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Update Thiazide Diuretic Evidence Review for CARI Guidelines Kidney Stones Recommendations

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INTRODUCTION

Recently, a double-blind randomized controlled trial (RCT) NOSTONE compared hydrochlorothiazide (12.5 mg/d, 25 mg/d, 50 mg/d) to placebo in adults with at least 2 episodes of kidney stones (at least 50% calcium oxalate, calcium phosphate, or a mixture of both) within 10 years from 12 centers in Switzerland. The participants in the trial were mostly male (80%), of White ethnicity (99%) with a median age of 49 (interquartile range, 39–55) years, and 63% had hypercalciuria. The study found hydrochlorothiazide had no effect on kidney stone recurrence compared to placebo and no hydrochlorothiazide dose-response relationship over the mean 34 months of follow-up. There was a reduction in radiologic recurrence of kidney stones, and there are concerns regarding the participants' adherence to recommended high-fluid intake and reduced sodium intake.[1]

A high-quality systematic review[2] with similar baseline characteristics of participants from included studies to NOSTONE[3] demonstrated that thiazide diuretics (referred to as thiazide throughout) may reduce the incidence of kidney stone recurrence compared to placebo or no treatment (8 studies, $n = 581$, risk ratio: 0.44, 95% CI: 0.33–0.58; $I^2 = 21\%$). Thiazides have been a mainstay in preventing kidney stone recurrence in clinical practice guidelines.[4,5] Given the differences between the well-conducted RCT[3] and systematic review,[2] there is a need for clear up-to-date evidence to support clinical decision-making. To the Working Group's knowledge, clinical guidelines on kidney stone management still need to be updated to incorporate the NOSTONE trial into the recommendation of thiazides use in recurrent kidney stone formers. As the Caring for Australians and New Zealanders with kidney Impairment (CARI) Guidelines (https://www.cariguidelines.org/) Working Group tasked with updating guidelines on the management of kidney stones for the Australian and New Zealand nephrology community,[6] we aimed to evaluate the efficacy and safety of thiazides in the prevention of kidney stone recurrence.

METHODS

We searched MEDLINE using MeSH terms and text words (Supplementary Table S2) from the research question developed by the Working Group to identify systematic reviews on thiazides in the management of recurrent kidney stones (Supplementary Table S1). The most up-to-date review was identified (Supplementary Figure S1) by reviewers (DJT and BC) and underwent dual critical appraisal (BC and DJT) using AMSTAR2.[7] We updated the published systematic

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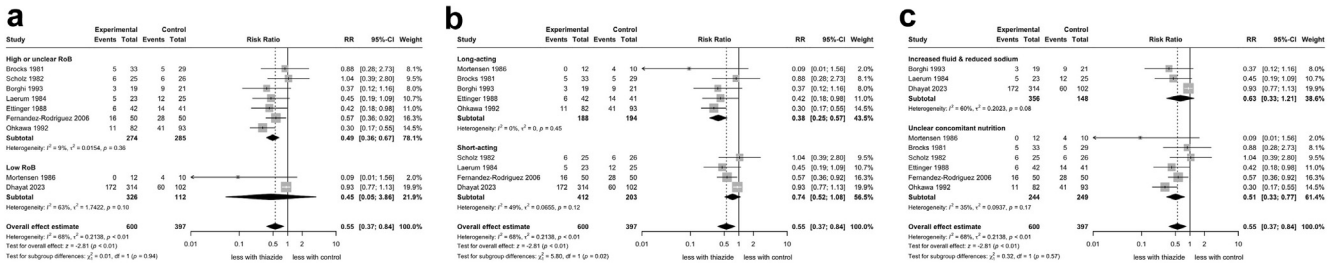

Figure 1. Forest plots effect modification of thiazide diuretics versus placebo or no treatment (a) high and unclear risk of bias and low risk of bias for allocation concealment, (b) short-acting and long-acting subgroups, and (c) concomitant nutrition therapy and no nutrition therapy reported. CI, confidence interval; RR, risk ratio

review after dual abstraction (BC and DJT) of the outcome data from NOSTONE[3] and critical appraisal of the RCT using the Cochrane Risk of Bias Tool 1.0.[8] Data were pooled using random-effects meta-analysis. The random-effects model was chosen because of its conservative estimate of effect in the presence of potential heterogeneity.[8] The incidence of kidney stone recurrence as a dichotomous outcomes were expressed as risk ratio with 95% confidence interval. Heterogeneity was assessed using I^2 statistic and visual expectation of the forest plots. Absolute effects per 100,000 person-years were calculated using the baseline events in the control of trials. Publication bias would be evaluated using funnel plots and Egger's test if more than 10 studies were included in the meta-analysis. The statistical method used was Mantel Henzel meta-analysis using R Studio.[9] The certainty of the evidence was rated using GRADE.[10]

Sensitivity Analyses

To explore potential heterogeneity of the study results, we examined the following subgroup analyses: shorter-acting versus longer-acting thiazides, comparison group involving placebo versus no treatment, concomitant high fluid and low salt diet reported or not reported, definition of recurrence (recurrence or passage only or symptom or radiological), era of publication (1980s, 1990s, 2000s), and risk of bias (high and unclear vs. low). We also examined the robustness of the data using fixed-effects meta-analysis.

RESULTS

Overall, the combination of the NOSTONE[3] to the systematic review data indicates that thiazides may decrease the incidence of symptomatic recurrence of kidney stones (9 studies, $n = 997$, risk ratio: 0.55, 95% confidence interval: 0.37–0.84; $I^2 = 68\%$; absolute effects: 202 fewer per 100,000 person-years, 95% confidence interval: 285–72 fewer) (Figure 1). The overall certainty of the evidence was graded as low due to methodological limitations and inconsistency of study results. The use of a fixed-effect meta-analysis did not change the overall findings.

