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Topiramate-Associated Nephrolithiasis – A Literature Review

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Abstract

Introduction and Purpose. Topiramate alters renal acid–base handling through carbonic anhydrase inhibition and can produce hypocitraturia, increased urinary pH, and metabolic acidosis, creating a urinary environment that favors stone formation. The extent to which these metabolic changes translate into clinically relevant nephrolithiasis is less certain. This review examines the mechanisms of topiramate-associated stone formation, the available evidence on clinical risk, and current approaches to risk assessment, monitoring, and prevention.

Materials and Methods. A structured literature search of PubMed/MEDLINE was performed, with the final search completed on 16 August 2026. Clinical and observational studies, systematic reviews, and relevant mechanistic studies addressing topiramate-associated nephrolithiasis, urinary metabolic abnormalities, risk assessment, and preventive interventions were considered. Older studies were included when they provided relevant mechanistic or long-term clinical data. Evidence specific to topiramate was distinguished from studies in which topiramate was analyzed together with other carbonic anhydrase-inhibiting drugs, particularly zonisamide.

Results. Topiramate produces a consistent lithogenic metabolic profile, particularly hypocitraturia and increased urinary pH, but the frequency of clinically apparent nephrolithiasis remains difficult to define. Reported estimates vary according to the population studied, duration of exposure, and the method used to identify stone disease. Metabolic abnormalities, imaging-detected stones, diagnosed urolithiasis, and symptomatic events requiring healthcare intervention have been used as different outcomes, limiting direct comparison between studies. Recent population-based analyses have also produced non-uniform estimates of clinical risk. No validated topiramate-specific model predicts which patients will develop nephrolithiasis. Potassium citrate can improve hypocitraturia in stone-forming patients who continue treatment, although evidence that this reduces subsequent stone events is lacking.

Conclusions. Topiramate has a well-established lithogenic metabolic effect, but the absolute risk of clinically significant nephrolithiasis and the factors determining individual susceptibility remain incompletely defined. Metabolic findings can guide assessment and management once abnormalities or stone disease are identified, but they cannot currently

provide reliable individual risk prediction. Preventive strategies should therefore be interpreted according to the strength of the available evidence, particularly because improvement in urinary parameters has not yet been shown to translate consistently into fewer clinical stone events.

Keywords: topiramate; nephrolithiasis; urolithiasis; kidney stones; hypocitraturia; metabolic acidosis

1. Introduction

Topiramate is a carbonic anhydrase-inhibiting drug used primarily in the treatment of epilepsy and prevention of migraine. Its clinical use has expanded over time, and prolonged exposure is common in patients who achieve adequate disease control. Although generally well tolerated, topiramate can produce metabolic disturbances that are relevant to the urinary tract, including metabolic acidosis, hypocitraturia, and an increase in urinary pH [1–4]. These effects provide a plausible basis for an increased tendency toward nephrolithiasis [2–5].

Kidney stone formation is a recognized adverse effect of topiramate, but its frequency is difficult to define precisely. Early reports and metabolic studies identified a biologically plausible increase in stone-forming potential [2–5], whereas subsequent clinical studies using longer follow-up or active imaging reported variable rates of nephrolithiasis [6–9]. More recent population-based analyses have provided additional but non-uniform evidence regarding clinically diagnosed or symptomatic stone events [10–12]. Differences in treatment duration, dose, patient characteristics, outcome definitions, and methods used to detect stones complicate direct comparison of the available data [6,9–12].

The distinction between metabolic abnormalities and clinical stone disease is important. Changes in urinary citrate and pH may develop during treatment [3–6], but these abnormalities do not identify which patients will subsequently form stones. No validated method currently allows individual risk to be predicted, and the clinical value of routine metabolic or imaging surveillance in otherwise asymptomatic patients remains uncertain [6].

