SYSTEMATIC REVIEW

Effect of citrus-based products on urine profile: A systematic review and meta-analysis [version 1; referees: 2 approved]

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Abstract

Background. Urolithiasis is a disease with high recurrence rate, 30-50% within 5 years. The aim of the present study was to learn the effects of citrus-based products on the urine profile in healthy persons and people with urolithiasis compared to control diet and potassium citrate. ***Methods.*** A systematic review was performed, which included interventional, prospective observational and retrospective studies, comparing citrus-based therapy with standard diet therapy, mineral water, or potassium citrate. A literature search was conducted using PUBMED, COCHRANE, and Google Scholar with “citrus or lemonade or orange or grapefruit or lime or juice” and “urolithiasis” as search terms. For statistical analysis, a fixed-effects model was conducted when $p > 0.05$, and random-effects model was conducted when $p < 0.05$. ***Results.*** In total, 135 citations were found through database searching with 10 studies found to be consistent with our selection criteria. However, only 8 studies were included in quantitative analysis, due to data availability. The present study showed a higher increased in urine pH for citrus-based products (mean difference, 0.16; 95% CI 0.01-0.32) and urinary citrate (mean difference, 124.49; 95% CI 80.24-168.74) compared with a control group. However, no differences were found in urine volume, urinary calcium, urinary oxalate, and urinary uric acid. From subgroup analysis, we found that citrus-based products consistently increased urinary citrate level higher than controls in both healthy and urolithiasis populations. Furthermore, there was lower urinary calcium level among people with urolithiasis. ***Conclusions.*** Citrus-based products could increase urinary citrate level significantly higher than control. These results should encourage further research to explore citrus-based products as a urolithiasis treatment.

Open Peer Review

Referee Status: ✓ ✓

	Invited Referees 1	2
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Introduction

Humans have suffered urinary tract stones for centuries[1]. The incidence and prevalence of urolithiasis are different between geographic locations, depending on age and sex distribution, stone composition and stone location[2]. Risk of stone development has been shown to be 5–10% with a higher prevalence in men than women[3]. Urolithiasis is a common disease with significant morbidity and cost worldwide[4–6]. Based on National Health and Nutrition Examination survey, kidney stones affect 1 in 11 people in the United States, and an epidemiological increase was found in 2012 compared to 1994[7]. Additional data from Dr. Cipto Mangunkusumo National General Hospital, Indonesia's national referral hospital, showed an increase in stone disease prevalence from 182 patients in 1997 to 847 patients in 2002[8]. Moreover, it is further worsen by its high recurrence rate reaching 30–50% within 5 years[7].

Calcium-based urinary tract stone is the most common stone composition found in urolithiasis[9,10]. Supersaturation is believed to be the mechanism behind calcium stone formation[11]. One factor in determining urine stone formation or stone recurrence is urine profile, which is defined as urine volume and its composition. Hypercalciuria and hypocitraturia are the most common urine abnormalities found among calcium stone-formers[12]. A high fluid intake could prevent stone formation by lowering supersaturation, whereas citrate could prevent stone formation by ionizing urinary calcium[13,14]. Food that is rich of citrate is citrus. There are wide variety of citrus fruits and derivate products that can be easily obtained, such as lemonade, grapefruit, orange, lime, and citrus-based juice. Several studies had already been conducted to learn the effect of citrus-based products on urine profile. However, the results between those studies were contradictive. Therefore, our study aimed to systematically review and quantify the available studies regarding the effects of citrus-based products on urine profile and its comparison to a control diet and potassium citrate.

Methods

Eligibility criteria

We included both healthy people and patients with urolithiasis history in our selection criteria. Study subjects must have consumed citrus fruits, such as orange, lime, grapefruit, or juices made from the fruits. Study designs could be interventional, prospective observational, or retrospective with standard diet therapy (any kind of mineral water), or potassium citrate, as a control group therapy. We included studies with urine profile as the outcome. We only included articles written in English or Indonesian, and those with full text article available. We excluded non-systematic review articles. We did not limit studies based on their year conducted.

Search strategy

A literature search was conducted using PUBMED, COCHRANE, and Google Scholar as search engines on August 2016. The terms "citrus OR lemonade OR orange OR grapefruit OR lime OR juice" AND "urolithiasis" were used as search terms. We also searched the list of references in included studies. We did not use any limitation in study searching.

Study selection and data extraction

All studies were screened for duplication using EndNote X6 software. Duplication-free articles underwent title and abstract examination using predetermined inclusion and exclusion criteria mentioned above. Selection of studies was selected by two authors independently. Discrepancies of opinion were resolved by discussion. All studies, which fulfilled the inclusion and exclusion criteria, underwent full text review. For every eligible full text, we extracted the following data, if available: subjects specific condition, citrus-based product used in the study, number of patients consuming citrus-based product, citrate content or its concentration, control intervention, number of individuals under control intervention. For the outcomes, we extracted urine profile data as follows: volume, pH, calcium level, citrate level, oxalate level, and uric acid level. Measurement units used in this study are L/day for urine volume and mg/day for urinary calcium level, urinary citrate level, urinary oxalate level, and urinary uric acid level. All data in the form of numbers were extracted manually as mean and standard deviation for variable measurement.

