REVIEW

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Thiazides for kidney stone recurrence prevention

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Purpose of review
Kidney stones are the most common condition affecting the kidney, and characterized by a high rate of recurrence. Thiazide and thiazide-like diuretics (thiazides) are commonly prescribed to prevent the recurrence of kidney stones. This review offers a comprehensive up-to-date assessment of the evidence supporting the use of thiazides for kidney stone recurrence prevention, highlights potential harms associated with treatment, and identifies areas of knowledge that require further investigation.

Recent findings
The clinical routine to prescribe thiazides for kidney stone prevention has recently been challenged by the findings of the large NOSTONE trial that failed to show superiority of hydrochlorothiazide at doses up to 50 mg daily over placebo in preventing a composite of clinical or radiological recurrence in patients at high risk of recurrence. Yet, adverse events such as new onset diabetes mellitus and gout were more common in patients receiving hydrochlorothiazide compared to placebo. As demonstrated by a novel meta-analysis presented in this review encompassing all randomized placebo-controlled trials with thiazide monotherapy, current trial evidence does not indicate that thiazide monotherapy is significantly better than placebo in preventing kidney stone recurrence.

Summary
Given the limited efficacy and possible adverse effects, we advocate for a restrictive use of thiazides for kidney stone recurrence prevention. Clearly, there remains a high unmet medical need for effective, targeted therapies to prevent recurrence of kidney stones.

Keywords
hydrochlorothiazide, hypercalciuria, kidney stone, nephrolithiasis, NOSTONE trial, recurrence prevention, thiazide

INTRODUCTION

Nephrolithiasis is the most common kidney disorder, carrying a lifetime risk of up to 20% for males and 10% for females [1]. Incidence and prevalence of kidney stones have both increased over the past few decades, regardless of age, gender and ethnic background [2,3]. Kidney stones are highly recurrent, extremely painful, and cause enormous costs, excess morbidity, and reduced quality of life [4–6]. Therefore, the prevention of kidney stone recurrence is of utmost importance [7–9].

Most kidney stones are composed of calcium oxalate (CaOx), calcium phosphate (CaP) or a mixture of both, and a high urine calcium ("hypercalciuria") is the most frequent metabolic abnormality among patients with kidney stones [10]. Thiazide and thiazide-like diuretics, commonly referred to as "thiazides," reduce urine calcium and have therefore been the standard medical treatment for the prevention of kidney stone recurrence for many decades [11–13]. The efficacy of thiazides in the prevention of kidney stone recurrence has been evaluated in several randomized controlled trials (RCTs) [14–25]. Clinical endpoints evaluated in these trials were either symptomatic recurrence alone, or a composite of symptomatic or radiologic recurrence, and study duration was typically 2–3 years [26]. Thiazides reduced kidney stone recurrence in nine trials [14–21,23], whereas no difference between thiazide treatment and the control intervention was observed in three trials [24,25,27].

Unfortunately, all these trials had methodological limitations with a high risk of bias including a small sample size, unclear allocation concealment,

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KEY POINTS

- Thiazides have been the standard medical treatment for kidney stone prevention, but the evidence supporting their use for this indication is limited.
- In patients with calcium-containing kidney stones, the large outcome trial NOSTONE recently showed no superiority of hydrochlorothiazide at doses up to 50 mg daily in preventing kidney stone recurrence, yet adverse events were more prevalent in patients receiving hydrochlorothiazide as opposed to placebo.
- A meta-analysis encompassing all double-blind, placebo-controlled trials performed to date indicates that thiazide monotherapy does not confer a greater advantage over placebo in preventing the recurrence of calcium-containing kidney stones.
- There is currently no robust data showing superiority of thiazide-like compounds such as chlorthalidone or indapamide.
- Collectively, these recent findings indicate that thiazides are not as effective in preventing kidney stones as previously assumed and underscore the critical medical need for novel therapeutic strategies for kidney stone patients.

lack of double-blinding and placebo control, no intention-to-treat analysis, outdated dietary recommendations (low calcium diet) and low sensitivity and specificity imaging (KUB) for radiological outcomes (reviewed in [26,28,29]). Furthermore, only high doses of thiazides were studied, which are known to increase the risk for adverse effects [30,31]. A meta-analysis published in 2020 on the use of thiazides for the prevention of kidney stone recurrence concluded that trial evidence quality is low and benefits of treatment are insufficient [29]. Considering adverse effects, poor patient compliance, and economic burden of long-term medication, the authors recommended against the use of thiazides in preventing kidney stone recurrence. Together, these findings highlighted the critical need for a well designed, randomized controlled trial.

