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Effect of Oral Vitamin C Supplementation on Serum Uric Acid: A Meta-analysis of Randomized Controlled Trials

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Abstract

Objective—To assess the effect of vitamin C supplementation on serum uric acid (SUA) by pooling the findings from published randomized, controlled trials (RCTs).

Methods—A total of 2,082 publications identified through systematic search were subjected to the following inclusion criteria: (1) RCTs conducted on human subjects; (2) reported end-trial SUA means and variance; (3) study design with oral vitamin C supplementation and concurrent control groups; and (4) trial duration of at least one week. Trials that enrolled children or patients on dialysis were excluded. Two investigators independently abstracted trial and participant characteristics. SUA effects were pooled by random-effects models and weighted by inverse variance.

Results—Thirteen RCTs were identified in MEDLINE, EMBASE, and CENTRAL databases. The total number of participants was 556, median dose of vitamin C was 500 mg/d, trial size ranged from 8 to 184 participants, and median study duration was 30 days. Pretreatment SUA values ranged from 2.9 to 7.0 mg/dL (SI: 172.5 – 416.4 μmol/L). The combined effect of these trials was a significant reduction in SUA of -0.35 mg/dL (95% CI: -0.66, -0.03; $P = 0.032$; SI: -20.8 μmol/L). Trial heterogeneity was significant ($I^2 = 77\%$; $P < 0.01$). Subgroup analyses based on trial characteristics indicated larger reductions in uric acid in trials that were placebo-controlled.

Conclusions—In aggregate, vitamin C supplementation significantly lowered SUA. Future trials are needed to determine whether vitamin C supplementation can reduce hyperuricemia or prevent incident and recurrent gout.

Hyperuricemia is a well-established risk factor for gout (1). In population-based studies, the risk of gout steadily increases at successively higher levels of serum uric acid (SUA) (2) with a ten-fold increase in risk reported among those with serum urate levels > 9 mg/dL (3). Medications to prevent gout recurrence either act by reducing uric acid synthesis (e.g. xanthine oxidase inhibition) or via enhanced uric acid excretion (e.g. probenecid) (1). Although medical therapy is effective at preventing gout flares (4), both classes of drugs carry significant side effect profiles (5-7). Dietary approaches to lower uric acid thus provide an alternative and attractive approach to gout management (8). Recommendations to reduce consumption of high protein foods such as meat or seafood (to reduce purine intake), consume vegetable-based proteins, and lower alcohol consumption continue to play a critical role in disease management (9). Supplementation with vitamin C has also been examined as an alternative dietary approach (10).

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In vitro and animal models have demonstrated that vitamin C has uricosuric properties, inhibits uric acid synthesis (11), and lowers SUA (12, 13). Furthermore, in small lab-based, clinical studies in humans, ascorbic acid has been shown to lower SUA (14-20). Human observational studies have also reported an inverse association between plasma ascorbic acid (21) or vitamin C intake (22) and SUA concentrations. A prospective cohort study reported that vitamin C intake from diet sources was associated with a lower risk for developing gout (23). Moreover, a recent randomized trial of daily intravenous infusion of 500 mg of vitamin C for 10 days in patients with acute ischemic stroke resulted in a significant reduction in serum uric acid compared to placebo infusion (24).

Over the past 30 years at least 13 randomized, controlled clinical trials have examined the effect of oral vitamin C supplementation on SUA measurements (10, 25-36). However, these trials have yielded inconclusive results. To date, there have been no published systematic reviews which have pooled the results of these individual studies together. To provide more stable estimates of the efficacy of vitamin C supplementation on SUA and to examine trial characteristics that predict stronger effects, we performed a meta-analysis of these published trials.

