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# Hydrochlorothiazide and kidney stone recurrence; an in-depth analysis of the NOSTONE trial

Mohammad Zakeri Ghazaani<sup>1</sup>, Fatemeh Sadat Damanpak Rizi<sup>1</sup>, Elena Malekpour<sup>2</sup>, Elham Momeni<sup>3</sup>, Fatemeh Abbasi<sup>4\*</sup>

<sup>1</sup>School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

<sup>2</sup>School of Health, Isfahan University of Medical Sciences, Isfahan, Iran

<sup>3</sup>Shahid Beheshti Hospital, Isfahan, Iran

<sup>4</sup>Department of Obstetrics and Gynecology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

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## ABSTRACT

Kidney stones constitute a distressing and often recurring condition with increasing prevalence in the last decades. Despite successful outcomes following kidney stone treatment, the recurrence rate remains notably high. Thiazides have conventionally been the mainstay for preventing kidney stone recurrence, with studies exploring their efficacy at various doses. The NOSTONE study is an exceptional placebo-controlled randomized controlled trial on the effectiveness of different doses of hydrochlorothiazide in preventing kidney stones. Notably commendable for its methodological rigor and comprehensive approach, the study serves as a noteworthy contribution to advancing our understanding of kidney stone prevention strategies. Our study provides a critical evaluation of the NOSTONE study's investigation into the effectiveness of hydrochlorothiazide in preventing the recurrence of kidney stones, with a primary emphasis on the statistical flaws identified within the NOSTONE study.

### *Implication for health policy/practice/research/medical education:*

Kidney stones represent a disease with a rising prevalence and a notable recurrence rate. Thiazides have long been prescribed to mitigate recurrence; however, studies assessing their effectiveness in varied doses for preventing kidney stone recurrence have consistently faced limitations. The NOSTONE study has numerous strengths, but some limitations warrant scrutiny, particularly in analysis and statistical outcomes. Such examination can significantly contribute to refining future recommendations to prevent kidney stone recurrence.

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## Dear Editor,

Kidney stones constitute a distressing and often recurring condition that is widespread globally. Over the last few decades, kidney stones have risen in both sexes, contributing to an augmented economic burden on health systems (1,2). Kidney stones can adversely impact kidney function, potentially leading to infection, chronic kidney disease, and end-stage renal failure. Additionally, they are linked to an increased risk of myocardial infarction, peripheral arterial disease, and hypertension, resulting in substantial financial losses due to absences from work and healthcare expenses (3-5). Treatment options encompass conservative and medical approaches, culminating in

various surgical interventions such as extracorporeal shock wave lithotripsy, ureteroscopy, super-mini percutaneous nephrolithotomy, percutaneous nephrolithotomy, and open surgery. Despite the favorable treatment outcomes, kidney stone recurrence remains high (6,7). Thiazides have been traditionally used as the primary medication to prevent the recurrence of kidney stones. Various studies have investigated their efficacy at different doses; however, these investigations have noteworthy limitations. The effectiveness of thiazides in preventing kidney stone recurrence and the impact of dosage require more extensive, comprehensive, and less biased investigations (8). In the NOSTONE study, Dhayat et al admirably explored the

\*Corresponding author: Fatemeh Abbasi, Email: fateme.abbassii@gmail.com

**Table 1.** Comparison of kidney stone incidence between study groups by logistic regression

Dosage*	Endpoint	RR**, 95% CI (Minimum-Maximum)	Post Hoc Power	Minimum Sample Size (per group)	P value
12.5 mg	Primary endpoint	1.00 (0.58-1.75)	3%	950 000	0.97
	Secondary endpoint (Symptomatic)	1.21 (0.67-2.15)	9%	2259	0.50
	Secondary endpoint (Radiologic)	0.85 (0.48-1.50)	8%	2443	0.57
25 mg	Primary endpoint	0.90 (0.52-1.57)	6%	4261	0.73
	Secondary endpoint (Symptomatic)	1.27 (0.72-2.22)	14%	1015	0.41
	Secondary endpoint (Radiologic)	0.48 (0.27-0.86)	68%	130	0.015
50 mg	Primary endpoint	0.66 (0.38-1.15)	30%	778	0.14
	Secondary endpoint (Symptomatic)	0.73 (0.40-1.33)	15%	932	0.31
	Secondary endpoint (Radiologic)	0.55 (0.30-0.99)	54%	168	0.047

\*Dosage of hydrochlorothiazide, \*\*Reference: Placebo group.

effectiveness of hydrochlorothiazide at various doses in preventing the recurrence of kidney stones (8). This double-blind, placebo-controlled, randomized clinical trial (RCT) entailed a relatively prolonged treatment period and follow-up, meticulously examining over 400 patients. Despite the study's numerous strengths and the commendable efforts of those involved, it is essential to acknowledge that certain constraints exist, particularly in statistical analysis and the formulation of definitive conclusions. Despite commendable aspects, Dhayat et al's study has some statistical inadequacies that limit the results. Reporting P-values solely for the primary endpoint and not properly comparing study groups. Furthermore, the statement "There was no relationship" in the results is incorrect; a  $P$  value  $\geq 0.05$  must be interpreted as "no significant relationship". Using logistic regression, a more flexible analysis rather than the test for trend could have yielded different results. The results obtained through logistic regression are summarized in Table 1.

The 50 mg group had the lowest incidence of kidney stones in primary and symptomatic secondary endpoints. In the secondary radiological endpoint, the 25 and 50 mg groups showed a lower incidence of kidney stones than the other groups. In other cases, the groups had no notable differences based on effect size. Therefore, high-dose hydrochlorothiazide reduced the recurrence of kidney stones in the study population, which is consistent with previous studies. However, due to the study's small population and low post-hoc power, the results have limitations in terms of generalizability.

#### Authors' contribution

**Conceptualization:** Mohammad Zakeri Ghazaani, Fatemeh Sadat Damanpak Rizi, Elena Malekpour, Elham Momeni, and Fatemeh Abbasi

**Investigation:** Mohammad Zakeri Ghazaani, Fatemeh Sadat Damanpak Rizi, Elena Malekpour, Elham Momeni, and Fatemeh Abbasi

**Methodology:** Mohammad Zakeri Ghazaani, Fatemeh Sadat Damanpak Rizi, Elena Malekpour, Elham Momeni, and Fatemeh Abbasi

**Project administration:** Mohammad Zakeri Ghazaani, Fatemeh Sadat Damanpak Rizi, Elena Malekpour, Elham Momeni, and Fatemeh Abbasi

**Resources:** Mohammad Zakeri Ghazaani, Fatemeh Sadat Damanpak Rizi, Elena Malekpour, Elham Momeni, and Fatemeh Abbasi

**Supervision:** Mohammad Zakeri Ghazaani, Fatemeh Sadat Damanpak Rizi, Elena Malekpour, Elham Momeni, and Fatemeh Abbasi

**Validation:** Mohammad Zakeri Ghazaani, Fatemeh Sadat Damanpak Rizi, Elena Malekpour, Elham Momeni, and Fatemeh Abbasi

**Writing—original draft:** Mohammad Zakeri Ghazaani, Fatemeh Sadat Damanpak Rizi, Elena Malekpour, Elham Momeni, and Fatemeh Abbasi.

**Writing—review & editing:** Mohammad Zakeri Ghazaani, Fatemeh Sadat Damanpak Rizi, Elena Malekpour, Elham Momeni, and Fatemeh Abbasi.

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The authors declare that they have no competing interests.

#### Ethical issues

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