NOSTONE TRIAL

NOSTONE was specifically designed to address limitations of past thiazide trials [32▪▪]. Hydrochlorothiazide was chosen because it was by far the best studied thiazide for this indication [16,19,21,23–25], and results of trials with the long-acting thiazides chlorthalidone and indapamide (one trial each) did not differ substantially from hydrochlorothiazide trials [14,15]. Hydrochlorothiazide was dosed once daily because the pharmacodynamic response is much longer than predicted by the half-life, and past trials with once daily and twice daily dosing regimens of hydrochlorothiazide yielded similar results [31]. The hydrochlorothiazide dosage range in NOSTONE comprised 50 mg, the daily dose typically utilized in previous trials for the prevention of kidney stones [16,21,23–25], and 12.5 and 25 mg, which are commonly used doses for the treatment of arterial hypertension. Patients were randomly assigned in a 1 : 1:1 : 1 ratio to four parallel groups to receive hydrochlorothiazide 12.5, 25, 50 mg or placebo once daily. Key eligibility criteria were very similar to past kidney stone prevention trials and included age $\geq$18 years, $\geq$2 stone episodes in the last 10 years, and any past kidney stone containing $\geq$ 50% of CaOx, CaP or a mixture of both. Since urine calcium is a continuous risk factor for stone formation starting from values greater than 150–200 mg/24 h and can vary daily based on dietary sodium intake [33–35], the authors did not include this variable in the eligibility criteria. The main objective was to investigate the dose–response relation for prevention of a composite of symptomatic or radiologic stone recurrence. Secondary end points were symptomatic recurrence, radiologic recurrence and changes in blood and urine parameters, including urine relative supersaturation ratios (RSR) of CaOx and CaP.

NOSTONE KEY FINDINGS AND INTERPRETATION OF RESULTS

NOSTONE enrolled 416 patients at 12 sites throughout Switzerland. Median follow-up time was 2.92 years, and 387 patients (93%) completed follow-up as planned. In the placebo group, 60 of 102 patients (59%) experienced the primary composite end point of symptomatic or radiologic recurrence. Numbers in the hydrochlorothiazide arms were 62 of 105 patients (59%) receiving 12.5 mg [rate ratio as compared to placebo (RR), 1.33; 95% confidence interval (CI), 0.92–1.93], 61 of 108 patients (56%) receiving 25 mg (RR, 1.24; 95% CI, 0.86–1.79), and 49 of 101 patients (49%) receiving 50 mg (RR, 0.92; 95% CI, 0.63–1.36). There was no relation between hydrochlorothiazide dose and the primary end point (ratio of rate ratios, 0.98; 95% CI, 0.87–1.09; test for trend, $P = 0.66$). These results were confirmed by several sensitivity analyses, and subgroup analyses showed no evidence of heterogeneity of the treatment effect.

The NOSTONE results indicate that hydrochlorothiazide is not efficiently preventing recurrence of kidney stones. This presents a significant deviation from prevailing recommendations and the majority of prior thiazide trials, thus necessitating an extensive analysis. We highlight in the following section

several important aspects of the NOSTONE trial design, and reconcile NOSTONE trial findings with the existing trial literature pertaining to the prevention of kidney stones.