This review examines nephrolithiasis associated with topiramate use, with emphasis on the mechanisms of stone formation, estimates of clinical risk, differences between treated

populations, and the evidence supporting current approaches to assessment, prevention, and management. Particular attention is given to the distinction between metabolic changes and clinically relevant stone outcomes, as this remains a major limitation of the available literature.

2. Pathophysiology and Stone Formation

Topiramate inhibits renal carbonic anhydrase, interfering with normal bicarbonate handling and acid–base regulation. Increased renal bicarbonate loss can produce a hyperchloremic, non-anion gap metabolic acidosis, while reduced hydrogen ion secretion contributes to a higher urinary pH [1,3,4]. These effects may occur during otherwise uncomplicated treatment and form the metabolic background for topiramate-associated stone formation [1–6].

Hypocitraturia is another consistent finding during topiramate therapy [3,4,6]. Systemic acidosis promotes proximal tubular citrate reabsorption and metabolism, reducing the amount of citrate excreted in urine. This is relevant because urinary citrate binds calcium and inhibits calcium salt crystallization [1,4]. A fall in citrate excretion therefore removes an important protective factor against stone formation. Changes may occur relatively early after treatment initiation. In a small prospective study, urinary citrate declined within the first month of therapy, and hypocitraturia was present in most participants by 60 days [13]. The small sample size limits any estimate of how frequently this occurs across the wider population, but the study supports a direct and relatively rapid metabolic effect of topiramate.

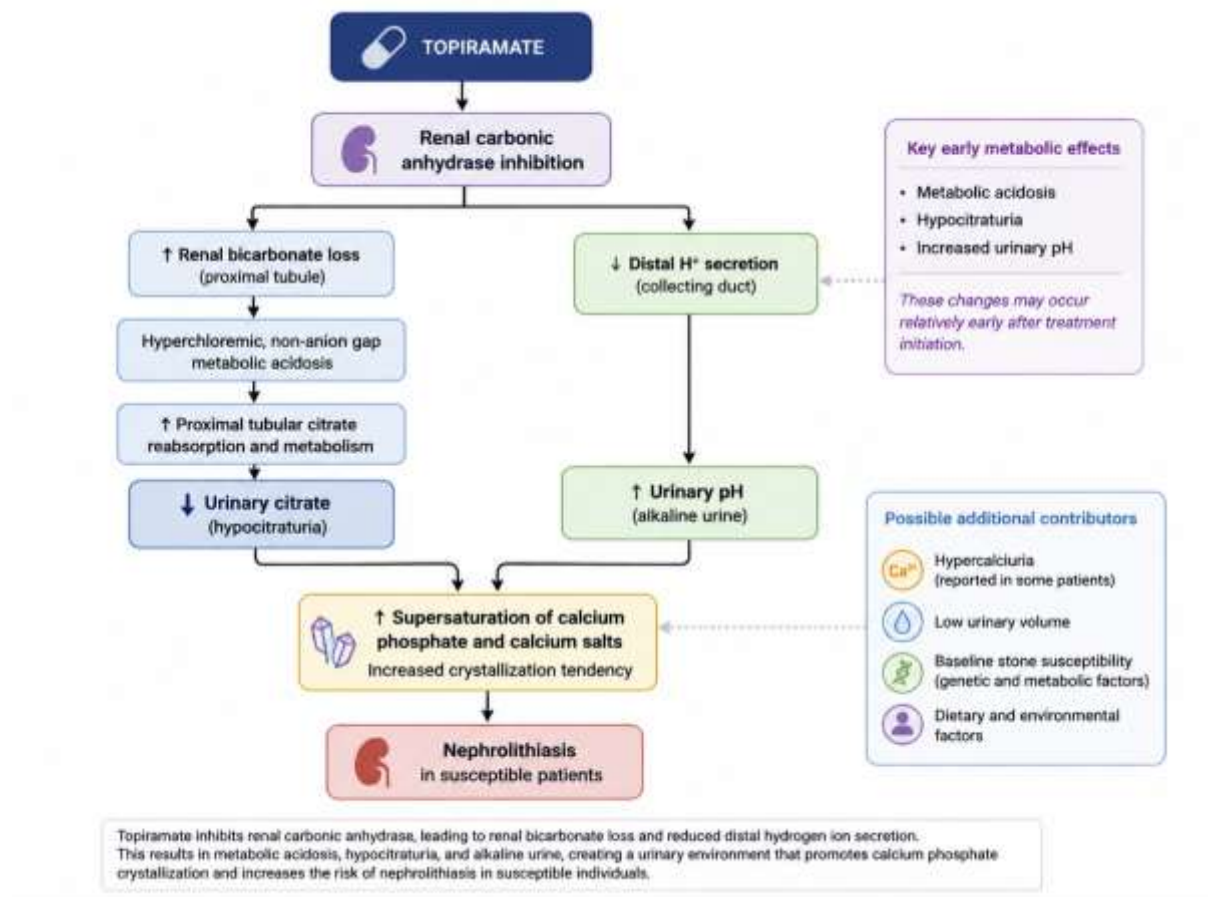
The combination of hypocitraturia and increased urinary pH is particularly relevant to calcium phosphate crystallization [2–6,22–24]. Higher urinary pH favors calcium phosphate supersaturation and is an established characteristic of calcium phosphate stone formation [23,24]. Reduced citrate further removes an important inhibitor of calcium salt crystallization [4,23]. Calcium phosphate stones are therefore commonly associated with the urinary phenotype produced by topiramate, although stone composition is not uniform and other stone types may occur [2,4–6,22].