Assessment of bias and statistical methods

This study used Cochrane Risk of Bias assessment tools[15] and Newcastle-Ottawa scale[16] to assess interventional and retrospective study's quality, respectively. These assessments of study quality were done by two authors independently. Quantitative synthesis of included studies was analyzed using Review Manager (RevMan) 5.0 software and mean difference was used as its effects size measurement. Heterogeneity of studies was assessed using chi-square. A fixed-effects model was conducted when $p > 0.05$, whereas a random-effect model is conducted when $p < 0.05$. We also conducted subgroup analysis to differentiate between healthy and urolithiasis populations.

Studies which could not be included in quantitative analysis were described qualitatively.

Results

We found 135 citations through database searching. Literature searching from the list of references found similar studies that were all already included in this study. Ten studies were found to be consistent with our selection criteria (Figure 1).

Two of ten studies had to be excluded from quantitative analysis because of the following reasons: (1) Penniston *et al.*[17] only published baseline data and its maximal change following intervention; and (2) Tosukhowong *et al.*[19] used medians as their outcome measurement, and due to its non-uniform distribution, we were unable to convert these to means. Therefore, eight studies were analyzed to find the effect of citrus-based products on urine profile compared to controls. However, not all of the eight studies were included in urine profile outcome measurement, due to data availability. Characteristics of the included studies and their risk of

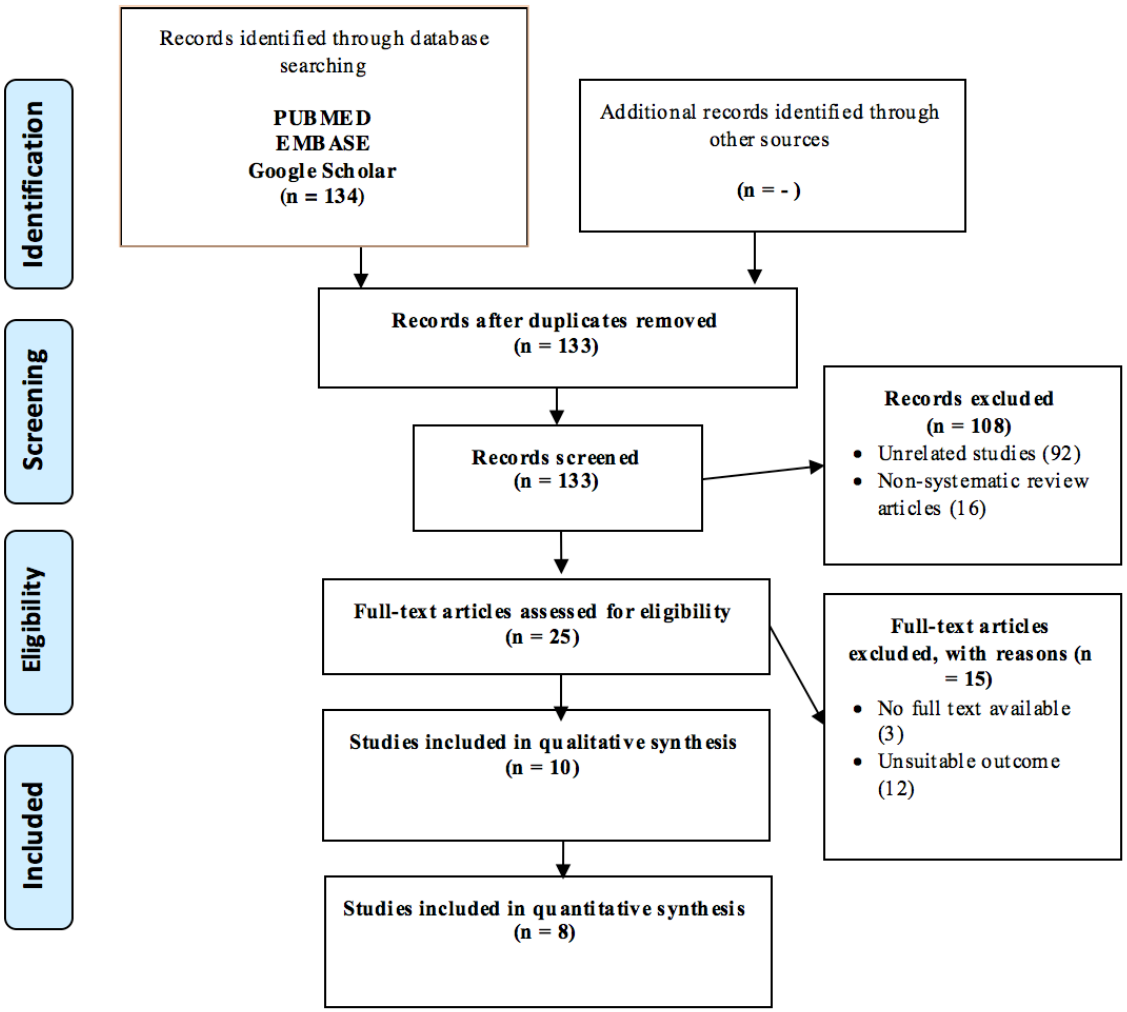

Figure 1. Study flow diagram.

bias assessment can be seen in Table 1 and Figure 2/Supplementary Table 1, respectively.

