Kidney Medicine

Hydrochlorothiazide and Prevention of Kidney Stone Recurrence: A #NephJC Editorial on the NOSTONE Trial

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#NephJC is a recurring twitter-based journal club. #NephJC editorials highlight the discussed article and summarize key points from the NephJC TweetChat.

BACKGROUND

Kidney stones are a global health concern with increasing incidence and prevalence, affecting individuals regardless of age, sex, culture, or region.[1,2] Without effective treatment, recurrence rates for kidney stones are high, with 40% of patients experiencing recurrence within 5 years and 75% within 20 years.[3] Secondary prevention of kidney stones involves a multifaceted approach, including behavioral and nutritional interventions as well as pharmacologic treatment tailored to the specific type of stone.

Thiazides and thiazide-like diuretics have been used for >5 decades to prevent the formation of kidney stones.[4] These medications augment the reabsorption of calcium in the proximal tubule, effectively reducing urinary calcium excretion and decreasing the risk of calcium crystal formation.[5] Multiple studies showed the benefit of these drugs in kidney stone prevention.[6,7] Although they are considered to be a cornerstone of pharmacologic nephrolithiasis prevention, the evidence for their efficacy compared with placebo is limited, with only few dose–response data available. A recent meta-analysis assessing the use of thiazide diuretics for the prevention of recurrent kidney stones concluded that the quality of evidence is low.[8] Thus, there was a critical need for a well-designed, randomized controlled trial (RCT) to evaluate the efficacy of thiazides at preventing kidney stone recurrence.

THE TRIAL

The standard and low dose hydrochlorothiazide (HCTZ) in the recurrence prevention of calcium nephrolithiasis (NOSTONE) trial was a double-blinded, randomized, placebo-controlled trial of low to high doses of HCTZ to assess the ability of thiazide diuretics to prevent recurrence of kidney stones that was performed in multiple centers in Switzerland.[9] Those aged 18 years or older with recurrent kidney stones (≥2 events within 10 years) containing ≥50% of calcium oxalate/calcium phosphate/mixture of both were included in the study. Hypercalciuria was not mandatory for eligibility. Randomization was done at a 1:1:1:1 ratio to yield 4 groups: placebo, 12.5 mg HCTZ/d, 25 mg HCTZ/d, and 50 mg HCTZ/d. Radiologic monitoring was done using noncontrast computed tomography (CT) imaging at the start of randomization and then at the end of 3 years. Follow-up visits were every 3 months and then yearly, and telephone visits occurred every 3 months. The primary outcome was a composite of symptomatic recurrence (passage of stones, renal colic symptoms, or stone requiring surgical intervention) and radiologic recurrence (appearance of new stones on CT or enlargement of pre-existing stones). Secondary outcomes were individual symptomatic recurrence and radiologic recurrence, calculated urine relative supersaturation ratios.

A total of 416 patients were enrolled (104 in each group). Baseline characteristics were consistent in all groups, with a male preponderance. Baseline hypercalciuria (>200 mg/24 hour) was common and present in 63% of patients. Patients treated with HCTZ developed slightly lower urinary calcium excretion than those on placebo at follow-up, with the largest effect noted at the higher dose of 50 mg. However, there was no significant difference in urine relative supersaturation ratios for calcium oxalate and calcium phosphate between the placebo and HCTZ groups. Similarly, there was no statistical difference in primary outcome between the groups because it occurred in 59% of patients with placebo as well as in 59%, 56%, and 49% of patients in the 12.5, 25, and 50 mg/d HCTZ groups, respectively. There was no dose–response effect for the primary outcome. Lower radiologic recurrence only seen with higher doses (25 mg and 50 mg) of HCTZ, with no trend for a dose–response effect. Adverse events of new-onset diabetes mellitus, hypokalemia, gout, skin allergy, and an increase in creatinine >150% baseline were all more common among patients in the HCTZ groups than placebo despite no increase in serious adverse events.

THE TWEETCHAT

The NechJC Twitter chats occurred on April 11th and 12th, 2023 and included a total of 96 participants and 573 tweets. Participants included general nephrologists, nephrolithiasis experts, a study author, as well as medical trainees and educators. The importance of nephrolithiasis as a cause of chronic kidney disease and kidney failure was highlighted as well as the high rate of stone recurrence especially without treatment. The participants discussed their usual approach to kidney stone management, which includes increasing fluid intake, lowering dietary sodium chloride, maintaining adequate dietary calcium, as well as using citrate salts and thiazide diuretics. It was argued