Changes in calcium handling may contribute further, but the evidence is less consistent than for urinary citrate and pH. Hypercalciuria has been reported in some treated patients and may increase calcium salt supersaturation when present [4,6]. It should not, however, be regarded as a universal feature of topiramate exposure [6]. Urinary volume and other conventional determinants of stone formation remain relevant and may partly determine whether the drug-induced metabolic changes ultimately result in a clinical stone.

This distinction is important when interpreting the available evidence. Topiramate produces a recognizable lithogenic urinary profile, but biochemical abnormalities are more common than

clinically apparent nephrolithiasis [4,6,7]. The presence of hypocitraturia, alkaline urine, or metabolic acidosis therefore indicates a biological tendency toward stone formation rather than an inevitable clinical outcome. The factors determining why only some treated patients progress from metabolic abnormalities to symptomatic or radiologically detectable stones remain incompletely defined [6].

Figure 1. Proposed mechanism of topiramate-associated nephrolithiasis.



3. Epidemiology and Clinical Risk

The frequency of nephrolithiasis during topiramate treatment is difficult to define from the available literature. Reported estimates vary substantially according to study population, duration of exposure, method of stone detection, and the outcome used to define stone disease. Short-term clinical studies generally reported relatively few stone events, whereas studies involving longer treatment or active imaging have sometimes produced considerably higher estimates [6,7]. These figures should not be treated as directly comparable.

One of the most frequently cited long-term studies included 75 adults receiving topiramate at a median dose of 300 mg/day for a median of 48 months. Symptomatic nephrolithiasis was reported in 10.7% of patients. Among 15 patients without a history of symptomatic stone

disease who underwent computed tomography, three had previously unrecognized stones, corresponding to 20% of this small imaging subgroup [7]. The findings suggested that clinically silent stones may be missed when nephrolithiasis is identified only through symptomatic presentation. They should nevertheless be interpreted cautiously: the study was conducted at a single center, included only 75 patients, and the CT estimate was based on a particularly small subgroup [7]. The 10.7% prevalence therefore should not be interpreted as a general estimate for all patients receiving topiramate.