Effect of citrus-based products on urine profile

Data shows that citrus-based products increased urine pH (mean difference, 0.16; 95% confidence interval [CI] 0.01-0.32) and urinary citrate (mean difference 124.49; 95% CI 80.24-168.74) to a higher extent than control treatment (Figure 3).

However, there was no statistically significant difference in urine volume (mean difference -0.09; 95% CI -0.20-0.02), urinary calcium (mean difference -5.45; 95% CI -18.89-7.98), urinary oxalate (mean difference 0.76; 95% CI -0.47-1.98) and urinary uric acid (mean difference 2.15; 95% CI -23.96-28.27) between the two groups (Figure 4).

Subgroup analysis showed a significantly higher urinary citrate level in both the healthy population and the population with history of urolithiasis who received citrus-based therapy compared to control. However, urine pH, which showed a statistically significant increase in urine pH compared to controls, did not demonstrate any differences in a subgroup analysis. On the other hand, urinary calcium was lower after consumption of citrus-based products compared to controls in the urolithiasis population. Furthermore, this study demonstrated that there was a lower urine volume in the healthy population after drinking citrus-based products compared to controls (Figure 5). We did not find any differences in other urine profile variables, either in the healthy population or the population with history of urolithiasis (Supplementary Figure 1 and Supplementary Figure 2).

We tried to conduct further analysis by excluding Aras *et al.*[20] from quantitative analysis, due to its different study method (RCT). We still found a significant increase in urine citrate level in both mixed population (mean difference 132.46; 95% CI 70.48-194.44) and the population with a history of urolithiasis (mean difference 159.22; 95% CI 47.05-271.40]), as well as no statistically significant difference in urine pH (mean difference 0.16; 95% CI -0.02-0.33). Furthermore, other variables still demonstrate similar outcomes after exclusion of Aras *et al*.

Table 1. Characteristic of included studies.

Study author and year	Type of study	Subject condition	Intervention	n	Control	n
Study included in qualitative synthesis only						
Penniston *et al* (2007)[17]	RS	Subjects with calcium oxalate stone	Lemonade (5.9 gr citrate)	63	Lemonade (5.9 gr citric acid) plus potassium citrate	37
Tosukhowong *et al* (2008)[19]	RCT	Post-operative subjects with nephrolithiasis	• Lime powder (4.4 gr citrate) • Potassium citrate	13 11	Placebo	7
Study included in qualitative and quantitative synthesis						
Aras *et al* (2008)[20*]	RCT	Subjects with hypocitraturic calcium stone	• Lemon juice (4.2 gr citrate) • Potassium citrate	10 10	Water 3 L/day	10
Goldfarb and Asplin (2001)[21]	CBAS	Healthy subjects	Grapefruit juice	10	Tap water 240 ml, 3 times a day	10
Honow *et al* (2003)[22]	CBAS	Healthy subjects	• Orange juice • Grapefruit juice • Apple juice	3 3 3	Mineral water	3
Koff *et al* (2007)[23]	CS	Subjects with history of nephrolithiasis	Lemon juice (4.5 gr citrate)	21	Fluid except lemonade or citrus drink	21
Odvina (2006)[24]	CS	Healthy and stone former subjects	• Orange juice (2.3 gr citrate) • Lemonade (2.3 gr citrate)	14 14	Distilled water 400 ml	14
Seltzer *et al* (1996)[25]	CBAS	History of hypocitraturic calcium nephrolithiasis	• Lemonade (5.9 gr citrate)	12	Fluid maintaining 2 L urine	12
Sumorok *et al* (2011)[18]	CS	Healthy subjects	• Sunkist orange soda (3 cans)	12	Water 1.06 L/day	12
Trinchieri *et al* (2002)[26]	CS	Healthy subjects	• Grapefruit juice (1.4 gr citrate)	7	Water	7

RS – retrospective study; RCT – randomized controlled trial; CBAS – controlled before-after study; CS – crossover study. *Also included in qualitative synthesis for comparison between citrus-based product and potassium citrate.

Comparison between citrus-based products and potassium citrate in urine profile

Due to the reasons stated above, we decided to discuss the comparisons between citrus-based product and potassium citrate in a qualitative manner.

