

# The Influence of Increased Fluid Intake in the Prevention of Urinary Stone Formation: a Systematic Review

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## ABSTRAK

**Tujuan:** untuk menelaah apakah jumlah asupan cairan berpengaruh terhadap pencegahan pembentukan batu saluran kemih. **Metode:** dilakukan telaah sistematik dari database elektronik Pubmed. Semua penelitian dengan desain randomized controlled trial (RCT), kasus kontrol, atau kohort berbahasa Inggris dimasukkan ke dalam penelitian. Analisis data dilakukan terhadap desain penelitian, jumlah asupan cairan (volume lebih besar menjadi kelompok eksperimen dan sebaliknya menjadi kelompok kontrol), dan risiko pembentukan batu. **Hasil:** dari telaah sistematik didapatkan lima penelitian (1 RCT dan kasus kontrol pada pasien dengan riwayat batu saluran kemih, serta 3 kohort prospektif pada pasien tanpa riwayat batu). Tiga penelitian meningkatkan asupan cairan hingga 2,5 L/hari dan satu penelitian 2 L/hari, sedangkan satu penelitian lainnya menggunakan target produksi urin 2 L/hari. Semua penelitian tersebut menunjukkan bahwa peningkatan jumlah asupan cairan per hari dapat menurunkan risiko terjadinya batu saluran kemih baik primer maupun sekunder. Semua penelitian yang disertakan dalam telaah sistematik ini ditelaah secara kritis menggunakan metode telaah kritis the Oxford Center for Evidence-based Medicine. **Kesimpulan:** dapat dikatakan bahwa masih dibutuhkan bukti yang kuat untuk menyimpulkan bahwa peningkatan asupan cairan dapat digunakan sebagai strategi pencegahan batu saluran kemih primer karena tidak adanya data dari uji klinis yang mendukungnya. Namun untuk pencegahan rekurensi batu saluran kemih dapat direkomendasikan peningkatan asupan cairan dengan target volume urin lebih dari 2.000 mL per hari.

**Kata kunci:** batu saluran kemih, peningkatan asupan cairan, pencegahan batu primer, rekurensi.

## ABSTRACT

**Aim:** to assess whether the volume of fluid intake influence the prevention of urinary stone formation. **Methods:** a systematic review from MEDLINE Electronic database was conducted. All of the controlled trial (RCT), case-control, and cohort studies written in English language were included in the study. Data analysis was performed to the design of the study, volume of fluid intake (higher volume as experimental group and lower volume as control group), and risk of stone formation. All of the included studies were appraised using the Oxford Center for Evidence-based Medicine appraisal tool for therapy (Randomized Controlled Trial) and level of evidence. **Results:** our systematic review included five studies (1 RCT and case-control study in patients with history of urolithiasis, and 3 prospective cohorts in patients without history of urolithiasis). Three studies increased fluid intake to 2.5 Liters/day and one study to 2 Liters/day, while one other study used the urine production target of 2 Liters/day. All of these studies showed that increased fluid intake per day could decrease the risk of both primary and secondary stone formation. **Conclusion:** stronger evidence are still needed to conclude that increasing fluid intake could be utilized as a strategy to prevent primary urolithiasis because of the lack of data from the clinical

trials supporting it. However, to prevent the recurrence of urolithiasis, increasing fluid intake could be recommended with the urine volume target of more than 2,000 mL/day.

**Key words:** urolithiasis, increased fluid intake, primary stone prevention, recurrence.

## INTRODUCTION

It is undeniable that urolithiasis remains as the highlight in the urology clinic in many parts of the world, including in Indonesia. According to the guideline for the management of urolithiasis from the Indonesian Urological Association, the biggest portion of urology patients in Indonesia present with urolithiasis.<sup>1</sup> The prevalence and incidence tends to increase over time, which is associated with a modern lifestyle, which lacks fluid intake, with high calorie and salt diet, lack of diet fiber and alkali, and worsened by lack of exercise.<sup>2</sup> The healthcare costs incurred by episodic management of urolithiasis has not been cheap. A study in France demonstrated that the healthcare costs incurred for an episode of urolithiasis approached nearly five million Rupiahs.<sup>3</sup> Furthermore, with the high recurrence rate of 30-50% after 5 years,<sup>4</sup> urolithiasis certainly exhausted quite an expensive cost for each patient.

