patients were included in the study, of whom 13 were on SGLT-2i. Initial sample analysis revealed that while baseline SUA levels were similar between groups, SUA change was significantly lower after thiazide exposure among patients receiving SGLT-2i (0.6 vs. 0.2, p = 0.039). Similarly, baseline SUA levels were similar, but SUA change after thiazide exposure was significantly lower among patients receiving SGLT-2 on bootstrapped data (0.13 [-0.25 - 0.57, 95%CI], vs. 0.61 [0.45 - 0.78, 95%CI], mean difference = 0.48, [0.04 - 0.91, 95%CI], p = 0.029).

Conclusion: This study revealed that thiazide diuretics may be a safe anti-hypertensive medication in terms of hyperuricemia among patients using SGLT-2i. Further studies with similar outcomes may result in the elimination of restrictive recommendations for the use of thiazides in patients with hyperuricemia or gout, provided patients are on SGLT-2i.

Keywords: Sodium glucose cotransporter 2 inhibitors, hypertension, uric acid, thiazides

INTRODUCTION

Hypertension is one of the major cardiovascular risk factors and affects almost 1 in 2 adults in the United States [1]. Hypertension is also a component of the metabolic syndrome, a syndrome characterized by abdominal adiposity, insulin resistance characterized by high fasting glucose, hypertension, and dyslipidemia [2]. Metabolic syndrome itself is also a cardiovascular disease risk factor [3]. Although not a component of metabolic syndrome, increased serum uric acid (SUA) levels and gout disease are associated with metabolic syndrome [4].

Hypertension and metabolic syndrome are encountered in 74% and 63% of gout patients, respectively [5, 6]. Besides the association, SUA levels are correlated with blood pressure, as a 1 mg/dl increase in SUA level is associated with a 10 mm Hg increase in systolic blood pressure [7].

Hyperuricemia and gout are not only associated with hypertension and metabolic syndrome, but they are also associated with other cardiometabolic diseases such as chronic kidney disease and atherosclerotic heart disease [8]. These close associations result in many patients receiving drug therapies that target multiple components of these diseases. While plenty of these effects are beneficial, some are deleterious. For example, sodium glucose co-transporter 2 inhibitors (SGLT-2i) emerged as anti-diabetic medications due to their glycosuric effects [9]. However, it was also discovered that they improve cardiovascular and kidney outcomes, resulting in their use in heart failure and chronic kidney disease patients, regardless of diabetes [10]. Recent studies also illustrated that SGLT-2i, compared to other oral anti-diabetics, decreases SUA levels [11].

However, not all co-effects are beneficial. Thiazide diuretics, either hydrochlorothiazide or thiazide-like, elevate SUA levels to some extent [12]. It is known that thiazide diuretics are associated with higher rates of gout flares [13]. Although it is not absolutely contraindicated, some guidelines assert either a relative contraindication warning or remark cautious use [14-16]. These recommendations cause only renin-angiotensin-aldosterone system inhibitors (RAASi) and calcium channel blockers (CCB) to be used as first-line treatment options among hypertensive patients with gout. However, many patients require more than two anti-hypertensive medications in order to achieve target blood pressures [16]. At this point, clinicians are left with only spironolactone and doxazosin, which both have low tolerability due to their hormonal and vascular side effects, respectively [17, 18].

Main Points;

- SGLT-2i drugs have uric acid-lowering effects when initiated. This study demonstrated that baseline SGLT-2i presence attenuates the uric acid-elevating effects of thiazide diuretics as well. This finding indicates that thiazide use among patients with high baseline uric acid levels or patients with gout may be safe, provided that patients are on SGLT-2i.

In this study, we wanted to investigate whether baseline SGLT-2i use at the time of thiazide initiation had any effect on thiazide diuretics' uric acid-increasing effect compared to the absence of SGLT-2i at the baseline.

MATERIALS AND METHODS

Design, Settings, and the Study Population

This study was designed as a post-hoc analysis of our recently published retrospective cohort study on hypertensive patients [19]. We analyzed our patients' data via electronic medical records (EMR). Four clinics, consisting of secondary and tertiary-level general internal medicine and cardiology clinics, contributed to the study.

The inclusion criteria were as follows:

- Having a hypertension diagnosis
- Having a thiazide diuretic initiated or its dose increased if already on thiazide (collectively named "thiazide exposure")
- Having data regarding SGLT-2i use
- Having a control visit for renal function and an electrolyte check within 4 weeks
- Having the relevant EMR data for the study
- Being over 18 years old

In daily practice, renal functions and electrolytes are not routinely checked within 4 weeks when only thiazides are initiated or their doses increased (i.e., thiazide exposure). However, since our published study's aim was to evaluate the effect of RAASi dose change on renal parameters, we have the relevant data for this study as well. This also means that the data acquired via EMR represents both thiazide and RAASi exposure. However, because RAASi other than losartan—which was used only in a few patients in the study cohort—is known not to affect SUA levels, we did not consider which RAASi patients were exposed to due to their lack of effect on SUA levels.