Three studies showed both citrus-based products (lemon juice and lime powder) and potassium citrate increased the level of urinary citrate significantly[17,19,20]. Even though no significant difference in post treatment urine profile was found between citrus-based products and potassium citrate, post-treatment citrate level in the potassium citrate group showed a 3.5 times increase from pre-treatment level, while it was only 2.5 times in the lemon juice group[20]. Furthermore, Penniston *et al*. exhibited a greater maximum increase of urinary citrate level in lemonade therapy combined with potassium citrate compared to lemonade therapy alone[17].

Two studies also showed significant increase in urine pH in both treatment arms[17,19]. However, a study by Aras *et al*. only exhibit a significant increase in urine pH for the potassium citrate group[20]. In terms of side effects, patients in the potassium citrate group suffered gastric and oropharyngeal discomfort, although they did not require drug discontinuation[20]. Furthermore, potassium citrate had lower compliance compared to citrus-based therapy[19].

Dataset 1. Characteristics of studies included for urine pH

http://dx.doi.org/10.5256/f1000research.10976.d153056

Dataset 2. Characteristics of studies included for urinary citrate

http://dx.doi.org/10.5256/f1000research.10976.d153057

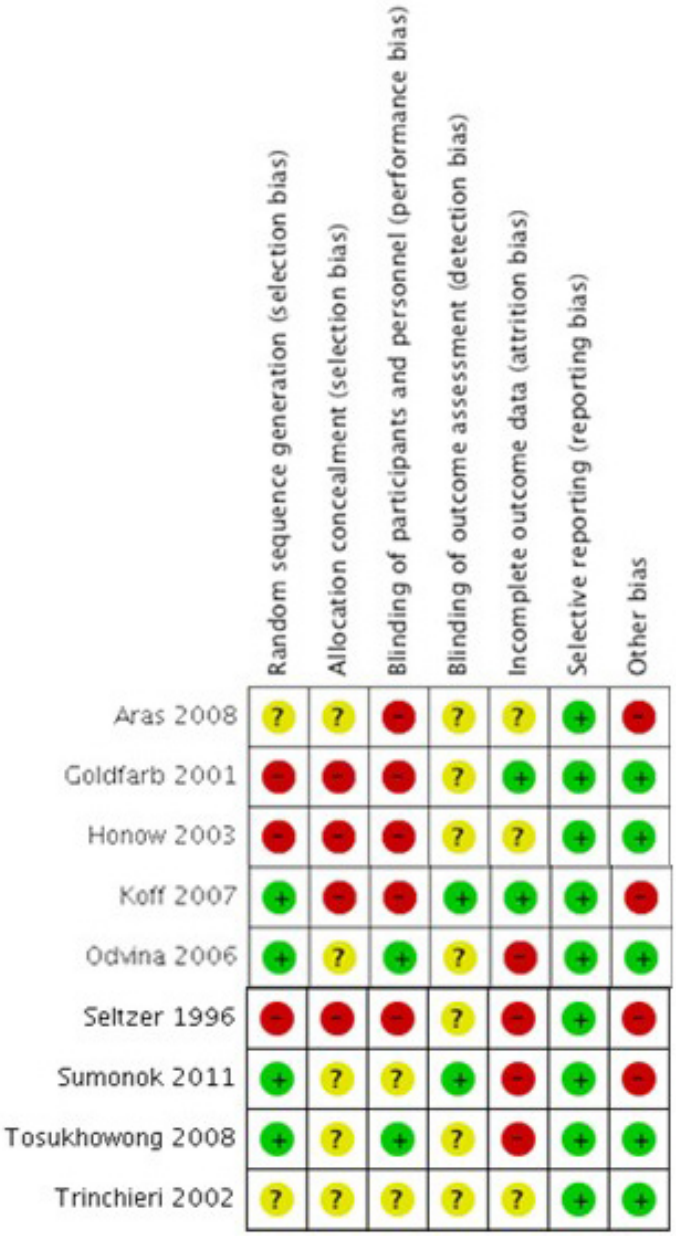

Figure 2. Risk of bias assessment summary.

Dataset 3. Characteristics of studies included for urine volume

http://dx.doi.org/10.5256/f1000research.10976.d153058

Dataset 4. Characteristics of studies included for urinary calcium

http://dx.doi.org/10.5256/f1000research.10976.d153059

Dataset 5. Characteristics of studies included for urinary oxalate

http://dx.doi.org/10.5256/f1000research.10976.d153060

Dataset 6. Characteristics of studies included for urinary uric acid

http://dx.doi.org/10.5256/f1000research.10976.d153061

Discussion

This study showed that citrus-based products, such as lemonade, orange juice and grapefruit juice, could increase urinary citrate levels and urine pH. Low citrate excretion, as in type I tubular acidosis, shows an increase in nephrolithiasis incidence[27]. Therefore, existence of citrate in urine is important since it is a well-known preventive factor in calcium stone formation, with an increase in