Population-based studies have produced less consistent results. In a nationwide cohort published in 2015, 1,377 topiramate users were compared with 1,377 age- and sex-matched controls. Urolithiasis-free survival did not differ significantly between the groups, and neither treatment duration nor cumulative topiramate dose was associated with stone risk [10]. These findings provided early population-level evidence that the metabolic effects of topiramate do not necessarily translate into a detectable increase in clinically diagnosed urolithiasis.

A much larger retrospective analysis published in 2025 examined 1,122,301 individuals using two US claims databases. New users of topiramate or zonisamide had more symptomatic stone events than matched nonusers. Between three months and three years after treatment initiation, the unadjusted cumulative incidence was 2.9% versus 1.2% in the Clinformatics cohort and 2.0% versus 1.3% in the Medicare cohort. After adjustment, exposure was associated with a higher hazard of symptomatic stone events in both databases (HR 1.58, 95% CI 1.49–1.68 and HR 1.22, 95% CI 1.11–1.34, respectively) [11].

These results provide stronger epidemiological evidence than earlier small cohorts, but they are not a topiramate-specific estimate of overall stone risk. The primary exposure combined new use of topiramate and zonisamide, both carbonic anhydrase-inhibiting drugs, and the outcome was restricted to symptomatic stones resulting in an emergency department visit, hospitalization, or surgical intervention. Less severe symptomatic episodes and asymptomatic stones were therefore outside the primary outcome definition [11]. The investigators also reported that the hazard of symptomatic stone events increased with higher topiramate doses, while the association with topiramate or zonisamide exposure was stronger among younger adults [11]. These findings suggest possible variation in risk with treatment exposure and age, but they do not establish a clinically useful dose or age threshold.

A nationwide Korean cohort published in 2026 produced a different result. After propensity-score matching, 1,560 topiramate users were compared with 6,240 controls and followed for five years. First-time urolithiasis occurred in 47 topiramate users (3.0%) and 170 controls (2.7%). Topiramate exposure was not significantly associated with urolithiasis in the fully

adjusted model (HR 1.13, 95% CI 0.817–1.562; p=0.461). Analyses based on current use and cumulative duration of exposure likewise did not identify a significant association [12].

The population-based findings should not be reduced to a simple distinction between positive and negative studies. The 2015 and 2026 cohorts evaluated topiramate specifically and did not demonstrate a statistically significant increase in urolithiasis, whereas the large US analysis combined topiramate with zonisamide and focused on symptomatic events requiring substantial healthcare use [10–12]. Differences in study population, exposure definition, outcome ascertainment, treatment indication, and residual confounding further limit direct comparison.

Taken as a whole, the epidemiological evidence supports a lithogenic effect of topiramate but does not provide a single reliable estimate of clinical stone risk [6,7,10–12]. Long-term cohorts, administrative databases, and imaging studies capture different manifestations of stone disease. The distinction between symptomatic events, incident diagnoses, and stones detected through active imaging is therefore essential when interpreting reported rates [6,7,10–12].

Table 1. Key clinical studies evaluating nephrolithiasis during topiramate treatment

Study	Population and outcome assessment	Main result	Key interpretation / limitation
Maalouf et al., 2011	75 adults on long-term topiramate; symptomatic history, with CT in 15 asymptomatic patients	Symptomatic stones: 8/75 (10.7%); CT-detected stones: 3/15	Long-term exposure may reveal more stone disease; small selected cohort and very small CT subgroup
Mahmoud et al., 2011	96 children treated ≥ 1 year; follow-up renal ultrasonography	Stones detected in 5/96 (5.2%)	Active imaging captures stones irrespective of symptoms; small pediatric cohort limits generalizability

Salka et al., 2025	Large US claims cohorts; new topiramate or zonisamide users; clinically significant symptomatic events	Adjusted HR 1.58 (95% CI 1.49–1.68) and 1.22 (1.11–1.34)	Supports increased risk, but primary exposure combined two drugs and captured healthcare-requiring events
Korean nationwide cohort, 2026	1,560 topiramate users vs 6,240 matched controls; first-time diagnosed urolithiasis	3.0% vs 2.7%; HR 1.13 (95% CI 0.817–1.562)	No significant association; observational design and different outcome definition limit comparison with US data

Abbreviations: CI, confidence interval; CT, computed tomography; HR, hazard ratio.

