Ascorbic Acid Supplements and Kidney Stones Incidence Among Men and Women: A Systematic Review and Meta-analysis

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Purpose: The relationship of ascorbic acid (AA) supplements and risk of kidney stones among men and women is controversial. This systematic evaluation was performed to obtain comprehensive evidence about the relationship of AA supplements and risk of kidney stones among men and women.

Material and Methods: A systematic search of Pubmed, the Cochrane Library, Web of Science, Embase was performed to identify studies that exhibited the relationship of AA supplements and risk of kidney stones among men and women and were published up to Mar 2017. Outcomes of interest included kidney stones incidence and risk factors.

Results: Four studies estimating the association between AA supplements and risk of kidney stones were included for meta-analysis. The kidney stones incidence was significantly higher in men than women with AA supplements (OR= 1.62; 95% CI: 1.09 to 2.42; P = 0.02). AA supplements (250-499mg/d, 1000-1499mg/d) was remarkably correlated with the risk of renal stones among men (OR= 1.14, 95% CI: 1.00 to 1.28, P = 0.04; OR= 1.12, 95% CI: 1.11 to 1.13, P < 0.00001; respectively). However, AA supplements (500-999 mg/d, >1500 mg/d) did not correlate with the risk of renal stones among men (OR= 1.20, 95% CI: 0.99 to 1.46, P = 0.06; OR= 1.28, 95% CI: 1.00 to 1.63, P = 0.05; respectively). In addition, AA supplements (250-499mg/d, 500-999mg/d, 1000-1499mg/d, >1500mg/d) did not remarkably correlate with the risk of renal stones among women (OR= 1.00, 95% CI: 0.82 to 1.22, P = 0.98; OR= 1.08, 95% CI: 0.99 to 1.18, P = 0.09; OR= 0.99, 95% CI: 0.90 to 1.08, P = 0.77; OR= 0.99, 95% CI: 0.99 to 1.09, P = 0.88; respectively).

Conclusion: AA supplements was remarkably correlated with higher risk for kidney stones incidence in men, but not in women. Further multicenter, prospective and long-term follow-up RCTs are required to verify these findings.

Key words: Ascorbic acid; Vitamin C; Kidney stones; Oxalate; meta-analysis

INTRODUCTION

The incidence of renal calculus is expected to increase worldwide over the next decade. A prominent risk factor for renal calculus is hyperoxaluria. Diet is thought to play a crucial role in the pathogenesis of calcium oxalate calculus, particularly intake of calcium[1,2], sodium[1,2], and ascorbic acid(AA)[3-5]. Many studies found that ascorbic acid(AA) supplements increase the risk of kidney stones[4-6]. The main dietary sources of AA or vitamin C are fresh fruits and vegetables. Ingested AA increased the risk of calcium oxalate calculus formation because AA is metabolized into oxalate and excreted in urine[7,8].

However, the relationship between AA supplements and kidney stones formation remains unclear. Many studies indicated that AA supplements might increase urinary oxalate excretion and risk for renal calculus formation among men[3-5,7], while some studies found that ingestion of AA does not increase the risk of renal calculus formation[9-11]. Thus, it can be seen that the results of the studies concerning the association between AA intake, and risk of kidney stones are controversial. Hence, we performed a meta-analysis of the available published literature to assess the association between AA supplements and risk of kidney stones among men and women.

MATERIALS AND METHODS

Literature Search Strategy

According to the Cochrane Handbook recommendations, a systematic review of published literature was performed up to Oct 1, 2017 which evaluated the relationship between AA supplements and kidney stones formation[12]. No ethical issues got involved in this study. A systematic dissertation was conducted using Medline, Embase, Pubmed, CNKI, and all relevant

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Table 1. Characteristics of included studies of ascorbic acid supplements and risk of kidney stones between men and women

First author, year	Country	Study interval	Design	Intervention	LOE	No.of patients men/women
Curhan, 1996	USA	1986-1992	Prospective	AA: < 250mg/d 250-499mg/d 500-999mg/d 1000-1499mg/d >1500mg/d	3b	45251/0
Curhan,1999	USA	1976-1994	Prospective	AA: < 250mg/d 250-499mg/d 500-999mg/d 1000-1499mg/d >1500mg/d	3b	0/85557
Ferraro,2016	USA	1976-1988	Prospective	AA: < 90mg/d 90-249mg/d 250-499mg/d 500-999mg/d >1000mg/d	2b	40536/156735
Taylor,2004	USA	1986-2000	Prospective	AA: 0mg/d 1-99mg/d 100-499mg/d 500-999mg/d > 1000mg/d	3a	45619/0

Abbreviations: AA= ascorbic acid; LOE= level of evidence.

studies have been identified by the Cochrane Library. The following keywords were used: "ascorbic acid", "vitamin C", "urolithiasis", "kidney stones", "renal stones", "ascorbate", and "oxalate calcium".