Materials and Methods

We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases from January 1966 through September 2010 using the following terms: kidney, kidney disease(s), nephropathy, glomerulonephritis, renal insufficiency, gout, uricosuria, hyperuricosuria, hypouricosuria, hyperuricemia, hypouricemia, nephrolithiasis, uric acid, ascorbic acid, antioxidant(s), vitamin(s), randomized controlled trials, and *clinical trials*. The search was limited to human studies without language restrictions. See Appendix for search details. Search results were complemented with trials found in bibliographies of original research papers and previous reviews.

For inclusion in the primary analysis, studies were required to meet the following pre-specified criteria: (1) randomized controlled trials on human subjects; (2) intervention and control groups reported end-trial SUA means and variance; (3) the intervention included oral vitamin C supplementation and a concurrent control group; (4) constituent differences between treatment and control groups did not include agents with known antihyperuricemic activity; and (5) trial was of at least seven days duration. Trials that included children or patients with end-stage renal disease were excluded. Each included trial was required to explicitly state the word “random” in the description of treatment assignment. Further details regarding randomization methods used (blocking, random number generation, etc.) were not required.

Two investigators (SPJ, ERM) independently abstracted the articles. Discrepancies were resolved by adjudication. The following information was retrieved from each article: (1) study population, mean age, and percent male; (2) mean pretreatment SUA and ascorbic acid concentrations; (3) mean trial-end SUA and ascorbic acid concentrations: and (4) characteristics affecting trial quality: design (parallel, crossover, factorial), blinding (open, single, double, triple), intervention dose, type of control, trial duration, mechanism of SUA measurement, mention of concealment, description of randomization, intention-to-treat analysis, evaluation of losses to follow-up, and subject compliance. We recorded blinding as reported by trial authors; however, when it was not explicitly mentioned, we examined trials’ Methods sections for blinding of participants, providers, and outcome assessors. An attempt was made to contact authors of publications where SUA was measured but not fully reported (37-41).

For each trial following a parallel design, effect was calculated as the difference in baseline and end-trial SUA between the intervention and placebo groups (25-27, 30, 32-35). This is demonstrated by the equation: $(E_T\text{-}B_T) – (E_C\text{-}B_C)$, where E is an end-trial SUA value and B is a baseline SUA value for treatment (T) and control (C) groups (42, 43). The variance in SUA baseline change, i.e. E-B, was calculated with the equation: Variance (E-B) = Variance (E) + Variance (B) – 2*Covariance. The correlation coefficient was assumed to be 0.7, and a sensitivity analysis was conducted using a correlation coefficient of 0.5. The standard error of the difference in baseline change, i.e. $(E_T\text{-}B_T) – (E_C\text{-}B_C)$, was calculated using the equation, Standard Error = $SQRT(SD_T^2/n_T + SD_C^2/n_C)$ (44). For the three crossover trials in this meta-analysis (28, 33, 36), we utilized the following equation: $E_T - E_C$, where E is an end-trial SUA value for treatment (T) and control (C) groups (44). Standard error was calculated as above using Standard Error = $SQRT(SD_T^2{}_T/n_T + SD_C^2{}_C/n_C)$(44). A sensitivity analysis for crossover trials using the equation, Variance (E-B) = Variance (E) + Variance (B) – 2*Covariance, with the correlation coefficient assumed to be 0.7, yielded virtually the same results (not shown).

Three of the thirteen trials did not conform to the algorithms described above. Huang *et al* directly provided the difference in baseline change and its variance (10), which was utilized in place of the abovementioned calculation. Furthermore, one parallel trial did not report baseline SUA values, instead providing only end-trial SUA measurements(31). This trial was treated as a crossover trial in our meta-analysis. In another trial, Vrca *et al* reported only median SUA values in the form of a figure (29). These values were estimated from the figure and assumed to be equal to mean SUA values. Variance was estimated from p-values given in the text using the most conservative estimate when a range was reported (e.g. $P < 0.01$ was estimated to be $P = 0.01$).