Source: Own elaboration based on the cited studies.

4. Clinical Context and Population-Specific Risk

The clinical context in which topiramate is prescribed is important when interpreting the available evidence on nephrolithiasis. Studies include children with epilepsy, adults receiving long-term antiseizure treatment, and patients treated for migraine, often with substantial differences in concomitant therapy and duration of exposure. Methods used to identify stone disease also vary. These differences do not necessarily represent independent risk factors, but they limit direct comparison of reported stone rates across populations [6–9,11].

Pediatric studies illustrate this problem particularly well. Some cohorts used scheduled renal ultrasonography and could therefore identify stones irrespective of clinical symptoms, whereas large adult database studies generally relied on diagnosed or clinically significant stone events [8,9,11]. The 5.2% stone rate reported in a pediatric surveillance cohort should be interpreted in this context rather than compared directly with rates based on symptomatic presentation [8]. Other pediatric studies have additionally documented nephrolithiasis, nephrocalcinosis, and urinary metabolic abnormalities during topiramate therapy, emphasizing that the outcome being measured is important when comparing pediatric estimates [9,14].

Pediatric populations themselves are also heterogeneous. Children receiving topiramate alone under routine neurological follow-up differ substantially from patients with refractory epilepsy receiving multiple antiseizure therapies or ketogenic dietary treatment [8,9,14–16].

Ketogenic dietary therapy is especially relevant because it carries an independent risk of nephrolithiasis [15,16,21]. Its metabolic effects include abnormalities that can favor stone formation, although the resulting urinary environment is not identical to that associated with topiramate. This makes concomitant treatment clinically plausible as a concern, but the available outcome data are less straightforward than the mechanism might suggest [15,16,21]. In a retrospective cohort of 301 children treated with a ketogenic diet, nephrolithiasis occurred in 15 of 221 patients who were not receiving a carbonic anhydrase inhibitor and in five of 80 receiving topiramate or zonisamide concurrently. The study did not demonstrate a higher observed stone rate in the combined-treatment group. Its ability to determine the effect of topiramate specifically was limited because topiramate and zonisamide were analyzed together [15].

In another cohort of 195 children receiving ketogenic dietary therapy, 13 patients (6.7%) developed kidney stones. Stone occurrence was not significantly associated with concomitant use of carbonic anhydrase inhibitors such as topiramate or zonisamide. The study also reported a lower prevalence of stones among children receiving potassium citrate, although these findings relate to ketogenic dietary therapy and should not be directly extrapolated to patients receiving topiramate outside this setting [21].

A later study further illustrates this difficulty. Among 93 children receiving ketogenic dietary therapy, six developed radiologically confirmed stones. Only one occurred among 22 children treated with ketogenic diet plus topiramate, compared with three among 17 receiving ketogenic diet plus zonisamide; the remaining cases occurred in other treatment groups. The numbers are too small for firm comparative conclusions, but they argue against assuming that all carbonic anhydrase inhibitors contribute equally to stone risk during ketogenic dietary therapy [16].

Treatment indication and age may also affect how results are interpreted, although neither currently provides a validated basis for individual risk prediction. Earlier long-term studies largely involved neurological populations treated for seizure disorders, whereas contemporary topiramate use includes substantial numbers of patients treated for migraine and other indications [7,11]. More recent claims-based evidence found a stronger association between topiramate or zonisamide exposure and symptomatic stone events among younger adults, while higher topiramate doses were associated with greater hazard [11]. These observations suggest that risk may not be uniform across treated populations, but they do not establish age, indication, or dose thresholds that can be used to classify an individual patient.

