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Exposure to topiramate may not increase the risk of urolithiasis: A nationwide cohort study

Kimoon Chang [a], Woo-Seok Ha [b,*]

[a] Department of Neurology, Uijeongbu Eulji Medical Center, Eulji University School of Medicine, Uijeongbu, the Republic of Korea
[b] Department of Neurology, Severance Hospital, Yonsei University College of Medicine, Seoul, the Republic of Korea

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ABSTRACT

Background and purpose: Although topiramate is mechanistically linked to an increased risk of urolithiasis, real-world evidence remains conflicting. This study aimed to evaluate the risk of a first-time episode of urolithiasis associated with topiramate exposure in the Korean population.
Methods: Using the Korean National Health Insurance Service-National Sample Cohort, we identified participants from the 2015 national health screening. After excluding individuals with a prior diagnosis of urolithiasis, we performed 1:4 propensity score matching between patients with and without topiramate exposure. Matching variables included age, sex, body mass index, comorbidities, and a history of gout. Participants were followed longitudinally, and the risk of urolithiasis was assessed using Kaplan-Meier analysis and Cox proportional hazards regression.
Results: The final cohort included 1,560 patients exposed to topiramate and 6,240 matched controls who were followed for five years. During the follow-up period, urolithiasis was diagnosed in 47 patients (3.0%) in the topiramate group and 170 patients (2.7%) in the control group. The risk of developing urolithiasis was not significantly different between the two groups ($p = 0.545$). Furthermore, subgroup analyses stratified by current use or the cumulative duration of topiramate exposure also showed no significant associations.
Conclusions: In this large, nationwide cohort, topiramate exposure was not associated with an increased risk of urolithiasis. Our findings suggest that in a real-world setting, the risk may not be as significant as suggested by its pharmacological mechanism.

1. Introduction

Topiramate is a widely prescribed medication for various neurological conditions, including epilepsy and migraine prophylaxis (1). It has also been discussed to use topiramate as anti-obesity treatment (2). However, its action as a carbonic anhydrase inhibitor is known to cause metabolic acidosis and reduce urinary citrate levels, which are established risk factors for the development of urolithiasis (3, 4).

Despite this well-known pharmacological mechanism, evidence from real-world practice has questioned this association. A nationwide population-based cohort study conducted in Taiwan, for instance, suggested that topiramate may not significantly increase the risk of urolithiasis (5). This discrepancy between the pharmacological theory and findings from real-world data highlights a knowledge gap and underscores the need for further investigation in different populations.

Therefore, this study aims to evaluate the influence of topiramate on the risk of experiencing a first lifetime episode of urolithiasis in the Korean population. By utilizing data from the Korean National Health Insurance Service-National Sample Cohort, we seek to clarify the real-world risk of urolithiasis associated with topiramate exposure and provide valuable clinical evidence to guide prescribing decisions.

2. Methods

2.1. Data source and study population

This retrospective, nationwide, population-based cohort study utilized data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC) (6). The NHIS is a mandatory system in South Korea that covers approximately 97% of the population, while the

* Corresponding author at: Department of Neurology, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, the Republic of Korea.
E-mail address: haha88@yuhs.ac (W.-S. Ha).

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remaining 3% of low-income individuals receive medical aid. The NHIS manages nationwide records on healthcare utilization and prescription data. It also provides a free biennial health screening program for beneficiaries over the age of 20, which includes medical history evaluation, laboratory testing, and anthropometric measurements. The NHIS-NSC consists of data from 1,000,000 individuals (representing 2.2% of the Korean population) selected with proportional representation, with each participant assigned a unique anonymous identifier to facilitate analysis.

Among the 270,443 participants from the NHIS-NSC who underwent the national health screening program in 2015, those aged ≥ 15 years were deemed eligible for inclusion. Their medical records, extracted from the NHIS database, were reviewed for the period spanning 2002 to 2019. The date of the 2015 health screening was defined as the baseline for follow-up. Patients with a prior diagnosis of urolithiasis between 2002 and the baseline date were excluded. Individuals prescribed topiramate before baseline were classified as the exposed group, whereas those who had never been prescribed topiramate were considered the unexposed group.