Inclusion Criteria and Exclusion Criteria

Studies should satisfy the following requirements[1] human studies[2] reporting original research[3] reporting indexes of AA supplements such as dosage, duration time, follow up[4] reporting evaluation kidney stone incidence[5] published in the English language. Studies were excluded if[1] the study did not satisfy inclusion criteria or[2] the outcomes of literature were not mentioned or the parameters were impossible to analysis for the relationship between AA supplements and risk of kidney stones or[3] studies published only as abstracts and reports from meetings.

Data Extraction and Outcomes of Interest

Two of the authors (JKH and TK) extracted the required data from the included studies through using a designed tabulation based on the inclusion criteria and a third author verified the data. All disagreements about eligibility reached a consensus by a third reviewer (LHR) by discussion. Based on the Cochrane Handbook, missing or vague information was imputed and was required from the authors of original articles or other relevant articles when necessary.

The following outcomes were extracted to evaluate the relationship between AA supplementation and kidney stones formation. Demographic and clinical baseline characteristics (age, male/female, AA daily supplementation). Follow-up and recorded the incidence of kidney stones (the primary outcome), the relative risk of stone

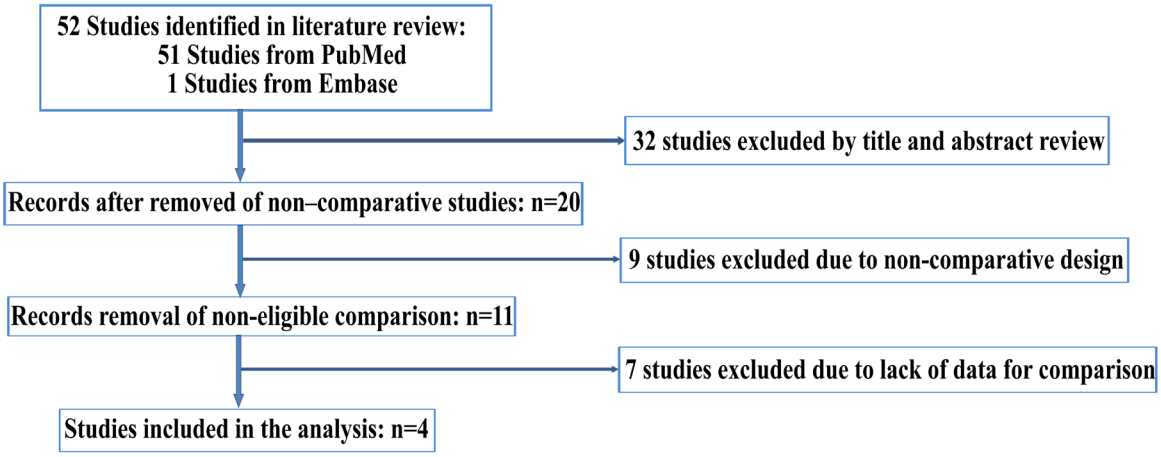

Figure 1. PRISMA diagram. The search strategy and number of studies identified for inclusion in this meta-analysis.

Table 2. Sensitivity analysis of high quality studies about the risk of AA supplements and kidney stones formation among men

AA supplements	No. of studies	OR (95%CI)	p-value	Study heterogeneity			
				Chi^2	df	I^2	*p*-value
250-499 mg/d	2	1.17[1.01,1.37]	0.04	0.07	1	0%	0.79
500-999 mg/d	2	1.32[1.13,1.55]	< 0.001	0.10	1	0%	0.75
1000-1499 mg/d	2	1.12[1.11,1.13]	< 0.001	3.62	1	72%	0.06
> 1500 mg/d	2	1.43[1.21,1.68]	< 0.001	0.00	1	0%	0.97

Abbreviations:bAA= ascorbic acid; OR = odds ratio; CI = confidence interval

formation was calculated for comparison.