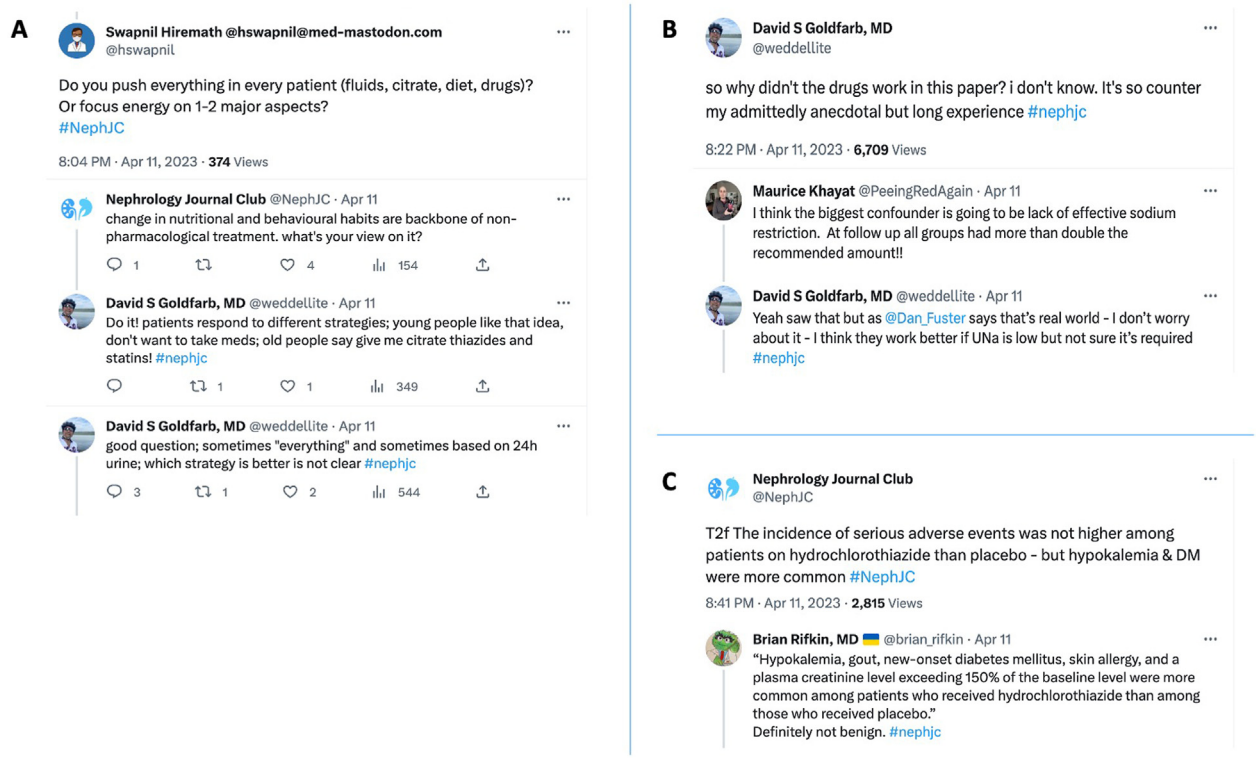

Figure 1. Tweetchat participants discussing nutritional and behavioral changes as a personalized approach to preventing kidney stones (A), opining on the study's unexpected outcome (B), and acknowledging the side effects of thiazide diuretics (C).

whether one should employ all the strategies together or base some interventions (including thiazides) on 24-hour urine studies to create a more individualized and patient-centered approach (Fig 1A).

The available evidence for thiazide use in kidney stone recurrence was deemed insufficient given that most previous trials were small and had weak methodology. This was a subject of a previous NephJC debate regarding American College of Physicians and American Urological Association guidelines,[10-12] with many chat participants recalling the desire for transparency about the poor state of evidence. Despite this, thiazides continue to be used widely in this setting and remain a recommended therapy by more recent guidelines.[13,14]

The NOSTONE results showing the lack of a thiazide benefit were surprising to many (Fig 1B). Despite the lower radiologic recurrence at higher doses (a secondary outcome), there was no statistically significant dose–response effect. It was noted that the previous kidney stone trials used higher HCTZ doses of 50-100 mg daily, whereas lower doses are commonly used in clinical practice. Many participants expressed concern about thiazide side effects, especially in light of the absence of a benefit in the study. Although serious adverse events were not increased in the thiazide groups in NOSTONE, the known side effects of HCTZ, including hypokalemia, gout, diabetes mellitus, and elevated creatinine levels, were noted (Fig 1C), which is important in the context of an absence of benefit of HCTZ. Chat participants asked whether there is any role for other longer-acting and more potent thiazide-like diuretics, such as chlorthalidone and indapamide. Most nephrologists favor their use in this setting; however, some noted concern for hypotension in otherwise normotensive young patients with recurrent stones. Notably, it is also likely that the adverse effects noted in this trial with HCTZ would be expected to be more common with the more potent thiazide-like agents.

The follow-up duration in this study was between 2-3 years, which can be a limitation because most stone prevention studies require at least 2 years to show a benefit. There was a debate about whether the follow-up period should have been extended beyond 3 years and whether the benefit would have manifested later (eg, some of the radiologic recurrence turning into symptomatic recurrences), but some chat participants commented that the event numbers and rates needed for an adequate sample as planned were reached (overall 232 events in 416 patients, 57%) with no benefit seen quite clearly. Hence, it is very unlikely a longer follow-up period would have provided a different result.