For a more detailed analysis of topiramate exposure, we further categorized the exposed group into several subgroups. First, based on their prescription status at the baseline date, patients were classified as either "current users" or "past users." A patient was defined as a current user if the end date of their most recent topiramate prescription (calculated as the prescription date plus the number of days supplied) extended beyond the baseline date. Additionally, we calculated the cumulative duration of topiramate exposure by summing the number of prescribed days from all previous prescriptions. Based on this cumulative duration, patients were stratified into three groups: <30 days, 30–179 days, and ≥ 180 days of exposure.

2.2. Propensity score matching

We performed 1:4 propensity score matching between patients exposed and unexposed to topiramate, considering age, sex, body mass index (BMI), waist circumference, and preexisting comorbidities. Individual-level covariates were obtained from the NHIS database. Preexisting comorbidities included hypertension, diabetes, heart failure, chronic kidney disease, and past history of gout. These comorbidities were identified using ICD-10 codes. Data on BMI, waist circumference, smoking status (current or not), alcohol consumption (none, mild-to-moderate, or heavy), serum creatinine level and estimated glomerular filtration rate (eGFR) were obtained from the national health screening database. Mild-to-moderate and heavy alcohol consumption were defined as the intake of < 30 and ≥ 30 g of alcohol per day, respectively. Data on proteinuria were obtained from urine dipstick test results and were treated as a binary variable (positive or negative) for the analysis.

2.3. Outcomes

The primary endpoint of the study was the development of urolithiasis. Urolithiasis was defined as the presence of the ICD-10 code N20 (calculus of kidney and ureter), N21 (calculus of lower urinary tract), N22 (calculus of urinary tract in disease classified elsewhere), N23 (unspecified renal colic), or N132 (Hydronephrosis with renal and ureteral calculous obstruction). The date of the first diagnosis was defined as the primary outcome. Each participant was followed up from the screening date in 2015 until 5 years later (December 31, 2019), or death, whichever occurred first.

2.4. Statistical analysis

A Cox proportional hazards model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for urolithiasis, comparing patients exposed to topiramate with those who were not. To ensure the robustness of our analysis, we employed three progressively adjusted models. Model 1 was a crude analysis without any adjustments beyond the initial propensity score matching. Model 2 was adjusted for age, sex, BMI, and comorbidities (hypertension, diabetes, heart failure, chronic kidney disease, and a history of gout). Model 3 included all variables from Model 2, with additional adjustments for smoking status, alcohol consumption, waist circumference, proteinuria, serum creatinine levels, and eGFR.

To address whether ongoing topiramate exposure after baseline carries a different risk of urolithiasis compared with treatment discontinuation, we performed subgroup analyses stratifying the topiramate-exposed group by current use status. In addition, to evaluate a potential duration-dependent relationship, patients were further stratified according to cumulative duration of exposure. The duration categories were defined as < 30 days, 30–179 days, and ≥ 180 days, which allowed relatively balanced distribution across subgroups. Multivariable Cox regression was then applied for each subgroup. A log-rank test was conducted as a sensitivity analysis, stratified by the same subgroups. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SAS statistical software (version 9.2, SAS Institute, Cary, NC, USA).

3. Results

3.1. Population characteristics

After 1:4 propensity score matching, a total of 1,560 patients with topiramate exposure and 6,240 matched controls were included in the final analysis (Table 1). The mean (standard deviation) age of the

Table 1
Baseline characteristics of the study population.

Variables		Control (n = 6,240)	Topiramate (n = 1,560)	P value
Age		52.6 (14.6)	52.1 (14.3)	0.224
Sex	Male	2,070 (33.2)	509 (32.6)	0.682
	Female	4,170 (66.8)	1,051 (67.4)	
BMI (kg/cm^2)		24.2 (3.6)	24.1 (3.9)	0.605
Comorbidities	Hypertension	2,769 (44.4)	674 (43.2)	0.405
	Diabetes	1,825 (29.3)	456 (29.2)	0.990
	Heart failure	255 (4.1)	68 (4.4)	0.629
	Chronic kidney disease	61 (1.0)	14 (0.9)	0.772
	Past history of Gout	554 (8.9)	143 (9.2)	0.721
	Migraine	1,542 (24.7)	1,135 (72.8)	< 0.001
	Epilepsy	95 (1.5)	257 (16.5)	< 0.001
Alcohol	Non-drinker	826 (13.2)	225 (14.4)	< 0.001
	Mild-to-moderate	4,226 (83.3)	1,291 (83.0)	
	Severe	218 (3.5)	41 (2.6)	
Current smoker		841 (13.5)	181 (11.6)	0.050
Proteinuria		193 (3.1)	40 (2.6)	0.272
Waist circumference (cm)		81.0 (9.9)	80.8 (10.1)	0.495
Serum creatinine level (mg/dL)		0.84 (0.44)	0.83 (0.25)	0.500
eGFR (mg/mmol)		89.8 (25.1)	89.7 (22.7)	0.849