Study Quality Assessment

In accordance with the criteria of Centre for Evidence-Based Medicine in Oxford, we evaluated the level of evidence (LOE) of included four studies. The Jadad Score was applied to evaluate the methodological quality of RCTs[13]. The Newcastle-Ottawa Scale (NOS) was applied to assess the methodological quality of non-RCTs observational studies[14]. Two authors (JKH and CZQ) evaluated the quality of the studies and discrepancies were rechecked by the third reviewer (CZQ), and the consensus was achieved by discussion.

Statistical Analysis

All meta-analyses were conducted by Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). Continuous and dichotomous variables were compared by weighted mean differences (WMDs) and odds ratios(ORs), respectively. All analysis results were reported with 95% confidence intervals(CIs). I2 test and chi-square-based Q test were applied to evaluate the quantity of heterogeneity, and when I2 > 50%, the evidence was considered to have substantial heterogeneity, the random- effects(RE) model would be applied. Otherwise, the fixed effects (FE) model was applied. The presence of publication bias was evaluated by Egger's test and funnel plot. Sensitivity analysis was used to estimate the influence of studies with a high risk of bias on the overall effect.

RESULTS

Characteristics of Eligible Studies

According to the search strategy, 4 studies[4-6,11] were included assessing the association of AA supplements and risk of kidney stones conformed to the inclusion criteria and were applied to performed this meta-analysis (**Figure 1**). Curhan et al. conducted a prospective study of the relationship between the intake of vitamins C and B6 and the risk of symptomatic kidney stones in a cohort of 45,251 men 40 to 75 years old with no history of kidney calculi. During 6 years of follow up 751 incident cases of kidney stones were documented. But these data do not support an association between a high daily intake of vitamin C or vitamin B6 and the risk of stone formation, even when consumed in large doses. Curhan et al. also conducted a prospectively study to examine the association between the intakes of vitamins B6 and C and risk of kidney stone formation in women. The study included 85,557 women with no history of kidney stones. A total of 1078 incident cases of kidney stones was documented during the 14-year follow-up period. The results also showed that vitamin C intake was not associated with risk for kidney stones formation in women. Ferraro et al. performed prospective cohort analysis and enrolled 156,735 women and 40,536 men. During a median follow-up of 11.3 to 11.7 years, 6,245 incident kidney stones were identified. The results showed that total and supplemental vitamin C intake was significantly associated with higher risk for incident kidney stones in men, but not in women. Taylor et al. conducted a prospective cohort study and enrolled 45,619 men without a history of nephrolithiasis. A total of 1473 incident symptomatic kidney stones were documented during 477,700 person-years of follow-up. The results indicated that the association between calcium intake and kidney stone formation varies with age. Magnesium intake decreases and total vitamin C intake seems to increase the risk of symptomatic nephrolithiasis. Because age and body size affect the relation between diet and kidney stones, dietary recommendations for stone prevention should be tailored to the individual patient. The demographic and clinical characteristics of the literatures were shown in **Table 1**.

Quality of the Studies and Level of Evidence(**Table 1**)

In this meta-analysis, the Newcastle-Ottawa Scale quality assessment method of the observational studies, and the US Preventive Services Task Force grading system were applied to evaluate the quality of included studies. 3 studies scored seven stars and were evaluated as high quality studies. Also, the demographic variables of AA supplements and risk of kidney stones were extracted

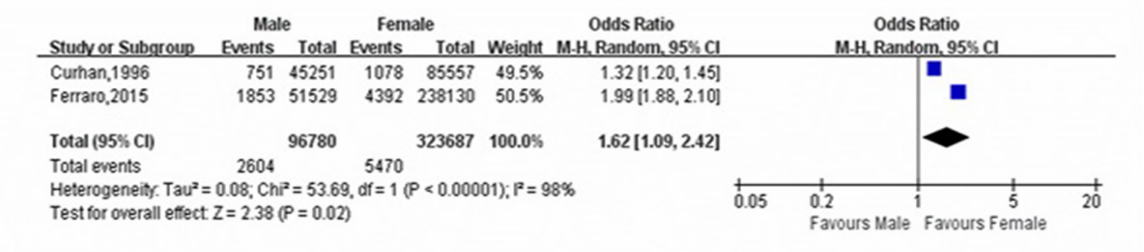

Figure 2. Forest plot and meta-analysis of AA supplements and kidney stones incidence among men and women; AA= ascorbic acid.