Clinical Data

The data acquired (and calculated) for each patient were as follows:

- Demographics: age and sex
- Relevant comorbidities: diabetes mellitus, coronary artery disease, heart failure, chronic kidney disease, and airway diseases
- Medications other than thiazides: RAASi, CCB, beta blockers, loop diuretics, beta-2 agonists
- Initial and Control Laboratory Values: Urea (mg/dL),

creatinine (mg/dL), estimated glomerular filtration rate (mL/min/1.73 m2), uric acid (mg/dL), sodium (mEq/L), potassium (mEq/L)

- Change in values: Initial renal function and electrolyte values (values at T0) were subtracted from control values (values at T1) to calculate the changes in values (values at T1 and T0).

Statistics and Bootstrapping

For descriptive statistics, continuous variables were presented as "mean (±standard deviation)" or "median (interquartile range)" according to their distribution pattern. Categorical variables were presented as "numbers (percentages)". For comparison of continuous variables' between-group differences, the student's t-test or Mann-Whitney U test was used according to the variables' distribution patterns. Pearson's chi-squared test ($\chi 2$ test) (or Fisher's exact test when needed) was used for comparison of categorical variables' between-group differences. Since the number of patients was small in the SGLT-2i receiving group and did not distribute normally, bootstrapping was performed for resampling, using 1000 samples. Simple random sampling was chosen as the bootstrap sampling methodology. Since bootstrapped samples were distributed normally, between-group differences were analyzed using a t-test. Confidence intervals were calculated for 95%, and lower-upper bound values were presented. Two-sided significance testing was performed to calculate p-values, and p-values less than 0.05 were considered significant. All analyses were conducted using IBM SPSS Software version 23.0 (SPSS Inc., Chicago, IL), licensed to the institution where the study was carried out.

Each patient in the study was assigned an anonymous identification number to protect confidentiality. The processing of the data did not require informed consent, and written informed consent was not obtained due to the study's retrospective design. The study complies with the principles outlined in the Declaration of Helsinki, and this study was approved by the Hacettepe University Institutional Review Board (Project number GO22/734).

RESULTS

Patient Characteristics

A total of one hundred and forty-four patients were found to be eligible and included in the study. Of whom, 13 were using SGLT-2i and 131 were not. Age and gender were similar between the two groups. All patients who were receiving SGLT-2i had diabetes mellitus, and none were receiving SGLT-2i solely for heart failure or chronic kidney disease progression slowing. Coronary artery disease was more frequent among SGLT-2i users. On the other hand, heart failure, chronic kidney disease, and airway disease rates were similar between SGLT-2i users and non-users. Considering initial anti-hypertensive medications, thiazides, calcium channel blockers, beta blockers, and loop diuretic use were similar between SGLT-2i users and non-users. However, RAASi use was slightly higher among SGLT-2i users (76.9 vs. 40.5%, $p < 0.01$). Table 1 illustrates patient characteristics in detail among SGLT-2 groups.

Renal Functions and Electrolytes of the Sample

Uric acid, urea, creatinine, estimated glomerular filtration rate, sodium, and potassium levels were similar between SGLT-2i users and non-users both during thiazide exposure (T0) and during the control visit (T1). Although T0 uric acid levels seemed lower among SGLT-2i non-users, they did not reach statistical significance (5.1 vs. 5.6, $p = 0.35$). Changes (Δ) in renal functions and electrolytes were also similar for urea, creatinine, estimated glomerular filtration rate, sodium, and potassium. However, Δ uric acid was significantly lower among SGLT-2i users compared to non-users (0.2 vs. 0.6, $p = 0.039$). Table 2 illustrates the renal functions and electrolytes of the sample before thiazide exposure, during the control visit, and the change between them in detail among the SGLT-2i groups.

Renal Functions and Electrolytes of the Bootstrapped Sample

Although Δ uric acid was significantly lower among SGLT-2i users, there were only 13 patients in the SGLT-2i user group. Because they did not meet parametric assumptions, this analysis was calculated via the Mann-Whitney-U test. We performed bootstrapping for uric acid at T0, T1, and Δ in order to compare newly generated data using a parametric test. Parametric testing of bootstrapped data showed uric acid levels at T0 and T1 were similar between SGLT-2i users and non-users. However, Δ uric acid was significantly lower among SGLT-2i users compared to non-users after thiazide exposure (0.13, -0.25 – 0.57, 95%CI vs. 0.61, 0.45 – 0.78, 95%CI, mean difference = 0.48, 0.04 – 0.91, 95%CI, $p = 0.029$). Table 3 illustrates uric acid values and changes in bootstrapped data according to patients SGLT-2i use and the results of the T-test in detail.