Population-specific findings therefore require cautious interpretation. Differences in age, underlying neurological disease, concomitant treatment, duration of exposure, and methods of

stone detection make direct comparison between studies difficult [6–9,11,14–16,21]. This is particularly relevant in pediatric epilepsy, where ketogenic dietary therapy and multiple antiseizure medications may coexist with topiramate use [15,16,21]. These differences should be considered when interpreting reported stone rates across treated populations.

5. Risk Assessment and Monitoring

There is currently no validated method for predicting which patients treated with topiramate will develop nephrolithiasis. Most factors considered in clinical practice are derived from general stone disease rather than from risk models developed specifically in topiramate users [6]. A previous history of nephrolithiasis is relevant because it identifies an existing tendency to form stones, but it has not been validated as a topiramate-specific predictor [6,17].

Serum bicarbonate has an established role in monitoring the metabolic safety of topiramate. Current prescribing information recommends measurement before treatment and periodically during therapy because topiramate can cause hyperchloremic, non-anion gap metabolic acidosis [18]. This should not be interpreted as a nephrolithiasis screening strategy. Serum bicarbonate has not been validated as a predictor of stone formation, and a normal value does not exclude hypocitraturia, alkaline urine, or other lithogenic changes [1,3,4,6].

Routine 24-hour urine testing in every asymptomatic patient receiving topiramate is not supported by current evidence. A detailed metabolic evaluation is more appropriate after a stone event or in patients who already meet criteria for more extensive evaluation as stone formers [19]. In this setting, urine volume, pH, citrate, calcium, oxalate, sodium, and other standard parameters can be assessed according to established urolithiasis practice [19]. Hypocitraturia and increased urinary pH are compatible with the metabolic effects of topiramate [3,4,6], but neither finding is specific to the drug and neither has been shown to predict a future stone event reliably.

Dose may influence the metabolic response to treatment. Small studies have reported lower urinary citrate concentrations with increasing topiramate dose [17], and more recent observational data have also suggested a stronger association with clinical stone events at higher doses [11]. These findings do not provide a clinically useful threshold. No dose has been established above which nephrolithiasis should be expected, and the relationship between treatment duration and clinical stone risk is even less clearly defined [6,10–12].

Routine imaging of asymptomatic adults solely because they are taking topiramate is also not supported by sufficient evidence [6]. Asymptomatic stones have been identified during imaging studies [7], but the available data are too limited to define a screening interval or to

show that systematic imaging improves outcomes. When nephrolithiasis is suspected clinically, diagnostic imaging should follow standard pathways used for other stone formers rather than a separate topiramate-specific approach [19].

Stone analysis and metabolic testing become more informative once nephrolithiasis has occurred [19]. A calcium phosphate component, particularly when accompanied by alkaline urine and hypocitraturia, is compatible with the metabolic profile associated with topiramate [2–6], but it does not establish causality. Other causes of calcium phosphate stone formation remain possible, and mixed stone composition is common [19].

The main limitation of current risk assessment is therefore predictive rather than diagnostic. Several measurable abnormalities are associated with topiramate treatment, but none has been validated as a reliable marker of future nephrolithiasis [3,4,6]. There is no topiramate-specific risk score and no established cut-off for serum bicarbonate, urinary citrate, urinary pH, dose, or treatment duration that can classify an individual patient as high risk [6,10–12,17].

6. Management and Follow-up

Management of nephrolithiasis during topiramate treatment depends both on the characteristics of the stone disease and on whether continued use of the drug remains clinically justified. Acute treatment does not differ from standard urological practice and is determined by stone size and location, symptoms, obstruction, infection, and renal function [19].

General measures used to prevent recurrent stones also apply to patients receiving topiramate. Adequate fluid intake is particularly important; current urolithiasis guidelines recommend maintaining a 24-hour urine volume above 2.5 L in stone formers [19]. Dietary advice should be based mainly on stone composition and metabolic findings, as there is no established topiramate-specific diet for stone prevention [19].