Stone formation in the urinary tract is highly affected by the urine concentration of the stone forming salt. A cheap and simple strategy to prevent urolithiasis that has been proposed for several decades is increasing the fluid intake. The society has already known about the advice of drinking eight glasses of water per day, but the advice is lack of evidence. This systematic review is aimed to assess the influence of increased fluid intake to the prevention of urinary stone formation. There was a similar systematic review from the Cochrane Collaboration that could not find any Randomized Controlled Trial (RCT) of increased water intake for the primary prevention of urinary stone.<sup>5</sup> In this review we were broadening our search to prospective cohort and case-control design.

## METHODS

Literature search was performed using the MEDLINE electronic database on March 17th, 2013. Keywords used in the searching include

“fluid and diet and urinary stone”, “fluid and diet and nephrolithiasis”, “water and urinary volume and nephrolithiasis”, “water and fluid and nephrolithiasis”, “fluid and renal stone”, “water and kidney stone”, “fluid intake and urolithiasis”, and “fluid intake and nephrolithiasis”. All of the RCT, case-control, or cohort studies written in the English language that assessed the prevention of both primary and secondary urolithiasis using increased fluid intake were included in this study.

### Extraction of Data from Included Studies

The studies obtained from the MEDLINE database were filtered and chosen based on the most suitable title and abstract. The data taken for assessment were total volume of fluids drank by the study subjects, in which the volume was higher in the experiment group compared to the control group. In addition, subjects outcomes including incidence of new (primary) or recurrence (secondary) urolithiasis between the experimental case and control groups was expressed as relative risk or odds ratio. The Number Needed to Treat (NNT) was calculated to point out the magnitude of effect from each study reporting the Control and Experimental Event Rate (CER and EER).

### Critical appraisal of included studies

All of the included studies were appraised using the Oxford Center for Evidence-based Medicine appraisal tool for therapy (Randomized Controlled Trial) and level of evidence.<sup>6</sup>

## RESULTS

From the search performed in the MEDLINE electronic database using the aforementioned keywords, we found 554 articles. Title and abstract filtering and selection excluded 502 studies not suitable with the inclusion criteria. Subsequently, 52 literatures were evaluated further and resulted in 26 literature reviews and 21 literatures with unsuitable intervention or outcomes. Five literatures suitable with the

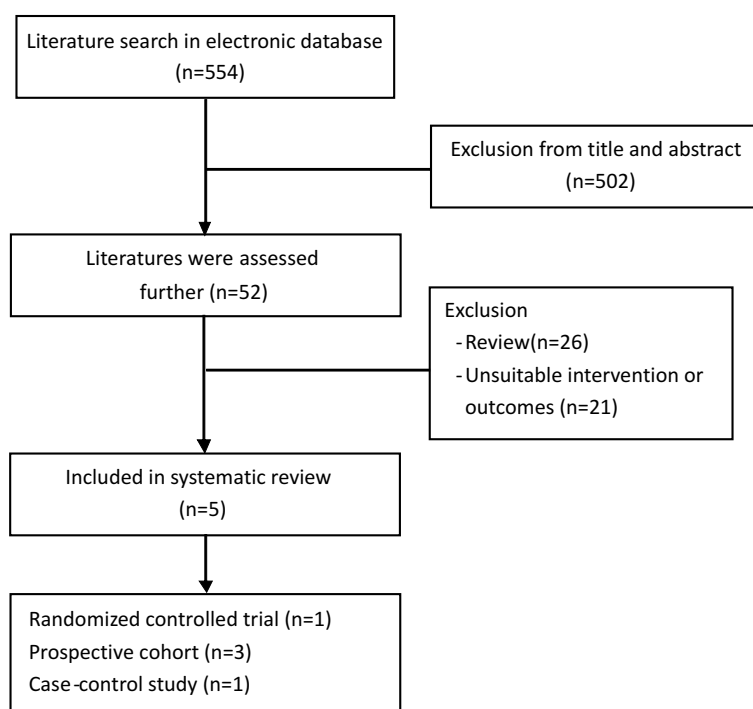


Figure 1. Literature search diagram

inclusion criteria with appropriate intervention and outcomes were assessed further in this systematic review (Figure 1).