Other abstraction nuances are as follows. One trial examined two distinct vitamin C interventions and was treated as two separate trials in our analysis (36). Another trial seemed to mislabel standard deviation as “SEM” (34). Close review of its Methods section supported interpretation of these data as mean +/- SD rather than SEM. Moreover, several trials examined the effect of vitamin C supplementation on SUA in the context of exercise (26, 30, 31, 34, 35). In general, we attempted to minimize this variable by examining SUA values measured prior to physical exertion, with the exception of Yanai *et al* who only reported post-training values (30). In similar fashion, whenever possible we attempted to avoid inclusion of other supplements and pharmaceuticals in our results by comparing vitamin C supplementation to placebo rather than to other treatment arms. In one trial, however, baseline SUA was provided for a vitamin E intervention, rather than placebo (35). In this case, we compared vitamin C to vitamin E since its baseline SUA values made it possible to calculate baseline change. Other circumstances in which vitamin C was administered with other supplements and pharmaceuticals are described in Table 1 and the Results section.

The pooled estimate and 95% confidence interval were calculated with a random effects model; trial effects were weighted by inverse variance. Heterogeneity between studies was assessed by the Q statistic and by the I^2 statistic (45). Individual trial influence was determined by removing each trial from the overall analysis. Publication bias was examined by funnel plot of standard error versus SUA effect, Begg's rank correlation test, and Egger's linear regression test. Statistical analyses were performed using STATA 8.2 (Stata Corp, College Station, TX). All SUA units were reported as mg/dL with International System of Units (SI) reported in parentheses, converting to μmol/L by multiplying by 59.48.

Subgroup analyses were performed on select trial characteristics. Trial characteristics included: vitamin C dose (median value, < 500; ≥ 500 mg/day), trial duration (median value,

< 30 days, ≥ 30 days), administration of vitamin C alone or with other vitamins, minerals, or pharmacologic agents (yes or no), trial design (parallel or crossover), double-blind design (yes or no), trial mention of participant compliance (yes or no), allocation concealment (yes or not reported), trial target population (healthy, yes or no), placebo use (yes or no), and trial size (median, < 29, ≥ 29 participants). Subject characteristics examined in subgroup analyses, according to the median value for the characteristic, were baseline serum ascorbic acid (median value, < 56.2 μmol/L, ≥ 56.2 μmol/L), mean age (median value, < 47.7, ≥ 47.7), percentage of male subjects (median value, < 53%, ≥ 53%), and baseline SUA (median value, < 4.85 mg/dL, ≥ 4.85 mg/dL; SI: 288.5 μmol/L).

Results

Search results are displayed in Figure 1. Among the trials abstracted, the principal exclusion factors were: (1) lack of randomization (46), (2) missing SUA variance (37, 38), and (3) incomplete SUA effects (39-41). Characteristics of the 13 clinical trials, satisfying our inclusion criteria are summarized in Table 1. These 13 trials were conducted between 1990 and 2009, comprising 556 participants. Trial size ranged from 8 to 184 participants; mean age ranged from 20 to 81. With regard to trial design, 3 of the 13 trials were crossover, 10 were parallel; 9 were double-blind trials, 1 was single blind, and 3 reported no blinding. Trials were conducted over the course of 7 to 90 days with a median duration of 30 days. Among crossover trials, washout periods ranged from 1 week to 2 months. Pretreatment SUA values ranged from 2.9 to 7.0 mg/dL (SI: 172.5 – 416.4 μmol/L); pretreatment plasma ascorbic acid ranged from 27.0 to 77.7 μmol/L. Eight trials administered vitamin C as the only intervention, while 5 trials administered vitamin C in combination with other vitamins, minerals, or pharmacologic agents. The median dose of vitamin C was 500 mg/d, ranging from 200 mg/d to 2000 mg/d. Trial subjects were quite heterogeneous, ranging from healthy adults, the most common subject description, to several inpatient populations diagnosed with stroke, Graves' Disease, or in long-term care.