The lack of an effect on urinary supersaturation for calcium oxalate and calcium phosphate despite the decrease in urinary calcium with HCTZ treatment also sparked some discussion as to whether this was due to an increase in urinary oxalate or some other unclear

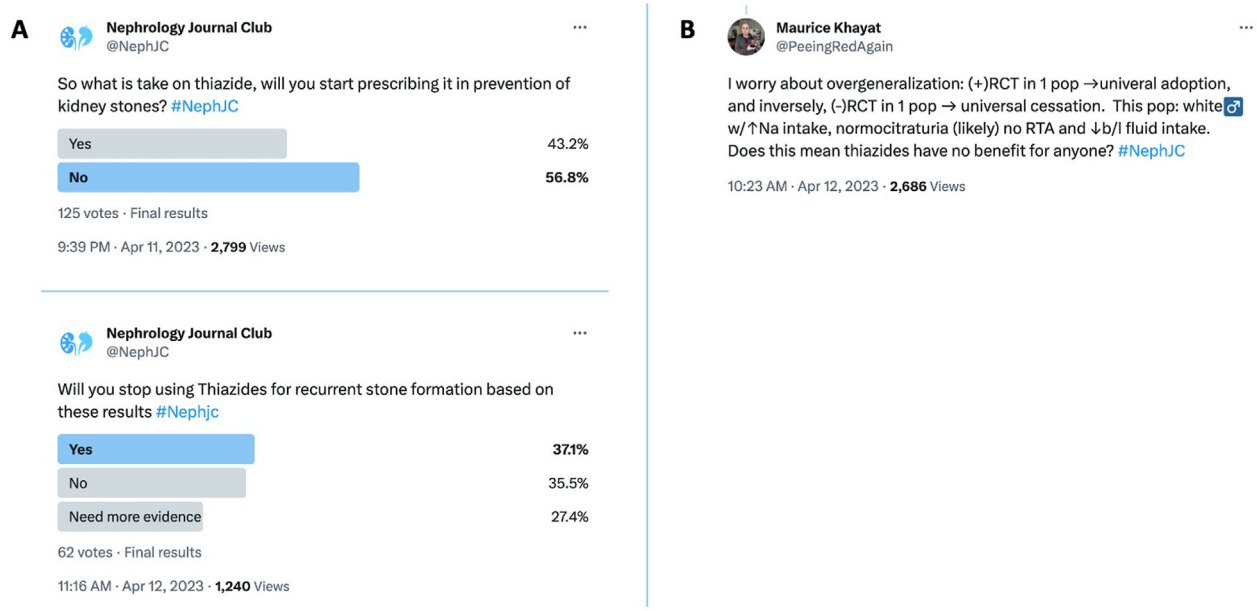

Figure 2. Twitter poll and participant responses from the 2 separate NephJC tweetchats asking participants about future thiazide prescribing patterns in patients with nephrolithiasis. From: Chat 1 https://twitter.com/NephJC/status/1645980040440725506?s=20 and Chat 2 https://twitter.com/NephJC/status/1646185550234406912?s=20 (A). A participant expressing concern about the study's limitations and thus reduced generalizability (B).

mechanism. Another point highlighted was that urinary sodium excretion was high at baseline and remained high during follow-up. In routine practice, there is an emphasis on reducing dietary and thus urinary sodium, increasing fluid intake, and adding HCTZ. Lastly, the role of potassium supplements also came up because hypokalemia itself (spontaneous or HCTZ induced) is a risk factor for hypocitraturia. This could explain the association of thiazides with hypocitraturia and may have diluted the potential benefit of hypocalciuria from thiazides.

Overall, the study was praised as having strong methods and answering the question it set out to address. Some strengths are that it was a double-blinded RCT, assessed symptomatic and radiologic recurrence, and was adequately powered. In addition, authors performed several sensitivity analyses, which were quite consistent in reporting a lack of any benefit. One limitation was that the population was mostly White men, although they have the highest prevalence of kidney stones. Patients with chronic kidney disease and secondary nephrolithiasis as well as those on medications that interfere with kidney stone formation were excluded. Participants also proposed that future RCTs are needed to assess whether the use of additional treatments, such as citrate, and the use of higher doses of HCTZ/long-acting thiazide-like diuretics are truly effective.

Although a majority (57%) of participants said that they would not initiate HCTZ to prevent kidney stones, a smaller plurality (37%) said that they would discontinue HCTZ for patients who were on it to prevent recurrent kidney stones (Fig 2A). Even the discussion argues that we need nuance in interpreting any trial findings and incorporating new knowledge into existing recommendations (Fig 2B).

CONCLUSION

NOSTONE did not demonstrate any benefit of HCTZ (at doses up to 50 mg daily) in the prevention of stones in patients at a high risk of recurrence. A major limitation was the study duration of 3 years. Many nephrologists, clearly including some of those participating in the NephJC tweetchat (Fig 2), are likely to continue using thiazide diuretics in certain patients with special attention paid to 24-hour urine results.

ARTICLE INFORMATION

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