Potassium citrate is of particular interest because hypocitraturia is one of the most consistent metabolic abnormalities observed with topiramate [3,4,6]. In a clinical effectiveness study of stone-forming patients receiving the drug, urinary citrate increased from 198 ± 120 to 408 ± 274 mg/day after alkali therapy, while the proportion of patients with hypocitraturia decreased from 85% to 40%. The increase in citrate was greater in patients receiving higher doses of potassium citrate [13]. These findings show that alkali therapy can improve topiramate-associated hypocitraturia in patients who remain on treatment [13].

Whether this metabolic improvement prevents further stones is less clear. The study was small and assessed changes in urinary citrate rather than stone recurrence [13]. Potassium citrate is used in recurrent hypocitraturic calcium stone disease more generally [19], but evidence from

these populations cannot establish the same clinical benefit specifically in patients who continue topiramate. Its use in this setting is therefore better considered in the context of a documented metabolic abnormality than as routine prophylaxis for every topiramate user.

Urinary pH also needs to be considered when alkali treatment is used. Topiramate already tends to increase urine pH [1,3,4,6], and potassium citrate may increase it further. In the clinical effectiveness study, mean urinary pH increased from 6.65 to 7.25 after potassium citrate, whereas calcium oxalate and brushite supersaturation did not change significantly [13]. Hypocitraturia should therefore not be considered in isolation; stone composition and the overall urinary profile are relevant when deciding whether alkali therapy is appropriate and when assessing the response to treatment.

A stone event does not necessarily require immediate withdrawal of topiramate. The decision to continue treatment depends on why the drug is being used, how effective it has been, the availability of suitable alternatives, and the severity or recurrence of stone disease. Continued exposure becomes more difficult to justify when stones recur or clinically relevant metabolic abnormalities persist despite preventive measures.

The urinary changes associated with topiramate appear to be at least partly reversible after the drug is withdrawn. In a retrospective study, 18 patients had 24-hour urine collections available before and after discontinuation. Mean urinary citrate increased from 225 to 614 mg/day ($p < 0.01$), while urinary pH decreased from 6.59 to 6.33; the latter change did not reach statistical significance ($p = 0.06$) [20]. These findings provide stronger evidence for reversibility of hypocitraturia than for normalization of the broader urinary profile, and they do not establish how discontinuation affects subsequent stone recurrence [20].

Dose reduction is another possible option when maintaining topiramate is clinically desirable, but the evidence is limited. An inverse relationship between topiramate dose and urinary citrate has been reported in a small group of stone-forming patients [17], and larger observational data suggest that higher doses may be associated with a greater risk of symptomatic stone events [11]. Neither finding provides a dose threshold or demonstrates that reducing the dose after a stone event prevents recurrence.

Follow-up can therefore be tailored to the clinical problem rather than to topiramate exposure alone. Patients with established nephrolithiasis should be managed according to standard stone disease practice, with repeat metabolic testing when the result is likely to influence management [19]. In patients who continue topiramate despite relevant metabolic abnormalities, or who receive potassium citrate, reassessment may be useful to determine

whether those abnormalities have improved [13,19]. There is currently no evidence-based topiramate-specific interval for repeat urine testing or imaging [6].

7. Current Challenges and Future Perspectives

The main uncertainty surrounding topiramate-associated nephrolithiasis is no longer whether the drug alters urinary chemistry. Hypocitraturia, increased urinary pH, and metabolic acidosis are well documented [1,3,4,6]. The more difficult question is how often these changes progress to clinically relevant stone disease and which patients are most susceptible [6,7].