Table 1. Patient characteristics according to baseline SGLT-2i use

	Total (N = 144)	**SGLT-2i absent** (N = 131)	**SGLT-2i present** (N = 13)	**p***
Demographics				
Age	61 (14)	61 (13)	58 (16)	0.78
Female sex	95 (66%)	85 (64.9%)	10 (76.9%)	0.54
Comorbidities				
DM	81 (56.3%)	50 (38.2%)	13 (100%)	**< 0.001**
CAD	29 (20.1%)	21 (16%)	8 (61.5%)	**0.001**
HF	4 (2.8%)	4 (3.1%)	0	1
CKD	7 (4.9%)	6 (4.6%)	1 (7.7%)	0.49
Airway diseases	15 (10.4%)	14 (10.7%)	1 (7.7%)	1
Initial Medications				
RAASi	63 (43.8%)	53 (40.5%)	10 (76.9%)	**0.01**
Thiazides	19 (13.2%)	16 (12.2%)	3 (23.1%)	0.38
CCBs	39 (27.1%)	36 (27.5%)	3 (23.1%)	1
Beta blockers	46 (31.9%)	39 (29.8%)	7 (53.8)	0.11
Loop diuretics	3 (2.1%)	3 (2.3%)	0	1

CAD: Coronary Artery Disease, CCB: Calcium Channel Blockers, CKD: Chronic Kidney Disease, DM: Diabetes Mellitus, HF: Heart Failure, RAASi: Renin-Angiotensin-Aldosterone System Inhibitors, SGLT-2i: Sodium-glucose cotransporter-2 inhibitors

* p values less than 0.05 are shown in bold

Table 2. Renal functions and electrolytes of patients during initiation (or dose escalation) of thiazides, at control visit, and the difference between, according to baseline SGLT-2i use

	T_0			**T_1**			**Δ**		
Parameter	**SGLT-2i absent**	**SGLT-2 present**	**p***	**SGLT-2i absent**	**SGLT-2 present**	**p***	**SGLT-2i absent**	**SGLT-2 present**	**p***
Uric acid	5.1 (1.4)	5.6 (1.8)	0.35	5.7 (1.7)	5.7 (0.8)	0.80	0.6 (1.0)	0.2 (0.9)	**0.039**
Urea	28 (11)	33.5 (5)	0.20	34 (13)	39 (18)	0.08	3.8 (10)	5.5 (5.4)	0.43
Creatinine	0.75 (0.24)	0.74 (0.26)	0.57	0.76 (0.27)	0.71 (0.32)	0.44	0.02 (0.11)	0.01 (0.07)	0.95
eGFR	94 (21)	97(18)	0.84	93 (25)	97 (24)	0.50	-2 (10)	-2 (3.5)	0.49
Sodium	139 (3)	140 (2.5)	0.69	139 (3)	139 (2)	0.85	-1.08 (3.8)	-1.18 (2.1)	0.76
Potassium	4.3 (0.4)	4.3 (0.4)	0.82	4.2 (0.5)	4.1 (0.8)	0.43	-0.1 (0.6)	-0.2 (0.4)	0.42

eGFR: Estimated Glomerular filtration rate, SGLT-2i: Sodium-glucose cotransporter-2 inhibitors

T_0: Value at the initiation (or dose increase) of thiazides, T_1: Value at control visit, Δ: Calculated as (value at T_1) minus (Value at T_0)

* p values less than 0.05 are shown in bold

Table 3. Uric acid values and changes of bootstrapped data according to baseline SGLT-2i use and results of the T-test

	SGLT-2i absent		SGLT-2i present		Bootstrapped T-Test		
Parameter	**Mean**	**95% CI Lower - Upper**	**Mean**	**95% CI Lower - Upper**	**Mean Difference**	**95% CI Lower - Upper**	**p***
T_0 Uric Acid	5.19	4.96 – 5.41	5.50	4.91 – 6.06	-0.30	-0.91 – 0.30	0.30
T_1 Uric Acid	5.81	5.56 – 6.06	5.63	4.96 – 6.22	0.18	-0.46 – 0.85	0.58
Δ Uric Acid	0.61	0.45 – 0.78	0.13	-0.25 – 0.57	0.48	0.04 – 0.91	**0.029**

CI: Confidence Interval, SGLT-2i: Sodium-glucose cotransporter-2 inhibitors

T_0: Uric acid at the initiation (or dose increase) of thiazides, T_1: Uric acid at control visit, Δ: Calculated as (Uric acid at T_1) minus (Uric acid at T_0)

* p values less than 0.05 are shown in bold

DISCUSSION

This study illustrated that the uric acid increase due to thiazide exposure is significantly lower among patients who receive SGLT-2i compared to non-users. While it has been recently shown that "SGLT-2i initiation" has uric acid-lowering effects, to the best of our knowledge, this is the first study to reveal the uric acid-attenuating effects of "existing SGLT-2i use" among thiazide-exposed patients.