NOSTONE selected patients with recurrent idiopathic calcium kidney stones, that would be treated with a thiazide according to current guidelines. However, as it was the case in most prior thiazide trials [15–17,19–22,24,25], NOSTONE did not specifically select patients with hypercalciuria. Indeed, urine calcium is a continuous risk factor for stone formation [36], and current guidelines recommend thiazides in all patients with recurrent calcium stones [13,37,38]. Median baseline urine calcium in NOSTONE was 244 mg/24 h (6.1 mmol/24 h), and 63% of participants were hypercalciuric (defined as urine calcium >200 mg/24 h or >5 mmol/24 h). A subgroup analysis of the NOSTONE trial showed no benefit of hydrochlorothiazide compared to placebo in patients with hypercalciuria.

Recurrence rate in NOSTONE was higher than anticipated (59% observed versus 45% expected in placebo arm), but actually was similar to the subgroup of patients with the highest risk of recurrence in the Borghi diet trial, where the dietary intervention did not result in a benefit [39]. Past thiazide trials had follow-up times of 2–3 years, and control and thiazide groups started to separate between 6 and 12 months of follow-up [14–16]. In NOSTONE, median follow-up time was 2.92 years and cumulative incidence plots of the primary endpoint or of symptomatic stone events showed a consistent null effect over the entire trial period with no indication that curves of higher doses start to separate towards the end of follow-up. Most importantly, even in the large fraction of patients that were stone-free at baseline, there was no difference in the incidence of primary endpoints or symptomatic stone events.

The frequency of the secondary end point symptomatic recurrence was similar across treatment groups, even in the subgroup of patients that were stone-free at baseline or when early recurrences up to 6 or 12 months were excluded. The secondary composite radiological endpoint, defined as new stones formed or stone growth on CT, was lower among patients receiving 25 mg [odds ratio (OR), 0.49; 95% CI, 0.27–0.87] and 50 mg hydrochlorothiazide (OR, 0.54; 95% CI, 0.29–0.98) compared to placebo. The absolute reduction, however, was small (17% in the 25 mg group and 15% in the 50 mg group compared to placebo), and there was no difference in new stones formed among groups over a period of 3 years.

Thiazides decrease urinary calcium excretion by increasing reabsorption of calcium in the proximal tubules, and the proposed mechanism responsible for kidney stone recurrence prevention has been mainly attributed to this unique property [40]. Urine calcium in patients receiving hydrochlorothiazide was indeed lower compared to patients receiving placebo in NOSTONE. However, consonant with lack of efficacy on clinical outcomes, urine relative supersaturation ratios (RSRs) CaOx and CaP, established proxies of risk of recurrence measured in clinical routine, were not lower in patients assigned to hydrochlorothiazide compared to placebo. The following factors likely contributed to this result:

(i) Reduction of urine calcium among patients receiving hydrochlorothiazide was modest (9–17% compared to baseline, 15–16% compared to placebo), without any dose-response effect. Although sodium consumption was similar across all groups, it exceeded the recommended level despite repeated dietary instructions by experienced professionals. This may have mitigated the hypocalciuric effect of hydrochlorothiazide to some extent. Yet, sodium intake in NOSTONE was comparable to that of some previous thiazide trials for the prevention of kidney stones; thus, differences in outcomes cannot be explained only by this factor [14,24]. Together, these results highlight the widely recognized challenge of maintaining a consistent decrease in sodium consumption in the outpatient setting over the period of several years.

(ii) There was a trend for lower urine citrate among patients receiving hydrochlorothiazide compared to patients receiving placebo during follow-up. Reduction of urine citrate is a well known adverse effect of thiazides. The mechanism is thought to be thiazide-induced hypokalemia resulting in intracellular acidosis, stimulating avid citrate reabsorption in the proximal tubule [41]. Indeed, patients receiving hydrochlorothiazide displayed a dose-dependent decrease in plasma potassium [32▪▪].