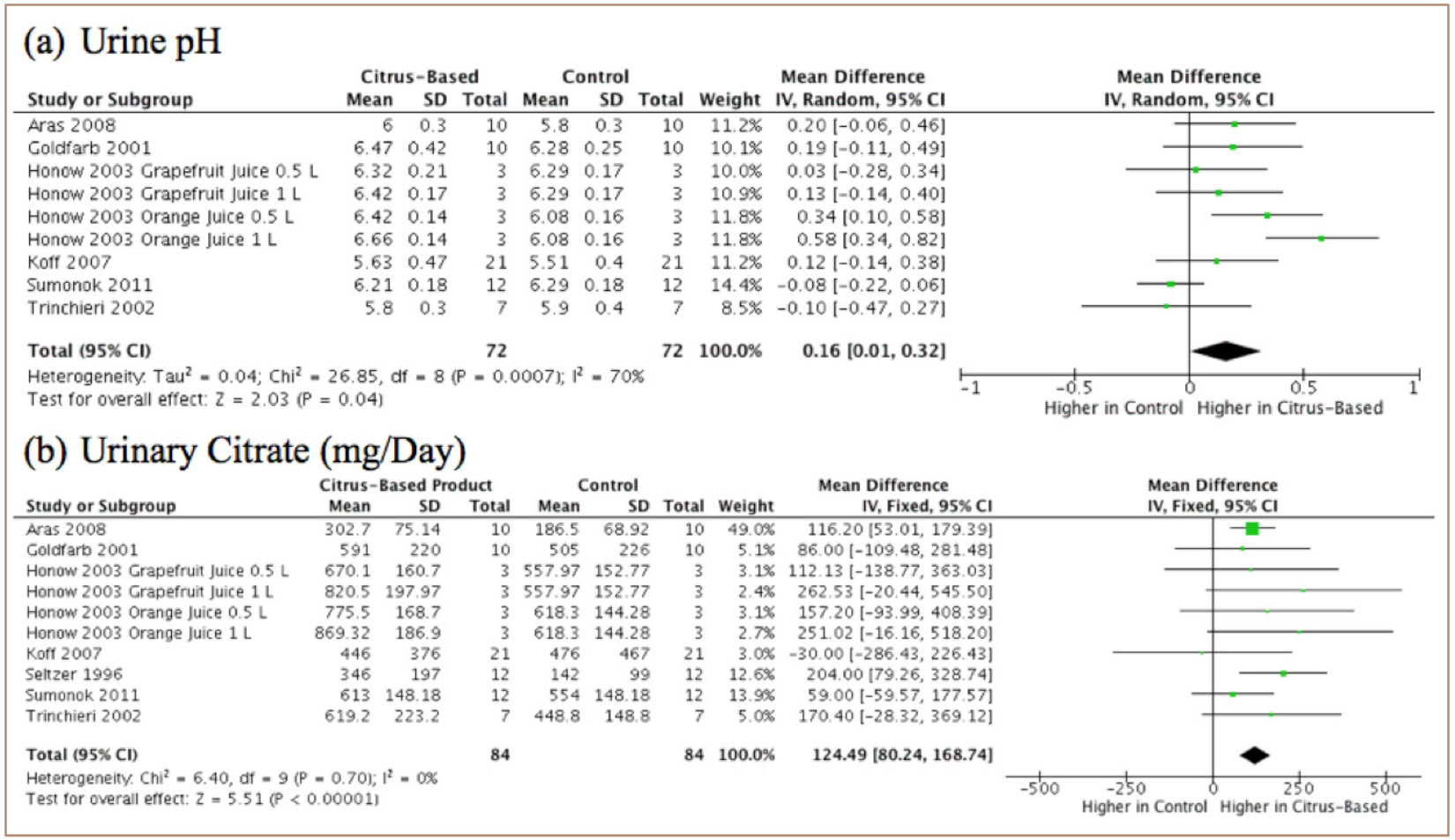

Figure 3. **Urine pH and urinary citrate levels represented by a forest plot.**

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