A major limitation of the available literature is the lack of a consistent clinical endpoint. Studies have assessed metabolic abnormalities, asymptomatic stones detected by imaging, diagnosed urolithiasis, and symptomatic events requiring emergency care or intervention [3,4,6–12]. These outcomes represent different stages of stone disease and cannot be treated as equivalent. Differences in outcome definition and ascertainment are therefore an important reason why reported stone rates vary and why direct comparison between studies remains difficult [6–12]. Recent population-based studies have not fully resolved this uncertainty. A large US claims analysis found a higher hazard of symptomatic stone events among users of topiramate or zonisamide, whereas a nationwide Korean cohort evaluating topiramate specifically found no statistically significant increase in first-time urolithiasis [11,12]. The studies differed in population, exposure definition, and outcome ascertainment, and both remain susceptible to residual confounding. Their findings should therefore not be interpreted as directly contradictory estimates of the same effect [11,12].

Risk prediction remains another important gap. Dose, age, previous stone disease, urinary citrate, urinary pH, and serum bicarbonate have all been considered potentially relevant, but none provides a validated basis for estimating an individual patient's probability of developing nephrolithiasis [3,4,6,10–12,17]. Observational evidence suggesting a greater hazard of symptomatic stone events at higher topiramate doses does not establish a clinically useful dose threshold [11]. Likewise, small metabolic studies showing lower urinary citrate with increasing exposure do not establish how well these changes predict subsequent stone formation [17].

Evidence for prevention remains limited by the outcomes used in existing studies. Most topiramate-specific intervention data concern changes in urinary chemistry rather than subsequent stone formation or recurrence [13,20]. Improvement in a metabolic surrogate therefore cannot yet be assumed to represent a reduction in clinically relevant events. This limits the evidence available to guide preventive treatment, dose modification, or decisions about continued topiramate exposure after nephrolithiasis. The available potassium citrate

study, for example, demonstrated improvement in urinary citrate but was small and did not establish a reduction in subsequent stone events.

Prospective studies beginning at treatment initiation are needed to determine whether baseline characteristics, drug exposure, and metabolic changes predict subsequent stone formation. Clinical outcomes should be defined in advance and should distinguish asymptomatic imaging findings from symptomatic stone events. Such studies would allow the predictive value of metabolic abnormalities to be assessed rather than simply confirming that they occur during treatment [6].

Prevention also requires clinical rather than purely biochemical outcomes. In patients who develop nephrolithiasis while benefiting from topiramate, studies should determine whether interventions such as alkali therapy or modification of drug exposure reduce stone recurrence [13,20]. Without recurrence data, the clinical benefit of correcting metabolic abnormalities remains uncertain.

Until such evidence is available, the limits of current knowledge should remain clear. Topiramate has a well-established lithogenic metabolic effect [1,3,4,6], but the absolute clinical risk [6,7,10–12], reliable predictors of susceptibility [6,11,17], and effectiveness of topiramate-specific preventive strategies [13,20] remain incompletely defined.

Conclusions

Topiramate produces a well-defined metabolic environment that can promote stone formation, particularly through hypocitraturia and increased urinary pH. These effects provide a convincing biological explanation for topiramate-associated nephrolithiasis. Their clinical consequences are less predictable. Reported stone rates vary considerably between studies, and recent population-based analyses have not produced uniform estimates of risk.

No validated method currently identifies which topiramate-treated patients will develop nephrolithiasis. Metabolic abnormalities can support clinical assessment once they are detected, but serum bicarbonate, urinary citrate, urinary pH, dose, and treatment duration cannot be used individually to predict a future stone event. Management should therefore be based on the clinical context and findings in the individual patient rather than on a topiramate-specific risk threshold that has not been established.

Potassium citrate can improve hypocitraturia in patients who continue topiramate, and the metabolic changes associated with the drug appear largely reversible after withdrawal. Whether these interventions reduce subsequent stone events remains uncertain. The available evidence therefore supports recognition and management of topiramate-associated metabolic

abnormalities while leaving important questions about absolute clinical risk and prevention of recurrent nephrolithiasis unresolved.

Author's contribution

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