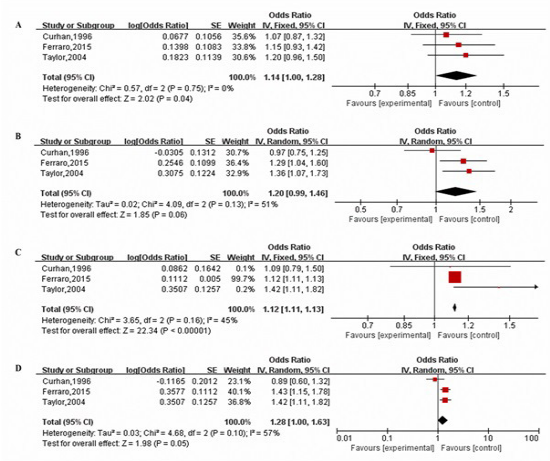

Figure 3. Forest plot and meta-analysis of AA supplements and risk of kidney stones

among men; A: AA supplements 499-250mg/d; B: AA supplements 999-500mg/d, C: AA supplements 1499-1000mg/d, D: AA supplements >1500mg/d; AA= ascorbic acid.

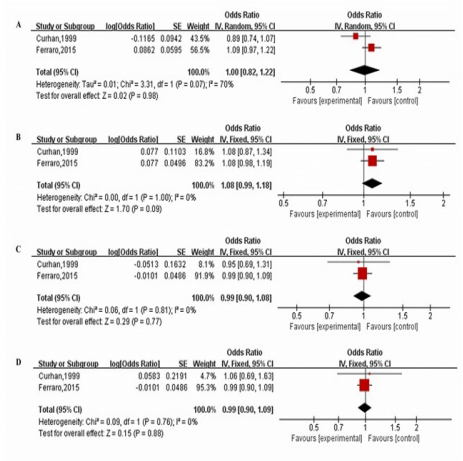

Figure 4. Forest plot and meta-analysis of AA supplements and risk of kidney stones

among women; A: AA supplements 499-250mg/d; B: AA supplements 999-500mg/d, C: AA supplements 1499-1000mg/d, D: AA supplements >1500mg/d; AA= ascorbic acid.

independently from included literature (**Table 1**).

Outcomes of Kidney Stones Incidence Among Men and Women(**Figure 2**)

Pooling data of two studies[4,5] reported on AA supplements and risk of kidney stones among men and women, the results showed that the kidney stones incidence of men was significantly higher than women with AA supplements (OR= 1.62; 95% CI: 1.09 to 2.42; P = 0.02) (**Figure 2**).

Outcomes of AA Supplements and Risk of Renal Calculus Among Men and Women (**Figures 3, 4**)

Pooling data of four studies[4-6,11] reported on AA supplements and risk for renal calculus among men and women by multivariate analysis. The results showed that AA supplements (250-499mg/d, 1000-1499mg/d) was remarkably correlated with the risk of renal stones among men (OR= 1.14, 95% CI: 1.00 to 1.28, P = 0.04; OR= 1.12, 95% CI: 1.11 to 1.13, P < 0.00001; respectively) (**Figure 3**). However, AA supplements (500-999 mg/d, >1500 mg/d) did not correlate with the risk of renal stones among men (OR = 1.20, 95% CI: 0.99 to 1.46, P = 0.06; OR = 1.28, 95% CI: 1.00 to 1.63, P= 0.05; respectively) (**Figure 3**). In addition, AA supplements(250-499mg/d, 500-999 mg/d, 1000-1499 mg/d, >1500mg/d) were not remarkably associated with risk of renal calculus among women (OR= 1.00, 95% CI: 0.82 to 1.22, P = 0.98; OR= 1.08, 95% CI: 0.99 to 1.18, P = 0.09; OR= 0.99, 95% CI: 0.90 to 1.08, P = 0.77; OR= 0.99, 95% CI: 0.99 to 1.09, P = 0.88; respectively) (**Figure 4**).