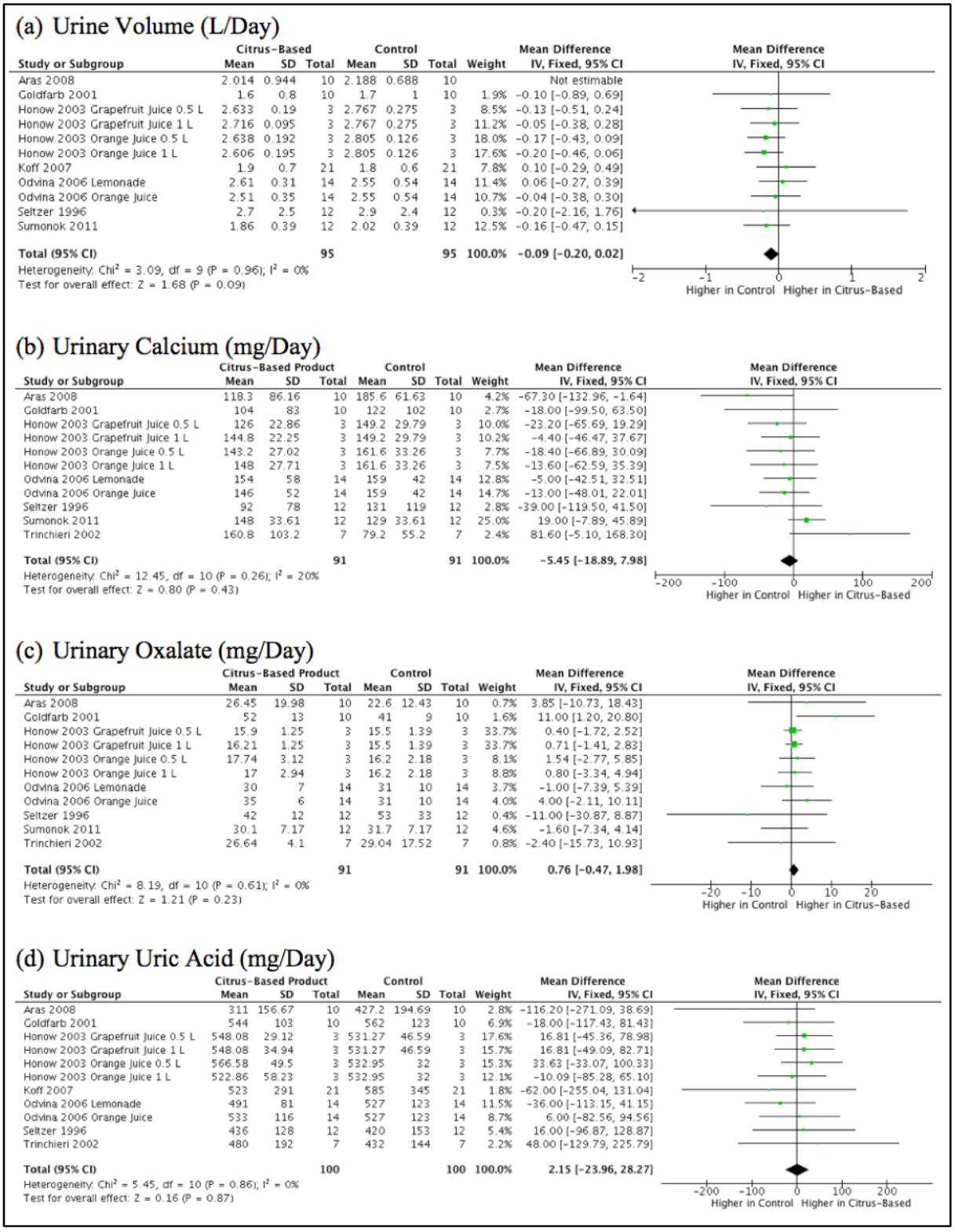

Figure 4. Urine volume, urinary calcium, urinary oxalate, and urinary uric acid levels represented by a forest plot.