### Study Characteristics

From five studies obtained in the search, one was a randomized controlled trial (RCT), three were prospective cohort, and one was a case-control study. The number of subjects in the RCT (Borghetti et al, 1996) was 199 subjects divided into two patient groups with history of first episode urolithiasis. The first group (n=99) were given education to increase the fluid intake to achieve urine output of >2 liters/day and the second group (n=100) were not given the education. In the prospective cohort with 14 years of follow-up (Taylor EN, et al, 2004), 45,619 subjects without previous history of urolithiasis were included. The questionnaire to assess the diet and fluid intake was evaluated every 4 years. Five groups were included with fluid intake of <1.2 liters/day, 1.2-1.6 liters/day, 2-2.5 liters/day, and >2.5 liters/day. In two other prospective cohorts, (Curhan GC, et al, 1996 and Curhan GC, et al, 1998) 45,289 male subjects were included with 6 years of follow-up and 81,093 females were included with 8 years of follow-up, all subjects without previous history of urolithiasis. Both

studies divided their subjects into 5 groups based on their daily fluid intake. However, the volume of fluid intake in these groups were not described further; only the highest quintile >2.5 L/day (Curhan GC, et al, 1996 and Curhan GC, et al, 1998) and the lowest quintiles of < 1.2 L/day (Curhan GC, et al, 1996) and <1.4 L/day (Curhan GC, et al, 1998) were mentioned and analyzed for urolithiasis formation risks. In a case-control study, (Dai M, et al, 2013) 1,019 patients with the diagnosis of first episode urolithiasis and 987 healthy subjects were included as the case and control groups, respectively. The subjects were divided into 4 groups based on the volume of fluid intake into <500 mL/day, 501-1000 mL/day, 1001-2000 mL/day and >2000 mL/day.

### Risk of Stone Formation and Number Needed to Treat

An RCT that compared the risk of stone recurrence in subjects with increased fluid intake (urine volume >2L/day) and without increased fluid intake (urine volume <1.3 L/day) reported reduced relative risk of more than half-fold (RR = 0.45; 95% CI=0.24-0.83) in increased fluid intake group. NNT calculated from this study was 6.7 (CER: 0.27; EER: 0.12).<sup>7</sup> In the three prospective cohort study with follow ups

**Table 1.** The result of systematic review of all literatures comparing the influence of fluid intake to the risk of urolithiasis formation

Author	Design	Number of samples	Experimental group	Control group	Risk of urolithiasis formation	Number needed to treat
Borghini L, et al <sup>7</sup>	RCT	199 samples with first episode of urolithiasis	Urine volume of $\geq 2$ L/day (educated to drink plenty of fluids)	urine volume $< 1.3$ L/day (without education)	RR = 0.45 (95% CI=0.24-0.83)	6.7
Curhan GC, et al <sup>8</sup>	Prospective cohort	81,093 females without history of urolithiasis	Drink $> 2.5$ L/day	Drink $> 1.4$ L/day	RR = 0.62 (95% CI=0.48-0.80)	1042
Curhan GC, et al <sup>9</sup>	Prospective cohort	45,289 males without history of urolithiasis	Drink $> 2.5$ L/day	Drink $> 1.3$ L/day	RR = 0.65 (95% CI=0.51-0.84)	N/A
Taylor EN, et al <sup>10</sup>	Prospective cohort	45,619 males without history of urolithiasis	Drink $> 2.5$ L/day	Drink $> 1.2$ L/day	RR = 0.71 (95% CI= 0.59-0.85)	N/A
Dai M, et al <sup>11</sup>	Case-control	2,006 patients with known daily water intake volume	Patients with first episode of urolithiasis	Healthy subjects	OR = 0.58 (95% CI=0.39-0.85)	N/A

of 14, 8, and 6 years, fluid intake of  $> 2.5$  L/day was demonstrated to have a protective effect to the risk of urolithiasis formation with  $< 1.4$  L/day (RR=0.62; 95% CI=0.48-0.80),<sup>8</sup>  $< 1.3$  L/day (RR=0.65, 95% CI=0.51-0.84),<sup>9</sup> and  $< 1.2$  L/day (RR=0.71, 95% CI=0.59-0.85).<sup>10</sup> NNT can only be calculated from the last study (1042, CER: 0.00311; EER: 0.00215). In a case-control study comparing the risk of urolithiasis in the group with fluid intake volume of  $> 2$  L/day with the intake volume of  $< 500$  mL/day a half-fold risk reduction was obtained (RR=0.53, 95% CI=0.31-0.90).<sup>11</sup>

### Critical Appraisal and Quality of the Studies

There was only one RCT in this systematic review that can be assessed using the Oxford Center for Evidence-based Medicine tool (**Table 2**). The quality of all of the prospective studies were level IIB (individual cohort study, including low quality RCT) and IIB (individual case-control study) for the case-control study.