Sensitivity Analysis

Sensitivity analysis was performed for studies matched for general variables by the method of higher quality studies. There was no change in the significance of another outcome except that the risk of AA supplements (500-999 mg/d, >1500 mg/d) and renal stones formation among men was significantly different in sensitivity analysis (P = 0.06 vs P < 0.001; P = 0.05 vs P < 0.001; respectively) (**Table 2**). The method of sensitivity analysis can reduce the heterogeneity of studies to a certain extent.

DISCUSSION

Urolithiasis is a worldwide issue, and approximately 75% to 80% of kidney stones diagnosed consist predominantly of calcium oxalate[15-17]. Hyperoxaluria is the prominent risk factors for calcium oxalate calculus, and AA supplements are thought to be the prominent source of hyperoxaluria, where increasing dosages are associated with increases in urinary oxalate because AA may increase urinary oxalate excretion[7,18]. The study of Baxmann et al. found urinary oxalate was remarkably increased in patients who received 1g of AA, but no statistically significant difference in urinary PH[7]. Another study of 29 patients with a history of calcium oxalate calculus and 19 non-stone formers, the results showed that oxalate level of stone formers had significantly higher than non-stone formers with AA supplements[19].

Many studies have investigated the effect of AA on urinary oxalate excretion and risk of renal calculus. However, their results are not consistent. Chai et al. found that AA supplementation increased urinary oxalate levels, and the results indicated that AA was a risk factor for individuals predisposed to renal calculus[19]. The study of Baxmann et al. also found that ascorbic acid supplementation may increase urinary oxalate excretion and the risk of kidney stones forming, but no statistically significant difference was observed in urinary creatinine, sodium, potassium, calcium and chloride between healthy subjects and stone formers[7]. Taylor et al. showed that AA intake increases the risk for renal calculus formation[6]. However, Curhan et al. showed that there is no association between AA intake and kidney stones formation in men and women, even when consumed in large doses[5,11]. Ferraro et al. showed that AA supplementation was remarkably associated with higher risk of renal calculus in men, but not in women[4].

In our meta-analysis, the results showed that the kidney stones incidence of men was significantly higher than women with AA supplements (OR= 1.62; 95% CI: 1.09 to 2.42; P = 0.02). Pooling data of four studies reported on AA supplements and risk of kidney stones among men and women by multivariate analysis was performed. The results showed that AA supplements

(250-499mg/d, 1000-1499mg/d) was remarkably correlated with risk of renal calculus among men(OR= 1.14, 95% CI: 1.00 to 1.28, $P = 0.04$; OR= 1.12, 95% CI: 1.11 to 1.13, $P < 0.00001$; respectively). However, AA supplements (250-499 mg/d, 500-999mg/d, 1000-1499mg/d, >1500mg/d) did not remarkably correlate with risk of renal calculus among women (OR= 1.00, 95% CI: 0.82 to 1.22, $P = 0.98$; OR= 1.08, 95% CI: 0.99 to 1.18, $P = 0.09$; OR= 0.99, 95% CI: 0.90 to 1.08, $P = 0.77$; OR= 0.99, 95% CI: 0.99 to 1.09, $P = 0.88$; respectively).

The reason for the disparate results between men and women is unclear. However, some studies previously reported differential associations by sex for several dietary risk factors for stones, including animal protein, sucrose, potassium and sodium[2,6]. It is possible that the effect of AA on renal calculus risk is different in men and women, and the potential reason was sex differences in AA metabolism[20,21].

However, There were several limitations when analyzing and interpreting results in our meta-analysis. Firstly, we did not have stone composition analysis, nor plasma levels of AA or 24-hour urine data for participants in studies. Secondly, included studies were predominantly white, and results of our meta-analysis might not be generalizable to different races. Thirdly, the heterogeneity of the included studies is high and may be due to the differences in ethnicity, especially measurement methods and AA supplementations.

CONCLUSIONS

AA supplements remarkably correlated with higher risk of renal calculus incidence in men, but not in women. We advise that male stone former of calcium oxalate calculus abstain from supplemental but not dietary AA intake. Further studies are needed to examine associations between AA, oxalate metabolism, and urolithiasis formation and explore the possible mechanism of sex on the relationship between AA intake and risk for kidney stones.

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CONFLICT OF INTEREST

The authors report no conflict on interests.

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