Thiazide Use for the Prevention of Recurrent Calcium Kidney Stones

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CJASN ■: 1–3, 2024. doi: https://doi.org/10.2215/CJN.0000000000000399

Among individuals with calcium oxalate or calcium phosphate stones, the recurrence rate is approximately 15% per year. Higher urine calcium is a well-documented risk factor for calcium oxalate and calcium phosphate stones, and arbitrary cut-points have been used to define "hypercalciuria." However, this relation seems linear with no threshold, so a reduction of urine calcium at any level should reduce the risk of stone recurrence.[1]

There are several recommended nonpharmacologic interventions to prevent recurrence of calcium-containing stones: higher fluid intake to raise urine volume, adequate but not excessive calcium intake, and a low-sodium, low-oxalate, and potassium-rich diet.[2] The use of a thiazide or thiazide-like diuretic (henceforth referred to as "thiazide") is a common pharmacologic intervention to lower urine calcium excretion.

Thiazides decrease calciuria by increasing renal proximal tubule calcium reabsorption due to a reduction in intravascular volume[3]; thus, a low-sodium diet is likely essential to obtain maximal benefit when using a thiazide and to limit potassium loss. Thiazides with a longer half-life may have a more sustained action, but studies of the comparative effects on urinary calcium have not been published. The reduction in urine calcium leads to reduced stone formation and growth of existing stones. There is no evidence that thiazides alter the time to passage of asymptomatic stones in the kidney.

There is substantial published evidence of the benefits of thiazides and reduced risk of incident and recurrent stone formation that comes from previous randomized controlled trials (RCTs) and observational data, but there were differences in study design, including sample size, type and dose of drug used, eligibility criteria, dietary and other recommendations, and duration. The outcomes of the RCTs also differed, including time to first recurrence, symptomatic recurrence, and radiographic recurrence. Meta-analyses of these trials have come to similar conclusions. In 1999, Pearle *et al.* reported on eight studies of recurrent calcium stone formers (two of which were limited to "hypercalciuric" patients).[4] The calculated risk reduction for the intervention group was 21% (95% confidence interval [CI], 13% to 29%). In 2009, the Cochrane group reported on five studies of patients with "idiopathic hypercalciuria."[5] There was a significant increase in the number of patients free of kidney stone recurrences in those treated with thiazides (relative risk, 1.61; 95% CI, 1.33 to 1.96), and there was no significant heterogeneity. The stone formation rate also showed a statistically significant decrease in the patients treated with thiazides. This study and the Pearle study did not report on changes in urine chemistries. In 2020, Li *et al.* reported on eight RCTs, and the pooled relative risk for stone recurrence in the thiazide group was 0.44 (95% CI, 0.33 to 0.58) compared with the placebo/untreated group.[6] The pooled standardized mean difference for 24-hour urinary calcium excretion was lower in the thiazide group. The Li meta-analysis also importantly reported that the thiazide users had a higher incidence of adverse reactions. Another recent study showed that "empiric therapy," that is not based on 24-hour urine testing, with thiazides was associated with significantly lower odds of subsequent stone-related events.[7]

There were many limitations of the previous RCTs of thiazides for the prevention of stone recurrence.[8] The recent NOSTONE study by Dhayat *et al.* (ClinicalTrials.gov, NCT03057431) published in the *New England Journal of Medicine* was undertaken to answer some unresolved questions about hydrochlorothiazide efficacy, dose-response, and stone recurrence and to address some of the limitations from previous studies.[9] There are many strengths of this study, such as the randomized, placebo-controlled design and use of different doses. Contrary to the prevailing expectation, the authors concluded from the results that there was no apparent benefit from using hydrochlorothiazide.

Given the authors' conclusion of no benefit of hydrochlorothiazide over placebo, it is essential to discuss some of the limitations before deciding whether this study should change current practice. One major issue is that the primary outcome was a composite of symptomatic or radiologic recurrence of kidney stones (the latter defined as stone growth and new stone formation) rather than just radiologic recurrence. As mentioned above, we would not expect thiazides to reduce symptomatic events due to preexisting stones in the kidney. This is why sufficient duration of follow-up is essential and that a study be powered to detect clinically meaningful differences after excluding stone events that occur too close in time to randomization.

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Although sensitivity analyses were performed using a lag period up to the first 12 months, this may be too short[10] and the power was reduced. We would have preferred evidence of new stone formation or stone growth as the primary outcome. In that analysis presented in Figure 1, panel C, and Table S12 of the article, there was the expected large statistically significant reduced risk (approximately 50%) in the two higher-dose hydrochlorothiazide groups.

A second major limitation is that sodium intake was high at baseline and even higher at the end of follow-up. The high sodium intake would diminish the potential positive effect of hydrochlorothiazide; this was seen in the small reduction in 24-hour urine calcium excretion during follow-up. In the real-world clinical setting, many practitioners would titrate the thiazide dose on the basis of the resulting change in urine calcium, but that was not part of this study's design. A third limitation is that a reduction in serum potassium was not proactively prevented, which may have led to a reduction in urine citrate in some individuals. In addition, urine oxalate was also higher at the end of follow-up in all groups. Higher urine oxalate is associated with a higher risk of calcium oxalate stone formation in a linear fashion independent of urine calcium,[1] so this would diminish the power of detecting a potential beneficial independent effect of hydrochlorothiazide on stone recurrence. In clinical practice, reducing urine sodium and urine oxalate are major foci of stone prevention; the dietary recommendations presumably given to study participants were not effective (and in fact, changes in the opposite direction occurred). Given the issues above, the sample size in each dosing group and the duration of follow-up may not have been sufficient to provide adequate power to answer whether hydrochlorothiazide is efficacious in reducing kidney stone recurrence. Thus, we do not feel this is an informative null study for the primary analysis, which used the composite outcome.