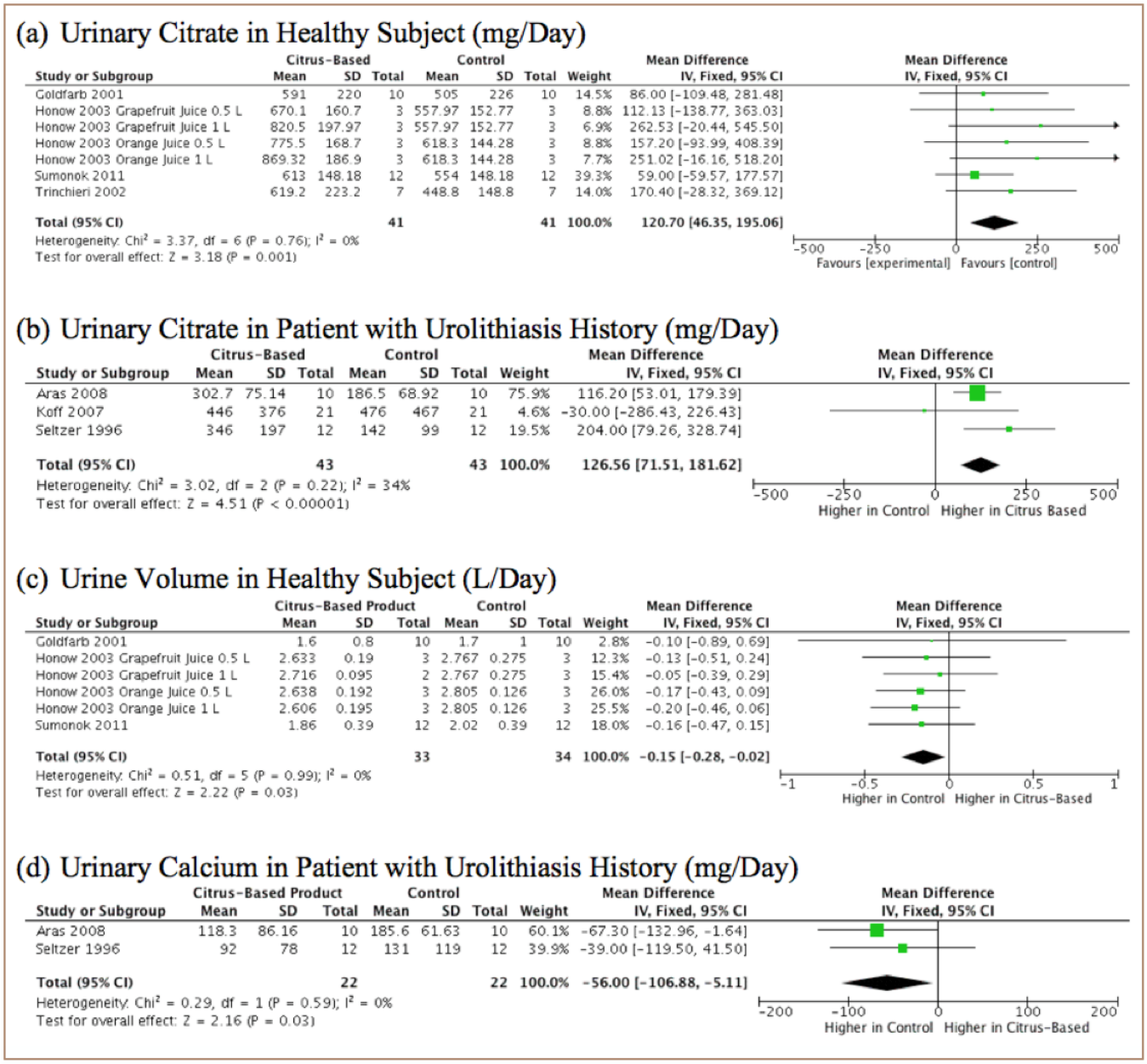

Figure 5. **Subgroup analysis of urine profiles represented by forest plot.**

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calcium salt solubility and calcium oxalate crystal growth inhibition as its primary mechanism. It also can reduce bone resorption and increase calcium reabsorption in kidneys. Furthermore, citrate fixes the inhibitory properties of Tamm-Horsfall protein[28]. Citrate and Tamm-Horsfall protein are related to inhibition of calcium oxalate agglomeration[29]. An increase in urine pH is due to metabolism of citrate into bicarbonate[13]. Moreover, an increase in urine pH could reduce reabsorption of citrate[30]. Thus, it could induce more citrate excretion. A study conducted by Curhan *et al.*[31] found an increased risk of stone formation associated with grapefruit juice consumption; although, the exact mechanism is still unclear. One theory suggests that grapefruit juice contains sugar, which can increase calcium excretion[31]. However, this study proved that citrus-based products could increase urinary citrate level, which could be a protective factor for urinary tract stone formation.

Potassium citrate has been used as urolithiasis stone treatment for more than two decades. Its effectiveness in urolithiasis treatment has been established from several studies[32,33]. From one meta-analysis conducted by Phillip *et al.*, potassium citrate significantly reduced stone size, reduced new stone formation, and increased citrate levels[34]. The stone prevention mechanism of potassium citrate is thought to be due to alkali loading and its citrate-uric effect[35]. In this study, potassium citrate showed a significant increase in urinary citrate and is superior to citrus-based products in elevating urinary citrate. However, the use of potassium citrate has a limitation due to its side effect if used for a long term period, such as epigastric discomfort and frequent large bowel movement, and it requires the consumption of many tablets daily to reach sufficient therapeutic doses, which could dramatically decrease patient compliance[36]. Therefore, citrus-based products could be an alternative therapy with lower cost and better urinary citrate level than control therapy.

This is the first systematic review and meta-analysis that focuses on citrus-based product and its effect towards urine profile compared to standard therapy. However, this study only searched for published article which could lead into publication bias. Moreover, most of the included studies were not conducted using the best method for interventional studies, which is randomized controlled trials. Therefore, from the positive results this study has shown, we encourage other researchers to conduct randomized controlled trials to provide stronger evidence the beneficial effects of citrus-based products on urinary stone disease.

Conclusions

Citrus-based products increase urinary citrate and urine pH significantly compared to control treatments. Compared to standard potassium citrate therapy, there was a smaller increase in urine pH and urine citrate using citrus-based products. However, due to potassium citrate side effects and patient's poor compliance, citrus-based products could be alternative therapy in preventing stone formation. These study's results should encourage further research to explore citrus-based product as a urolithiasis treatment.