Continuous variables were presented as mean (standard deviation), and categorical variables as number (percentage).
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate.

topiramate group was 52.1 (14.3) years, and the majority were female (67.4%).

The baseline characteristics were well-balanced between the two groups after matching, with no significant differences observed in age, sex, BMI, waist circumference, or the prevalence of most comorbidities, including hypertension, diabetes, heart failure, and chronic kidney disease. As expected, the prevalence of migraine (72.8% vs. 24.7%) and epilepsy (16.5% vs. 1.5%) was significantly higher in the topiramate group (both P values < 0.001). The topiramate group had a higher proportion of non-drinkers (14.4% vs. 13.2%) and lower proportion of severe drinkers (2.6% vs. 3.5%) compared with the control group ($P < 0.001$), whereas current smoking was less prevalent in the topiramate group (11.6% vs. 13.5%; $P = 0.05$).

3.2. Risk of urolithiasis associated with topiramate exposure

Over a median follow-up period of 4.6 years, urolithiasis was diagnosed in 170 patients (2.7%) in the control group and 47 patients (3.0%) in the topiramate group. Overall, exposure to topiramate was not associated with a significantly increased risk of developing urolithiasis (Table 2). In the fully adjusted Cox proportional hazards model (Model 3), the HR for the topiramate group compared to the control group was 1.13 (95% CI 0.817–1.562; $P = 0.461$), which did not reach statistical significance.

The Kaplan-Meier analysis also showed no significant difference in the cumulative incidence of urolithiasis between the topiramate users and matched controls (Fig. 1). The log-rank test was not statistically significant ($P = 0.497$).

3.3. Subgroup analyses of the topiramate-exposed group

We conducted subgroup analyses based on the recency and cumulative duration of topiramate exposure (Table 2). When stratified by current or past use, neither group showed a significantly elevated risk of urolithiasis compared to controls in the fully adjusted model (Past users: HR 1.098, 95% CI 0.780–1.546, $P = 0.591$; Current users: HR 1.407, 95% CI 0.622–3.184, $P = 0.413$). The Kaplan-Meier curve for this comparison is presented in Fig. 2 (log-rank test, $P = 0.648$).

However, when stratified by the cumulative duration of exposure, patients with short-term exposure of less than 30 days had a significantly increased risk of urolithiasis (Model 3: HR 1.578, 95% CI 1.043–2.388; $P = 0.031$). In contrast, no significant risk was observed for those with exposure durations of 30–179 days or $\geq$ 180 days. The Kaplan-Meier curves for the duration subgroups are shown in Fig. 3 (log-rank test, $P = 0.111$).

4. Discussion

In this nationwide population-based cohort study, we found that exposure to topiramate was not significantly associated with an increased risk of developing urolithiasis among Korean adults. Subgroup

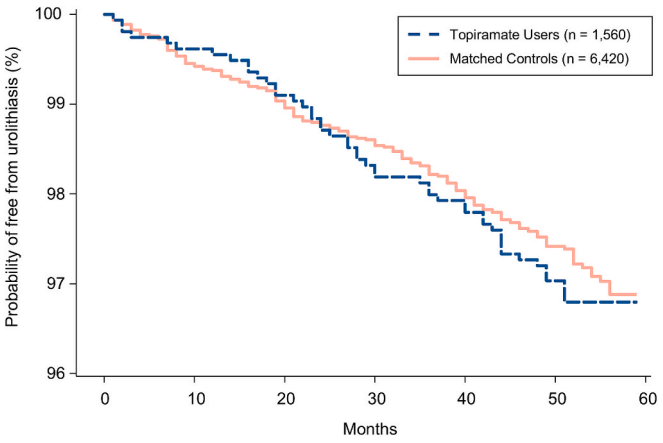

Fig. 1. Kaplan-Meier curve for the cumulative incidence of urolithiasis in patients exposed to topiramate and matched controls.