The subgroup analyses included less than 10 studies and should be considered exploratory but may help to explain the heterogeneity in treatment effects (Table 1). Effect modification was evident when short-term versus long-term thiazides were compared (test for subgroup differences $P = 0.02$; $I^2 = 82.8\%$). The 4 RCTs that have examined the use of short-term thiazides demonstrated little to no difference in the incidence of kidney stone recurrence compared to placebo or standard of care; whereas long-term thiazides compared to placebo, or no treatment decreased the incidence of kidney stone recurrence. The 3 RCTs that compared thiazides to standard-of-care without a placebo may have overestimated the treatment effect compared to the 6 RCTs that compared to placebo. Despite no subgroup difference ($P = 0.13$, $I^2 = 82.8\%$), the subgroups summary effect estimates are qualitatively distinct and should be considered in the overall interpretation of the systematic review results, which indicates a benefit of long-term thiazides use in preventing kidney stone recurrence. In addition, 2 RCTs that were appraised as low risk of bias for allocation concealment demonstrated little or no difference in incidence of kidney stones compared to the 7 RCTs that were high or unclear risk of bias for allocation concealment. Finally, no effect modification was found with concomitant nutrition therapy. Studies that recommend a high fluid and low sodium intake in both the intervention and control groups found no effect; whereas studies with no reporting of concomitant nutrition therapy varied, with some studies finding a reduction in incidence of kidney stones and others finding no difference.

Conclusions

NOSTONE[3] was conducted according to modern standards and the results demonstrate uncertainty about the benefit of thiazides in managing kidney stones. However, the pooled analysis still suggests that

Table 1. Sensitivity analyses of thiazide diuretic versus placebo or no treatment

Sensitivity analysis	Test for subgroup differences	Description
Short-term vs. long-term thiazide diuretics	$P = 0.02$, $I^2 = 82.8\%$	Effect modification was evident with short-term diuretics having little or no effect on kidney stone recurrence and long-term diuretics indicating a decrease in kidney stone recurrence.
Placebo vs. no treatment trials	$P = 0.13$, $I^2 = 57.5\%$	Effect modification was evident with RCTs conducted with placebo control group demonstrating no difference, and RCTs conducted with a no treatment control group having a decrease in kidney stone recurrence.
Definition of recurrence – recurrence or passage only vs. symptoms and radiological	$P = 0.80$, $I^2 = 0\%$	No effect modification was evident between the definition of kidney stone recurrence.
High fluid and low salt therapy vs. no reported nutrition therapy	$P = 0.57$, $I^2 = 0\%$	In trials with reported high fluid and low salt intake recommendations, there was no difference across the studies; whereas in the studies that did not report any nutrition therapy, there was variation in treatment effects, with some studies indicating benefit and or no difference.
Year of clinical trial publication (1980s, 1990s and 2000s), without Dhayat *et al.*[3] 2023	$P = 0.21$, $I^2 = 36.4\%$	Trials published before Dhayat *et al.*[3] 2023 found no effect modification across the eras of the clinical trial.
High or unclear risk of bias vs. low risk of bias for allocation concealment	$P = 0.94$, $I^2 = 0\%$	Limited data with only 2 studies with low risk of bias for allocation concealment. However, studies with high or unclear risk of bias may show a decrease in kidney stone recurrence.
High or unclear risk of bias vs. low risk of bias for attrition	$P = 0.46$, $I^2 = 0\%$	No effect modification was evident in studies with low vs. high or unclear risk of bias for attrition.

RCT, randomized controlled trial.

thiazides are beneficial in preventing recurrent kidney stones. Despite finding no effect modification due to concomitant dietary control, first-line management of recurrent kidney stones remains high fluid, and low sodium according to international guidelines.[4,5] Of note, there are concerns that NOSTONE participants[3] had poor dietary control, which may have masked the benefit of thiazides.[1]

It is important to note that we have not conducted a comprehensive review and may have missed a more recent systematic review or additional RCTs. However, because of our limited resources, we have focused our expedited process[11] to provide rapid guidance to the kidney stones community (Supplementary Table S4). The clinical trials have been conducted over 3 decades with varying environmental and clinical parameters (Supplementary Table S3), which may impact kidney stone recurrence. However, our sensitivity analysis without NOSTONE[3] found no effect modification according to the era of RCT publication. Another limitation in our review is that the majority of events are from NOSTONE[3]; however, the random-effects meta-analyses, which places a larger weight on smaller studies, found no difference in the relative effects compared to fixed-effects meta-analysis.

Thiazides should remain in the armamentarium to prevent kidney stones; however, we suggest that physicians should work closely with patients to carefully consider clinical, demographic, and practical aspects before prescribing. Future research should be undertaken to improve the precision and provide further certainty regarding thiazides effect on stone recurrence, especially on long-term outcomes. Future trials should ensure participants receive and adhere to appropriate first-line nutrition management for kidney stones, particularly sodium intake which is known to decrease calcium reabsorption,[1] which impacts stone recurrence.

APPENDIX

List of Caring for Australians and New ZealandeRs with kidney Impairment (CARI) Guidelines Kidney Stones Working Group

Alex Currie, Edward Smith, Nadia York

DISCLOSURE

All the authors declared no conflicting interests.

DATA AVAILABILITY STATEMENT

The data from clinical trials reported in this study are published and referenced. The code and data used to undertake the analysis is available at https://github.com/djtunnicliffe/thiazide-diuretics.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. PRISMA Diagram.

Table S1. Research question.

Table S2. Search strategy.

Table S3. Summary of included studies.

Table S4.PRISMA checklist.

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