Vitamin C supplementation was associated with reductions in SUA in 8 of the 13 trials included in this meta-analysis (10, 26, 28, 30, 31, 33, 34, 36). Six of the 13 trials reported significant baseline reductions in SUA (10, 25, 29, 31, 33, 36). The overall pooled effect of vitamin C supplementation on SUA was -0.35 mg/dL (95% CI: -0.66, -0.03; $P = 0.032$; SI: -20.8 μmol/L) (Figure 2). Notably, the pooled effect was significant for heterogeneity with $Q = 57$ ($I^2 = 77\%$; $P < 0.01$). Using a covariance correlation value of 0.5 rather than 0.7 (see Methods), yielded a similar magnitude SUA effect at -0.34 ($P = 0.027$).

Subgroup analyses are summarized in Table 2. SUA reduction was -0.78 mg/dL (95% CI: -1.46, -0.09; SI: -46.4 μmol/L) in trials with subjects possessing baseline SUA values ≥ 4.85 mg/dL (SI: 288.5 μmol/L). There was a significant difference between trials with participants possessing baseline SUA values below 4.85 mg/dL (SI: 288.5 μmol/L) versus those above 4.85 mg/dL ($P = 0.030$). Furthermore, stratifying trials by reported use of placebo showed significant SUA reductions in trials utilizing placebo at -0.59 mg/dL (95% CI: -0.95, -0.24; SI: -35.1 μmol/L), while trials that did not use a placebo had no effect (0.19 mg/dL; 95% CI: -0.07, 0.45; SI: 11.3 μmol/L). The pooled effects of these groups were significantly different ($P = 0.01$). Also, trials utilizing at least a 500 mg daily dose of vitamin C, and trials where vitamin C was the only intervention, reduced vitamin C at -0.59 mg/dL (95% CI: -1.05, -0.13; SI: -35.1 μmol/L) and -0.54 mg/dL (95% CI: -0.96, -0.11; SI: -32.1 μmol/L), respectively. These effect sizes were not significantly different, however, when compared to trials utilizing smaller doses ($P = 0.10$) and trials administered vitamin C in combination with other vitamins, minerals, or pharmacologic agents ($P = 0.16$).

Trial quality features are contained in Table 3. The majority of trials did not report details regarding allocation concealment (3 of 13) or randomization method (0 of 13). Only 1 trial clearly reported intention-to-treat (10), and only 1 trial reported blinding of the assessor in addition to subjects and care provider (10). Five of 13 trials mentioned trial subjects' compliance with treatment protocol, and only 1 trial (10) discussed losses to follow-up.

In a plot of SUA effect versus standard error, trials appeared to follow the shape of a funnel (Figure 3). Publication bias was also examined by performing Begg's rank correlation test, which yielded a non-significant Kendall score of -22 ($P = 0.23$). Egger's linear regression test confirmed these findings with a non-significant SUA bias coefficient at $P = 0.67$ (44), suggesting that publication bias was not a significant factor in this meta-analysis. Furthermore, a random-effects analysis was conducted after the omission of each trial to examine the influence of the omitted study on the pooled effect. As such, the overall effects ranged from -0.20 mg/dL ($P = 0.09$; SI: -11.9 μmol/L) to -0.40 mg/dL ($P = 0.019$; SI: -23.8 μmol/L), following omission of trials with greatest weight for (30) and against (27) an overall reduction in SUA.

Discussion

This study is the first quantitative review of published randomized, clinical trials examining the effect of oral vitamin C supplementation on SUA. Overall, vitamin C supplementation reduced SUA with a mean aggregate effect of -0.35 mg/dL ($P = 0.032$; SI: -20.8 μmol/L). Although only 6 of the 13 trials reported significant reductions in SUA, pooling these small trials made it possible to estimate an overall effect, a key advantage of the meta-analysis method. These findings support the observed inverse associations between intake of dietary and supplemental vitamin C and SUA levels.

