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In Context

IN CONTEXT

Kidney stones and thiazide diuretics: revisiting old assumptions in light of the NOSTONE trial

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Kidney stones are common and exhibit a substantial risk of recurrence [1]. Standards of care include increased fluid intake, dietary modifications and pharmacological therapies, such as thiazide diuretics, which prevent new stone formation via their hypocalciuric action [2, 3]. However, data on their efficacy are limited by heterogenous, biased, underpowered studies, which predominantly used outdated dietary recommendations and mainly lacked state-of-the-art imaging [3, 4] (Table 1).

The NOSTONE trial was a Swiss multicenter, double blind, randomized controlled trial, which aimed to evaluate the efficacy of hydrochlorothiazide (HCTZ) in preventing the recurrence of nephrolithiasis in high-risk patients (defined as those with at least two episodes of calcium-containing kidney stones within the past 10 years) [5]. Patients were assigned to receive HCTZ 12.5 mg, 25 mg or 50 mg, or placebo, once daily. The primary endpoint was a composite of symptomatic or radiologic stone recurrence, the latter defined as new stones or enlargement of preexisting ones on repeat low-dose computed tomography imaging at the end of treatment. The median duration of follow-up was almost 3 years. Safety assessments were also performed.

The trial enrolled 416 adult patients, making it by far the largest trial in the field [4] (Table 1). Women (20%) and persons of non-white ethnicity were underrepresented. Notably, hypercalciuria was not an inclusion criterion, but was present in 63% of patients. All participants received dietary counselling and urinary volume increased >2 L/24 h in all arms.

The trial met the predefined power and the drop-out rate was low. The placebo group had a primary outcome rate of 59%, which was not statistically different from that of the HCTZ groups, ranging from 49% (50 mg group) to 59% (12.5 mg group). Moreover, there was no dose–outcome relationship in terms of the primary endpoint, even though the incidence of radiologic recurrence was lower among patients on 25 mg or 50 mg of HCTZ.

Most existing studies evaluated the efficacy of HCTZ (Table 1). In NOSTONE, a once daily dosing was employed to reduce the risk of side effects [4]. Despite this, non-adherence was relatively high, but did not differ between the placebo and the 50 mg group (26% each), a finding perhaps representative of real-life experience. As expected, the HCTZ groups had lower urinary calcium excretion than the placebo group. However, this did not result in a reduction in urine relative supersaturation ratios for calcium oxalate and calcium phosphate, a proxy of crystal precipitation risk. Hypocitraturia, a known risk factor for stone formation [1], occurred more frequently with the higher dose, an effect that could also counterbalance the benefits of more potent hypocalciuric compounds, i.e. thiazides with a longer half-life, such as indapamide or chlortalidone. Sodium excretion was high in the entire cohort, also blunting the efficacy of diuretic therapy [2]. However, patients were not instruction-naïve, illustrating the difficulties in sustained sodium restriction. Treated patients had a higher incidence of adverse metabolic effects and kidney injury (defined as >1.5× baseline value; one and two participants on 25 and 50 mg of HCTZ, respectively).

In conclusion, the NOSTONE trial did not find a significant protective effect of HCTZ in established calcium stone formers, irrespective of the dose used. This is contrary to previous assumptions and recommendations by pertinent guidelines [6].

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Table 1: Characteristics of trials using thiazides for kidney stones (modified from ref. 3 and 4).

Author (PMID)	Year	Gender (M/F)	Mean age (years)	Sample	Allocation concealment	Blinding	Events/ total (intervention)	Events/ total (control)	Drugs (intervention)	Drugs (control)	Lost visits	Percent of lost visits	Follow-up (months)
Borghi *et al.* (7508066)	1993	I: 18/7, C: 20/5	I: 46.5, C: 42.8	50	Unclear	Open-label	3/19	9/21	Indapamide	No treatment	10	20	36
Brocks *et al.* (6113485)	1981	NR	16–49	62	Unclear	Double-blind	5/33	5/29	Bendroflumethiazide	Placebo	0	0	48
Ettinger *et al.* (3280829)	1988	NR	I: L 49.8, H 49.3, C: 48.9	73	Adequate	Double-blind	6/42	14/31	Chlorthalidone	Placebo	NR	NR	36
Fernández-Rodríguez *et al.* (16749588)	2006	NR	NR	100	Unclear	NR	16/50	28/50	HCTZ	No treatment	0	0	36
Laerum *et al.* (6375276)	1984	38/12	T: 45.8, C: 42.7	48	Unclear	Double-blind	5/23	12/25	HCTZ + KCl	Placebo	2	4	12–51
Mortensen *et al.* (3533825)	1986	All male	20–49	22	Unclear	Double-blind	0/12	4/10	Bendroflumethiazide + KCl	Placebo	5	18.5	72
Ohkawa *et al.* (1638340)	1992	I: 45/37, C: 52/41	I: 48.7, C: 46.9	175	Unclear	Open label	11/82	41/93	Trichlormethiazide	No treatment	35	16.7	6–68
Scholz *et al.*, (7176047)	1982	I: 14/11, C: 17/9	I: 46, C: 41	51	Unclear	Double-blind	6/25	6/26	HCTZ	Placebo	3	5.6	12
Dhayat *et al.* (36856614)	2023	I: 255/59, C: 76/26	I: 49, C: 47	416	Adequate	Double-blind	172/318	60/102	HCTZ	Placebo	27	26	36

M: male; F: female; I: intervention group; C: control group; L: low dose; H: high dose; NR: not reported.

However, stone disease is multifactorial and a holistic treatment approach is warranted [2]. As such, a tighter salt restriction would be desirable and concomitant potassium citrate supplementation might show additional synergistic effects, but the practicability of this approach in the long-term appears questionable. Overall, the findings of the NOSTONE trial provide valuable and unexpected insights into the use of HCTZ for prevention of kidney stones and highlight the need for continued research in this area.

CONFLICT OF INTEREST STATEMENT

F.B. received consultancy fees from Chiesi and Alnylam.

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