Recommendations

We commend investigators for undertaking randomized trials, which are very difficult to perform, requiring tremendous amounts of time, effort, and resources. There continues to be some uncertainty, so we all need to keep an open mind about whether thiazides actually reduce new stone formation in the real-world setting. We agree with Dhayat *et al.* that using this study design and the specified primary composite outcome, which may very well reflect clinical practice in some settings, hydrochlorothiazide did not significantly reduce the *composite* outcome. However, the results provide randomized controlled evidence that hydrochlorothiazide reduces radiologic stone recurrence, which is consistent with the current intended use.

We do not feel there is sufficient justification to believe that thiazides would reduce the risk of symptomatic stone events due to preexisting kidney stones. In fact, it is essential to inform patients who have radiographically documented asymptomatic stones in the kidney that the existing stones will likely become symptomatic at some point and to explain that a clinical event does not that mean the recommended intervention (whether diet, fluid, or medication) is not working if an episode of renal colic occurs.[11]

We recommend thiazides to reduce new stone formation and stone growth in patients with calcium oxalate or calcium phosphate kidney stones. Although it has been our opinion to recommend longer-acting thiazides (chlorthalidone or indapamide) despite higher rates of adverse events, given the statistically significant findings of reduction in radiologic recurrence in NOSTONE, it seems that shorter-acting hydrochlorothiazide (25 or 50 mg/d) is also effective.

Clinically, we would not recommend a thiazide for a patient who has formed a single kidney stone. While the ultimate goal is to reduce the risk of new stone formation or stone growth, the shorter-term focus should be on the surrogate of reducing urine calcium excretion. This requires incorporating tailored dietary advice, including a low-sodium diet. It is not easy for patients to consume a low-sodium diet, so adherence should be confirmed by 24-hour urinary sodium excretion <2.5 g/d. Consistent higher fluid intake should be encouraged and urine volume measured. Dietary oxalate should also be reduced; reliable dietary oxalate data are now available, but extreme restriction is rarely required (https://www.hsph.harvard.edu/nutrition-questionnaire-service-center/nutrient-tables/). We typically use a thiazide after first trying other interventions mentioned above and perhaps using supplemental alkali. If the patient has evidence of new stones or stone growth and the urine composition does not reach the desired targets, then we might recommend a thiazide even if the urine calcium is not elevated. Published observational data show a nearly linear relation between urine calcium and likelihood of being a stone former *independent of other urinary factors*.[1]

Repeat 24-hour urine collections during follow-up should be used to assess the effect of the initial recommendations and to make adjustments in thiazide dose, dietary oxalate, and sodium and fluid intake.

Like all medications, the risks and benefits need to be carefully considered and discussed with the patient before initiating. Thus, side effects, nicely delineated in the Dhayat study, do need to be considered when deciding whether to start a thiazide. One mechanism by which hypokalemia influences the risk of new stone formation is that a reduction in serum potassium can lead to a decrease in urine citrate (an inhibitor of calcium stone formation). Hypokalemia does not require discontinuation if the serum potassium can be maintained in the middle of the reference range or higher using a potassium-sparing agent (preferably amiloride) and supplemental potassium if needed (in addition to the low-sodium diet). There are also extrarenal benefits of lowering of urine calcium by thiazides to consider, including improved bone mineral density and reduced risk of fracture. We note that thiazides are extremely inexpensive. Nonetheless, if the urine calcium does not appreciably decrease or if side effects develop that cannot be managed or outweigh the benefit of the medication's intended use, the thiazide should be discontinued and other approaches to prevent stone recurrence should be tried.

With careful initial and repeat measurements and patient-centered recommendations, thiazides should substantially reduce the burden and morbidity of recurrent calcium-containing kidney stones.

Disclosures

G.C. Curhan reports employment with OM1, Inc. (for profit); ownership interest in OM1, Inc.; grant funding from General Electric, GlaxoSmithKline, Royal National Institute for the Deaf (tinnitus research project), and US Highbush Blueberry Council; royalties from UpToDate (section editor and author of topics); and advisory or leadership role for OM1, Inc. (Chief Medical Officer). D.S. Goldfarb reports employment with New York Harbor VAMC; consultancy for Alnylam, AstraZeneca, Lilac, Novo Nordisk, Sanofi, Sumitovant, and Synlogic; ownership interest in Moonstone Nutrition, Inc.; research funding from Novo Nordisk and Travere; honoraria from Synlogic; patents or royalties from Moonstone Nutrition, Inc.; advisory or leadership roles for International Cystinuria Foundation and NKF of Greater New York; and role on the Editorial Boards of *CJASN*, *Current Opinion in Nephrology and Hypertension*, *JASN*, *Kidney International*, and *Urolithiasis*.

Funding

None.

Acknowledgments

The content of this article reflects the personal experience and views of the authors and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or *CJASN*. Responsibility for the information and views expressed herein lies entirely with the authors.

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Published Online Ahead of Print: December 14, 2023