Vitamin C is an essential micronutrient in a number of physiologic processes. When plasma ascorbate levels fall below 11 μmol/L, clinical features of scurvy may develop (47). The median dose of vitamin C used in trials was 500 mg/d, which is well above the recommended dietary allowance for vitamin C, 90 mg/d in men and 75 mg/d in women. Surpassing the tolerable upper intake level of 2 g/d (48) may cause osmotic diarrhea, gastrointestinal disturbance (49), and calcium oxalate nephrolithiasis (50). Most studies report few side effects, however, when doses are below the tolerable upper intake level (49). None of the trials included in this meta-analysis reported adverse effects from vitamin C supplementation.

Several studies have described biological mechanisms by which vitamin C reduces SUA. *In vivo* studies suggest that vitamin C has uricosuric properties, increasing renal fractional clearance of uric acid, thereby reducing SUA (14). This is likely due to competitive inhibition of an anion exchange transport system at the proximal tubule in the nephron (16). Vitamin C may act specifically at uric acid reabsorption sites in the apical brush border of the proximal tubule, such as urate transporter 1 (URAT1), and a sodium-dependent anion cotransporter, SLC5A8/A12 (22, 51-53). It is also possible that vitamin C increases the glomerular filtration rate by reducing glomerular microvascular ischemia and increasing dilatation of afferent arterioles (10, 54-56). Furthermore, as an effective antioxidant vitamin C decreases free radical-induced damage to body cells (57), thereby reducing production and ultimately serum concentration of uric acid (22).

There are a number of limitations to this meta-analysis that warrant consideration. Heterogeneity between trials was found to be significant ($I^2 = 77\%$; $P < 0.01$). An attempt to address heterogeneity by performing subgroup analyses based on trial characteristics did not fully explain differences in effect as demonstrated by elevated I^2 values within strata.

Significance observed among some subgroup strata may indicate that baseline SUA, dose of vitamin C, use of vitamin C alone without any other supplement(s), and placebo use play a greater role in heterogeneity than other subject and trial characteristics. However, strata based on the comparison of patient characteristics across trials, specifically mean age, percent male gender, baseline serum ascorbate, and baseline serum uric acid, are prone to ecological bias and should be interpreted with additional caution (58).

Another important consideration is publication bias. Although our funnel plot (Figure 3) and other analyses did not support the presence of publication bias (Egger's test: $P = 0.70$), during the search we identified one trial whose authors decided not to report SUA findings because of non-significant results (41). It is possible that other trials lacking significant results were never published, skewing the overall results toward an effect. Another interpretation of the asymmetrical funnel plot is “small study effects.” Smaller studies often lack methodological rigor in design and analysis, contributing to inflated treatment effects (44). This is particularly evidenced by trials’ rare mention of design quality features in this meta-analysis (Table 3). Further, even when optimally designed, small trials suffer from the inherent limitation of low statistical power. Indeed, small trial size and the paucity of reported assurances regarding trial quality constitute an important limitation of this meta-analysis.

Another important consideration affecting interpretation of our results is the method by which SUA is measured. Of the thirteen trials included in this study, there are considerable differences in the manner by which SUA was determined and in the detail provided to describe this critical aspect of trial methodology (Table 1). Prior research describes the ability of vitamin C to interfere with SUA measurements (19, 59-64). Moreover, depending on the biochemical assay, vitamin C has been demonstrated to artificially increase (15, 65, 66) or decrease measured SUA (67). Artificial reduction in SUA is particularly related to the use of a biochemical assay employing the oxidase-peroxidase system, i.e. the Trinder method (68). In one study, Martinello et al (2006) administered vitamin C to eighteen volunteers and measured SUA via the Trinder method and ultraviolent light (UV) (67). The Trinder method found a significant baseline decrease in SUA, while UV showed no change in SUA (67). Although the exact mechanism of interference is not understood, it is believed that vitamin C as an antioxidant depletes the hydrogen peroxide utilized by the Trinder method to produce chromophore and detect SUA (69). Contrary to expectations in this meta-analysis, however, the one trial that explicitly describes use of the oxidase-peroxidase system without addressing vitamin C interference (35) did not observe a reduction in SUA after vitamin C supplementation. A number of researchers note that the addition of ascorbate oxidase, which oxidizes ascorbic acid to dehydroascorbic acid, does not interfere with the chromogen system responsible for SUA detection (69-71). Of all the trials included in this meta-analysis, this method was only explicitly mentioned by Huang and colleagues (10). Despite potential interference in serum measurements, prior small clinical studies have documented concurrent increase in uric acid excretion after introduction of vitamin C (14, 16). Mitch et al (1980) notes, however, that urine uric acid measures are also susceptible to interference, depending on the measurement assay used (62). As SUA measurement integrally affects conclusions, future trials should employ methods that minimize vitamin C interference in serum measurements and also quantify urinary excretion of uric acid.