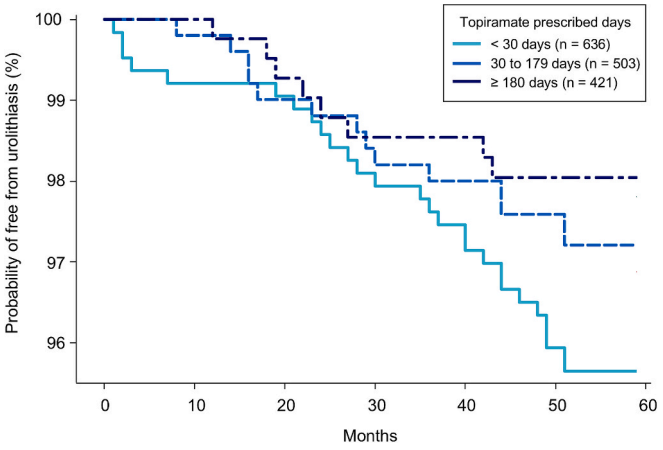

Fig. 2. Kaplan-Meier curve for the cumulative incidence of urolithiasis stratified by topiramate use status.

analyses further supported this finding, showing no consistent duration-dependent relationship according to cumulative treatment duration. While earlier pharmacological and mechanistic studies indicated that topiramate promotes stone formation through inhibition of carbonic anhydrase, leading to metabolic acidosis, hypocitraturia, hypercalciuria and elevated urine pH [3,4], our findings suggest these effects may not translate into a clinically significant risk in most real-world scenarios.

Several hypotheses may explain this discrepancy between the established mechanism and our real-world findings. First, the dosage and duration of topiramate used in contemporary clinical practice may be insufficient to induce a substantial risk. The historical association

Table 2
Cox proportional hazard regression analysis of urolithiasis risk in patients exposed to topiramate.

	Model 1[a]			Model 2[b]			Model 3[c]		
Groups	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Control	1 (ref.)			1 (ref.)			1 (ref.)		
Topiramate	1.118	0.810–1.545	0.498	1.123	0.813–1.551	0.483	1.13	0.817–1.562	0.461
Past topiramate users	1.092	0.777–1.536	0.612	1.096	0.779–1.541	0.600	1.098	0.780–1.546	0.591
Current topiramate users	1.335	0.592–3.014	0.486	1.350	0.598–3.050	0.470	1.407	0.622–3.184	0.413
<30 days	1.516	1.004–2.291	0.048	1.573	1.040–2.379	0.032	1.578	1.043–2.388	0.031
30–179 days	0.959	0.546–1.686	0.884	0.957	0.544–1.682	0.878	0.956	0.543–1.682	0.876
≥180 days	0.706	0.347–1.435	0.336	0.682	0.335–1.386	0.290	0.694	0.341–1.412	0.314

[a]Unadjusted; [b]Adjusted for age, sex, BMI, and comorbidities; [c]Adjusted for age, sex, BMI, comorbidities, smoking status, alcohol consumption, waist circumference, proteinuria, serum creatinine levels, and eGFR.
Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate.

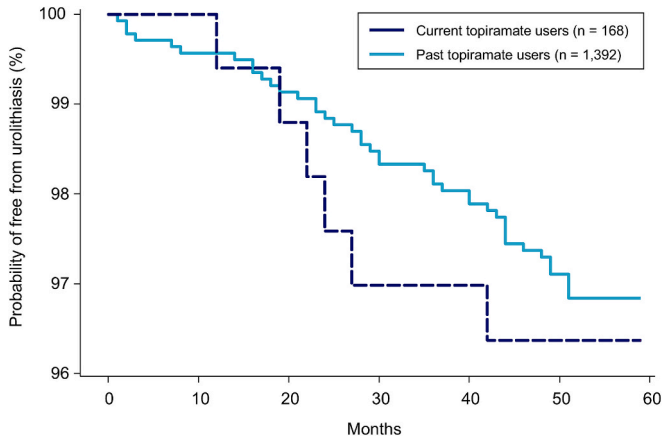

Fig. 3. Kaplan-Meier curve for the cumulative incidence of urolithiasis stratified by the duration of topiramate exposure.

largely relies on relatively small case series from the early 2000 s (7–9). For instance, one of the largest clinic-based studies reporting on this risk was a 2011 retrospective cohort in the United States, which found a 10.7% prevalence of symptomatic calculi among 75 epilepsy patients treated with a median daily dose of 300 mg for a median duration of 48 months (10).