### DISCUSSION

This systematic review demonstrated that increased fluid intake of more than 2500 mL/day or target of urine production of 2000 mL/day reduced the risk of urolithiasis formation in subjects both with and without prior history of urolithiasis (RR = 0.45-0.71).

We found similar result with previous systematic review elaborated nine years before this review that we did not find any RCT study that showed an association between increased fluid intake and prevention of urolithiasis in subjects without prior history of urolithiasis.<sup>5</sup> There is only one RCT showing that the relationship between increased fluid intake and prevention of urolithiasis in subjects with prior history of urolithiasis has protective effects of increased fluid intake with urine production target of  $> 2,000$  mL/day (RR=0.45; 95% CI=0.24-0.83).<sup>7</sup>

Another clinical trial in post-shock wave lithotripsy (SWL) patients compared the administration of verapamil and increased fluid intake with urine production target of more than 2.5 liters/day. From patients with stone-free status after the procedure, a long-term follow-up (30 months) was performed. Patients with increased fluid intake had lower risk of recurrence (8.3%) compared to patients who were given verapamil (40%), with  $p < 0.05$ .<sup>12</sup>

Other studies with either prospective cohort or case-control design in this systematic review is seeking the relationship between increased fluid intakes with the incidence of urolithiasis in patients without prior history of urolithiasis.

**Table 2.** Quality assessment of the therapy studies (only applicable for RCT design)

Author	Design	Method of randomization presented	I/C similar at the baseline	Both groups treated equally	Dropout rate	Intention-to-treat analysis	Double-blinded	Level of evidence
Borghini L, et al <sup>7</sup>	RCT	Yes	Yes	Yes	10%	No	Not clearly defined	IIB
Curhan GC, et al <sup>8</sup>	Prospective cohort	N/A	N/A	N/A	N/A	N/A	N/A	IIB
Curhan GC, et al <sup>9</sup>	Prospective cohort	N/A	N/A	N/A	N/A	N/A	N/A	IIB
Taylor EN, et al <sup>10</sup>	Prospective cohort	N/A	N/A	N/A	N/A	N/A	N/A	IIB
Dai M, et al <sup>11</sup>	Case-control	N/A	N/A	N/A	N/A	N/A	N/A	IIIB

The results of this systematic review showed that increased fluid intake (intake of more than 2,500 mL/day) showed protective effects from the incidence of urolithiasis with variable relative risks ranging from 0.53 to 0.71.<sup>8-11</sup> This result is similar with the general recommendation of urolithiasis prevention from the European Association of Urology and other literatures, which recommends fluid intake of 2.5-3 liters/day with minimal urine production target of 2 liters/day.<sup>13-21</sup>

Besides the aforementioned observational studies, the risk of urolithiasis formation can be measured by experimental studies in the laboratory. The RCT in our review also observed the incidence of urolithiasis in both fluid intake groups and measure the relative saturation of urine. There were statistically significant difference of calcium oxalate, brushite, and uric acid relative saturation between the two groups ( $p < 0.05$ ).<sup>7</sup> Another experimental study showed that both in vitro and in vivo dilution decreased supersaturation of calcium phosphate, calcium oxalate, and monosodium urate.<sup>22</sup>

From four prospective studies, NNT can only be extracted from two studies. The other two lacked of data to be calculated. Big difference observed between two studies may be resulted from different study design and subject characteristics (stone former and non-stone former subject).

## CONCLUSION

There is no strong conclusion to demonstrate that increased fluid intake could be used as

a strategy to prevent primary urolithiasis. However, to prevent recurrence of urolithiasis, increased fluid intake with urine volume target of  $>2,000$  mL/day could be recommended.

A multicenter RCT with a good design should be performed especially in tropical countries where the rate of body evaporation is relatively higher, to address whether increased fluid intake could become the strategy for either primary or secondary urolithiasis prevention. The study should also be designed to answer how much fluid is needed and whether water hardness has influence over the incidence of urolithiasis.

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