Nonadherence in NOSTONE was defined as missing >20% of the daily doses of hydrochlorothiazide or placebo on the basis of patient report, and further separated into medical reasons (e.g. adverse effects necessitating a treatment discontinuation) and nonmedical reasons. Nonadherence was not different in patients receiving hydrochlorothiazide compared to patients receiving placebo. However, significant nonadherence was observed, ranging from 15% in the 12.5-mg hydrochlorothiazide group, to 24% in the 25-mg hydrochlorothiazide group, and to 26% in the 50-mg hydrochlorothiazide and placebo groups, respectively. To assess if nonadherence could explain the lack of a treatment benefit with hydrochlorothiazide, a per-protocol analysis was conducted. This analysis yielded very similar results as the intention-to-treat analysis, indicating that poor

adherence cannot explain the trial results. Nevertheless, it cannot be excluded that the high incidence of nonadherence may have biased the treatment effects in favor of the null hypothesis.

No significant variation was observed among the groups in terms of serious adverse events. But patients assigned to hydrochlorothiazide had a higher incidence of adverse events of particular concern, including newly diagnosed diabetes mellitus, hypokalemia, gout, and deteriorated kidney function, than those assigned to the placebo. Clearly, these adverse events observed in a trial with a median duration of 3 years need to be reconciled with the fact that thiazides are typically prescribed on a long-term basis, and in the case of kidney stone prevention, treatment is frequently initiated in young adults.

WHAT IS THE CURRENT ROLE OF THIAZIDES FOR KIDNEY STONE PREVENTION?

NOSTONE has initiated an exciting debate in the kidney stone community and several critical points have been raised that we tried to address in this review. There remain areas of uncertainty that will need to be addressed in future studies, such as the possibility that hydrochlorothiazide may entail a relevant benefit in particular subgroups of patients (e.g. patients that are able to maintain a very low sodium intake on a long-term basis).

The NOSTONE findings and recent concerns about skin cancer associated with prolonged use of hydrochlorothiazide [42–44] will likely prompt a change in prescriptions to the two thiazide-like diuretics indapamide and chlorthalidone. Both indapamide (at a dose of 2.5 mg daily) and chlorthalidone (at doses of 25 or 50 mg daily) reduced kidney stone recurrence in one past RCT each [14,15]. Yet, both trials also had methodological limitations and a high risk of bias [26,29]. The indapamide trial was open-label without a placebo-control group, and sodium intake was significantly higher in patients in the control group compared to patients receiving indapamide [14]. The chlorthalidone trial had unclear allocation concealment, incomplete and selective outcome reporting, no intention-to-treat analysis and lacked follow-up urines - hence adherence to diet remains unknown [15]. Unfortunately, no head-to-head comparison of different thiazides for kidney stone recurrence prevention or for the established proxies of recurrence risk, urine RSR CaOx and CaP, has ever been performed. A crossover trial comparing hydrochlorothiazide, indapamide and chlorthalidone (INDAPACHLOR trial; NCT06111885) that addresses this critical knowledge gap is currently underway.

To comprehensively summarize the best available evidence on the use of thiazides for kidney stone prevention, we performed a novel meta-analysis that includes all trials evaluating a thiazide monotherapy for kidney stone recurrence prevention that were at least double-blind and placebo-controlled (Fig. 1). A total of four trials fulfilled these criteria [15,24,25,32▪▪]. Of these, three trials did not show a benefit of thiazide treatment on preventing kidney stone recurrence. As shown in Fig. 1, this meta-analysis indicates that there is currently insufficient trial evidence that thiazide monotherapy is superior over placebo for kidney stone prevention. These results align with a recent large observational study reporting a benefit of alkali but not of thiazide therapy in preventing clinically significant symptomatic stone events in patients with kidney stones [45▪].

HOW SHOULD PATIENTS WITH RECURRENT CALCIUM KIDNEY STONES BE MANAGED IN CONSIDERATION OF THESE RECENT FINDINGS?