In contrast, real-world data suggests that topiramate is prescribed more frequently for migraine prophylaxis than for epilepsy, by as much as threefold (11). The recommended daily dose for migraine prophylaxis is typically 50–100 mg (12), which is substantially lower than the 400 mg daily dose often targeted for epilepsy (13). Furthermore, treatment duration often differs; while topiramate may be a long-term therapy for epilepsy, it is often discontinued in migraine patients once headache frequency decreases. Therefore, although the pharmacological potential for urolithiasis exists, the majority of patients in a real-world setting may not reach the dose-duration threshold necessary to significantly elevate their risk. Notably, a recent large retrospective cohort study from the United States using claims data reported a dose-dependent increase in the risk of kidney stones among users of topiramate and zonisamide (14).

Additionally, the incidence of urolithiasis in our cohort (approximately 3% over a 5-year follow-up) is generally consistent with previous epidemiologic data from nationwide Korean study, where the 11-year cumulative incidence was reported as 5.71% and the standardized lifetime prevalence was estimated at 11.5% (15). The absence of a duration-dependent relationship in our analysis also suggests that any potential metabolic changes induced by topiramate may be transient or counteracted by compensatory mechanisms, such as physiological acid-base regulation or behavioral changes like increased fluid intake.

Our results suggest that routine discontinuation or avoidance of topiramate solely due to concerns about urolithiasis may not be necessary, particularly in patients without pre-existing metabolic risk factors (3). Nevertheless, counseling patients on maintaining adequate hydration and considering periodic metabolic monitoring remain prudent clinical practices, especially in those with a personal or family history of kidney stones.

This study's major strengths are usage of a large, nationally representative cohort with longitudinal follow-up and comprehensive adjustment for metabolic, lifestyle, and renal confounders. However, several limitations should be acknowledged. First, our analysis relied on administrative claims data based on ICD-10 codes, which may lead to underestimation or misclassification of urolithiasis (5). Second, detection bias may be present. Clinicians, aware of topiramate's potential side effects, might have been more likely to perform diagnostic tests on these patients, potentially leading to a higher incidental detection of urolithiasis compared to the control group. Third, data on urinary chemistry (e.g., citrate, calcium, pH) were unavailable, limiting mechanistic exploration (4). We attempted to mitigate this by adjusting for other known risk factors, including lifestyle variables, a history of gout, and proteinuria. Fourth, we were unable to perform analyses stratified by fixed topiramate dosage categories. In real-world, dosages vary over time and the limited number of urolithiasis events resulted in insufficient statistical power for reliable dose-based stratification. Instead, we analyzed cumulative treatment duration to evaluate duration-related effects on urolithiasis risk, although this does not directly reflect dosage or serum drug levels. Finally, although our follow-up period of five years was adequate for most cases, delayed effects beyond this timeframe cannot be entirely excluded.

Future research should focus on large-scale, prospective, multinational observational studies designed to evaluate urolithiasis risk across different topiramate dosage (e.g., <100 mg per day, 100–150 mg per day, >150 mg per day) and treatment duration strata. Such studies would enable more precise assessment of potential dose–response relationships and help reconcile discrepancies between pharmacological mechanisms and real-world clinical outcomes.

In conclusion, topiramate exposure was not associated with an increased risk of urolithiasis in this large Korean population-based cohort. This finding is consistent with a previous population-based study from Taiwan and suggests that in a real-world clinical setting, the risk of urolithiasis from topiramate may not be clinically significant.

Ethical statement

This retrospective cohort study utilized anonymized data from the Korean National Health Insurance Service–National Sample Cohort (NHIS-NSC). The study protocol was approved by the institutional review board (IRB No. 4–2023-1309), and the requirement for informed consent was waived due to the use of de-identified secondary data. All procedures were performed in accordance with relevant guidelines and regulations.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to assist with grammatical refinement. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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CRediT authorship contribution statement

Kimoon Chang: Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **Woo-Seok Ha:** Writing – review & editing, Visualization, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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