One trial in this meta-analysis that reported null effects of vitamin C on SUA included 300mg/d of aspirin in its combination therapy (27). Aspirin has a mixed effect on the uric acid excretion with doses >3 grams/day causing uricosuria, while doses between 1-2 grams promote UA retention (72). Recent studies suggest that even small doses of aspirin, i.e. doses between 75 - 325 mg/day, also decrease uric acid clearance, causing uric acid retention (73-75). It is hypothesized that aspirin competes with uric acid at tubular secretion

and reabsorption receptors and more globally suppresses glomerular filtration rate (72, 75-77). Consistent with this hypothesis, the trial utilizing aspirin in this meta-analysis (27) contributed the largest weight against vitamin C reduction of SUA. It is possible that aspirin inhibits the uricosuric action of vitamin C, nullifying its effect. Exclusion of this trial increased the magnitude and significance of our pooled effect to -0.40 mg/dL (P = 0.019; SI: -23.8 μmol/L).

Five of the 13 trials in this study (26, 30, 31, 34, 35) evaluated SUA in the context of exercise. As acute exercise is known to increase oxidative stress and levels of serum and salivary uric acid (39, 40, 78-82), we attempted to avoid inclusion of this variable in our pooled analysis. This was not possible in one of the trials, because the authors did not measure pre-exercise SUA values (30). Conducting the meta-analysis using the SUA values measured closest to the conclusion of exercise rather than pre-exercise SUA values, revealed an overall SUA reduction of -0.42 (P = 0.012), which is greater and more significant than the pooled effect reported in our analysis. This may suggest that the role of vitamin C is more pronounced in contexts of oxidative stressors and that greater protection against acute hyperuricemia could be achieved. Additional trials are necessary to evaluate this hypothesis.

Hyperuricemia has been associated with a wide range of diseases, including hypertension, obesity, renal disease, metabolic syndrome, obstructive sleep apnea, stroke, vascular dementia, and preeclampsia (83). However, large trials of vitamin C on cardiovascular events (84, 85) as well as a recent meta-analysis on mortality have failed to demonstrate significant protective effects (86). These studies did not examine gout among their outcomes. Among all of the aforementioned clinical outcomes, the strongest support for a casual relationship exists between elevated SUA and gout (1). Importantly, none of the trials included in this meta-analysis examined vitamin C in a population of patients with gout, though an exploratory subgroup analysis suggests that greater SUA reduction could be achieved in individuals with SUA above 4.85 mg/dL (Table 2). If vitamin C with its low cost and relatively innocuous side effect profile were administered to patients with gout as an adjunctive therapy, it is possible that a greater number would achieve target SUA levels, reducing the likelihood of flares. It has yet to be determined, however, whether vitamin C would enhance or add to the SUA reduction of standard anti-hyperuricemic agents.

In summary, this meta-analysis suggests that oral vitamin C supplementation results in modest SUA reduction. Future trials of adequate size and duration should address issues of vitamin C assay interference and should measure both SUA and renal excretion of uric acid. Furthermore, future trials should be adequately powered to evaluate whether or not the urate-lowering effects of vitamin C are enhanced in patients with elevated SUA as found in our exploratory subgroup analysis and described in a previous trial (10). Ultimately, whether vitamin C supplementation lowers the risk of gout or hyperuricemia needs to be determined.