We propose to invest energy and time in patient education, such as dietary and physical behavior changes, as first line intervention. If this does not suffice, pharmacological measures should be discussed on a case-to-case basis. Citrate salts are a valid option, although high quality trial evidence is limited [13,28,37,38,46–48]. Additionally, CaP stone formation may be triggered by alkali administration, necessitating careful monitoring of treatment and urine pH [49]. In patients with calcium kidney stones that are intolerant, or not responsive to citrate supplementation as monotherapy, long-acting thiazides such as chlorthalidone or indapamide may be tried. Importantly, however, there are currently only theoretical considerations and no robust trial data demonstrating an advantage of these thiazide-like compounds over hydrochlorothiazide for kidney stone recurrence prevention. Close monitoring of the patient should be started, and if there is no relevant change in stone activity after 2–3 years of treatment, discontinuation should be explored. The combination of thiazides and alkali therapy may be promising, but has not been tested rigorously so far. Benefits and potential risks associated with long-term use of thiazides should be discussed carefully with each patient.

CONCLUSION

The incidence of recurrence is high in patients with kidney stones. Initial treatment focuses on dietary and behavioral interventions, but this approach is

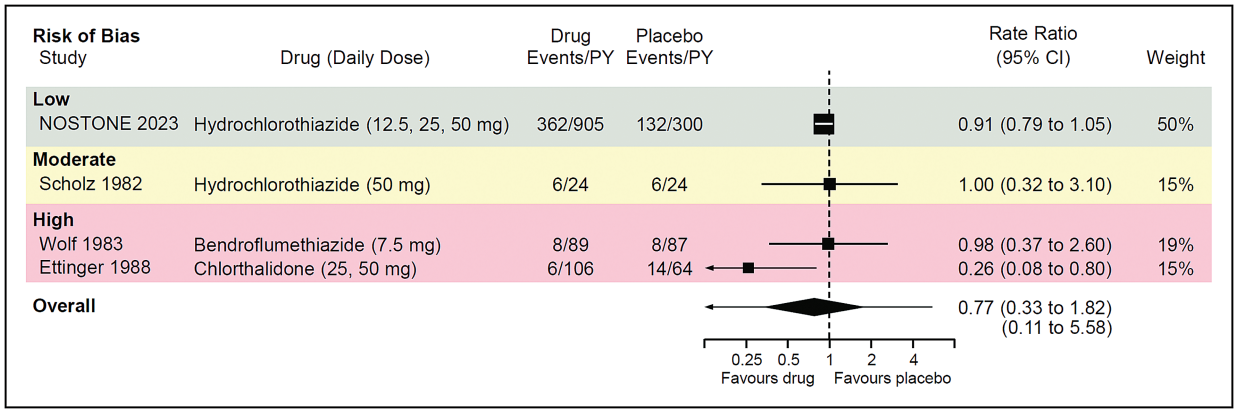

FIGURE 1. Random effects meta-analysis (using empirical Bayes (Paule Mandel) model with Knapp Hartung standard errors) of all placebo-controlled trials evaluating a thiazide (note: trials without placebo control or concomitant potassium supplementation were not considered). Size of squares is proportional to the weight of each trial in the meta-analysis with lines indicating the 95% confidence interval. The diamond shows the meta-analytic estimate with 95% confidence interval. The line indicates the 95% prediction interval. Heterogeneity statistics: $\tau^2 = 0.14$, $I^2 = 47\%$, $H^2 = 1.89$. CI, confidence interval; *N*, number; PY, patient years.

difficult to implement on the long-term and frequently fails to adequately suppress stone formation, necessitating pharmacological treatment. Thiazides have been one of the standard medical treatments for kidney stone prevention. The evidence supporting their use for this indication was largely based on observational data and small trials with methodological limitations. Recent findings challenge this long-held practice. Based on the results of a novel meta-analysis provided in this review that encompasses all double-blind, placebo-controlled trials to date, thiazide monotherapy does not confer a greater advantage over placebo in preventing the recurrence of calcium-containing kidney stones. There is currently also no head-to-head data showing an advantage of thiazide-like compounds, such as chlorthalidone or indapamide compared to hydrochlorothiazide. Given the limited efficacy and possible adverse effects associated with long-term use, we advocate for a restrictive use of thiazides for kidney stone recurrence prevention. Collectively, these recent findings underscore the high unmet medical need for effective therapies in patients with kidney stones.

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Conflicts of interest

There are no conflicts of interest.

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