Data availability

Dataset 1: Characteristics of studies included for urine pH. doi, 10.5256/f1000research.10976.d153056[37]

Dataset 2: Characteristics of studies included for urinary citrate. doi, 10.5256/f1000research.10976.d153057[38]

Dataset 3: Characteristics of studies included for urine volume. doi, 10.5256/f1000research.10976.d153058[39]

Dataset 4: Characteristics of studies included for urinary calcium. doi, 10.5256/f1000research.10976.d153059[40]

Dataset 5: Characteristics of studies included for urinary oxalate. doi, 10.5256/f1000research.10976.d153060[41]

Dataset 6: Characteristics of studies included for urinary uric acid. doi, 10.5256/f1000research.10976.d153061[42]

Author contributions

PB and NR developed the concept of this study. IW designed the research methodology. FR did the literature searching. FR and PB did the selection of studies. FR prepared the draft of manuscript. All author contributed in the revision of the draft manuscript and have agreed to the final content.

Competing interests

No competing interests were disclosed.

Grant information

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Supplementary material

Supplementary Table 1. Newcastle-Ottawa scale for retrospective study's risk of bias assessment.
Click here to access the data.

Supplementary Table 2: PRISMA checklist.
Click here to access the data.

Supplementary Figure 1. Urine pH, urinary calcium, urinary oxalate, and urinary uric acid in healthy subject population.
Click here to access the data.

Supplementary Figure 2. Urine volume, urine pH, urinary oxalate, and urinary uric acid in population with a history of urolithiasis.
Click here to access the data.

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38. Rahman F, Birowo P, Widyahening IS, *et al.*: **Dataset 2 in: Effect of citrus-based products on urine profile: A systematic review and meta-analysis.** *F1000Research.* 2017.
Data Source
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Data Source

Open Peer Review

Current Referee Status: ✔ ✔

Version 1

Referee Report 08 May 2017

doi:10.5256/f1000research.11834.r22426

✔ **Bhaskar K Somani**
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The authors present a comprehensive systematic review and meta-analysis of the effect of citrus-based products on urine profile. The paper is supplemented by the PRISMA flow chart and forest plot charts to present their results.

Although their search strategy is good, they should have used other terms such as 'kidney stones', 'stones', 'ureteric stones' and 'calculi' too. They have only used the term 'Urolithiasis' which could potentially miss on other relevant studies.

As a limitation of any systematic review the authors are correct in acknowledging that their is likely to be a publication bias. Similarly, the long term effect of the use of citrate-based products in not know from this study and whether their results translate into a reduction in stone recurrences remain unknown.

A recent cochrane review on the use of citrate salts on prevention and treatment of calcium containing kidney stones in adults showed a reduction in new stone formation and stone recurrences in these patients[1].

Overall the paper reads well and is a nice summary on the use of citrate based products on urine profile.

References

1. Phillips R, Hanchanale VS, Myatt A, Somani B, Nabi G, Biyani CS: Citrate salts for preventing and treating calcium containing kidney stones in adults.*Cochrane Database Syst Rev*. 2015. CD010057
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Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 02 May 2017

doi:10.5256/f1000research.11834.r21950

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1. The authors are correct in stating that no previous meta-analysis of the effects of citrus fruits has been performed. The results are not surprising as stone clinicians consider citrus supplementation (or potassium citrate) of important utility. However, the meta-analysis is reasonable to perform as the intervention is commonly administered.
2.The studies are similar enough to consider a meta-analysis worth doing. One study used diet orange soda which is not citrus juice (I am the senior author of that study). There is otherwise an appropriate selection of studies, based on availability of the requisite data which the authors explain in detail.
3. The limitations of the data include the relatively small sample size, so that the meta-analysis is also underpowered but shows the expected increase in urine citrate and the increase in urine pH only in stone formers and not in non-stone forming controls. No studies actually assess stone formation as an outcome, addressing only urinary chemistry.
4. The conclusions appear reasonable, and are well-stated, if not surprising.
5. Table 1 could be improved by including the dose of juice for all the interventions.
6. I did not find a legend for figure 2 about bias assessment. The figure is hazy, not of perfect resolution. There is no interpretation of the bias assessment in the manuscript. It is worth noting that it is probably not possible to blind participants to citrus juice vs water. The other criteria, such as blinding to sequence allocation may also not be critical to a study of urine chemistry and not of kidney stone outcomes.
7. Regarding Curhan's finding that grapefruit juice was associated with higher risk for stones, mentioned in the discussion, that finding was not confirmed in a later study[1].
8. In the introduction, the authors state "whereas citrate could prevent stone formation by ionizing urinary calcium": this is not quite correct. Citrate binds to ionic calcium and prevents it from binding to oxalate or phosphate.

References

1. Ferraro PM, Taylor EN, Gambaro G, Curhan GC: Soda and other beverages and the risk of kidney stones.*Clin J Am Soc Nephrol*. 2013; **8** (8): 1389-95 PubMed Abstract | Publisher Full Text

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: Owner of the Ravine Group, see http://www.filamentbiosolutions.com/Press-releases/filament-announces-licensing-agreement.html. Disclosure: I am an author of 2 of the papers included in the study: Goldfarb, and Sumorok.

Referee Expertise: Nephrolithiasis, kidney stones, calculi, renal, chronic kidney disease, end stage renal disease, electrolytes and acid-base balance, gout

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.