The link between uric acid and hypertension has been a subject of debate. Hyperuricemia is common among patients with hypertension as well as those with metabolic syndrome and diabetes mellitus, but hypertension is also a strong predictor of these comorbidities [11]. Clinical trials of uric acid-lowering medications for blood pressure reduction have resulted in inconsistent and conflicting results [20]; thus, although higher uric acid levels are associated with higher blood pressures, lowering uric acid levels via drugs is not part of the anti-hypertensive treatment strategy. Thiazide diuretics are among the major anti-hypertensive medication classes, with a uric acid-increasing effect. While thiazides' hyperuricemic effect does not alter their anti-hypertensive properties, it causes cautious use among patients with high uric acid levels [16]. Moreover, some guidelines [14, 15] recommend against the use of thiazides in gout patients due to the increased risk of gout flares [21] mediated via uric acid elevations. SGLT-2i initiation is shown to attenuate uric acid levels in type 2 diabetic patients when compared with other oral anti-diabetic medications [11, 22]. The mechanism responsible for the uric acid-lowering effect of SGLT-2i is the expression of glucose transporter 9 isoform 2 in the kidney tubules, which causes the excretion of D-glucose and uric acid in urine [22]. In vitro studies indicate that lower uric acid levels attained via SGLT-2i play a role in the anti-inflammatory effects of SGLT-2i [23].

Although not statistically significant, uric acid levels before thiazide exposure were higher among SGLT-2i users compared to non-users (5.1 vs. 5.6) in the study. This non-significant trend may be explained by the fact that all patients in the SGLT-2i user group were diabetic, which is associated with higher uric acid levels, but only 38.2% of the patients in the non-user group were diabetic. A meta-analysis illustrated that the uricosuric effect of SGLT-2i ranges between 0.6 and 0.7 mg/dl [24]. However, this meta-analysis shows the effect of SGLT-2i "initiation" on uric acid levels. Our study differs from the existing literature because we did not calculate the SGLT-2i initiation's uric acid-lowering effect but calculated whether baseline SGLT-2i presence could alter the uric acid-increasing effect of thiazide diuretics. We have shown that SGLT-2i presence during thiazide exposure was responsible for a 0.48 (0.04–0.91, 95%CI) mg/dL mean difference at uric acid levels compared to SGLT-2i absence. Moreover, uric acid levels only increased by 0.13 (-0.25–0.57, 95%CI) mg/dL in SGLT-2i users. Compared with the 0.61 (0.45–0.78, 95%CI) mg/dl at SGLT-2i non-users, this increase could be described as "negligible".

This finding is of particular importance since many hyperuricemic patients or patients with gout are deprived of the robust anti-hypertensive effects of thiazides due to their worrisome hyperuricemic effects. By adding SGLT-2i to eligible patients' treatment regimens, thiazides might find a role for hypertension treatment in hyperuricemic patients. This

strategy may also be the key to improving blood pressure target achievement rates.

Limitation

We acknowledge limitations of our study. The major limitation of the study was the fact that this was a post-hoc analysis of a retrospective study, thus prone to the limitations of retrospective analysis. Secondly, although SGLT-2i is used among non-diabetic heart failure and chronic kidney disease patients, patients in our study were receiving SGLT-2i for diabetes treatment; therefore, our results may not be generalized to non-diabetic patients. Thirdly, although we have performed bootstrapping in order to meet parametric assumptions, the number of patients in the SGLT-2i user group was low compared to non-users. And finally, we analyzed SGLT-2i medications as a group but did not analyze whether both empagliflozin and dapagliflozin, two SGLT-2i available in the area where the study was carried out, had the same effect on uric acid after thiazide exposure.

CONCLUSIONS

In conclusion, this study showed for the first time that not only the initiation but also the presence of SGLT-2i have profound effects on uric acid levels after thiazide exposure. The findings of our study should be tested in future pragmatic randomized trials. Results of this study as well as further trials may affect the hypertension guidelines' restrictive recommendations of thiazides, ease clinicians' hypertension management among patients with gout, and help patients achieve their target blood pressure.

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