Acknowledgments

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Appendix: Search Terms utilized on September 4th, 2010

MEDLINE: 1041 Publications

("1966/01/01"[PDAT] : "3000"[PDAT]) AND (kidney[TW] OR "kidney diseases"[MH] OR "kidney diseases"[TW] OR (kidney[TIAB] AND disease[TIAB]) OR (kidney[TIAB] AND diseases[TIAB]) OR nephropath*[TW] OR glomerulonephritis[MH] OR glomerulonephritis[TIAB] OR (renal[TIAB] AND insufficiency[TIAB]) OR "renal

insufficiency”[TIAB] OR gout[TW] OR uricosuria[TW] OR hyperuricosuria[TW] OR hypouricosuria[TW] OR hyperuricemia[TW] OR hypouricemia[TW] OR nephrolithiasis[TW] OR nephrolithiasis[MH] OR “uric acid”[TW] OR (uric[TIAB] AND acid[TIAB])) AND (“ascorbic acid”[TW] OR “ascorbic acid”[MH] OR (ascorbic[TIAB] AND acid[TIAB]) OR antioxidant*[TW] OR antioxidant*[MH] OR vitamin*[TW] OR vitamin*[MH]) AND ((“randomized controlled trial”[PT] OR “random allocation”[MH] OR “randomized controlled trials as topic”[MH] OR “randomized controlled trial”[TIAB] OR “randomised controlled trial”[TIAB]) OR (“controlled clinical trial”[PT] OR “clinical trial” [PT] OR “clinical trials as topic”[MH] OR “clinical trials”[TIAB]) OR (“double-blind method”[MH] OR “single-blind method”[MH]) NOT (animal[MH] NOT human[MH]) NOT (review[PT] OR meta-analysis[PT]))

EMBASE: 1198 Publications

‘kidney’/exp OR ‘kidney’:ab,ti OR ‘kidney diseases’/exp OR ‘kidney diseases’:ab,ti OR ‘kidney disease’/exp OR ‘kidney disease’:ab,ti OR (‘kidney’:ab,ti AND disease*:ab,ti) OR ‘nephropathy’/exp OR nephropath*:ab,ti OR ‘glomerulonephritis’/exp OR ‘glomerulonephritis’:ab,ti OR ‘renal insufficiency’/exp OR ‘renal insufficiency’:ab,ti OR (‘renal’:ab,ti AND ‘insufficiency’:ab,ti) OR ‘gout’/exp OR ‘gout’:ab,ti OR ‘uricosuria’/exp OR ‘uricosuria’:ab,ti OR ‘hyperuricosuria’/exp OR ‘hyperuricosuria’:ab,ti OR ‘hypouricosuria’:ab,ti OR ‘hyperuricemia’/exp OR ‘hyperuricemia’:ab,ti OR ‘hypouricemia’/exp OR ‘hypouricemia’:ab,ti OR ‘nephrolithiasis’/exp OR ‘nephrolithiasis’:ab,ti OR ‘uric acid’/exp OR ‘uric acid’:ab,ti OR (‘uric’:ab,ti AND ‘acid’:ab,ti) AND (‘ascorbic acid’/exp OR ‘ascorbic acid’:ab,ti OR (‘ascorbic’:ab,ti AND ‘acid’:ab,ti) OR ‘antioxidant’/exp OR antioxidant*:ab,ti OR ‘vitamin’/exp OR vitamin*:ab,ti) AND ([randomized controlled trial]/lim OR ‘randomized controlled trial’/exp OR ‘random allocation’/exp OR ‘randomized controlled trial’:ab,ti OR ‘randomised controlled trial’:ab,ti OR [controlled clinical trial]/lim OR [clinical trial]/lim OR ‘clinical trials’:ab,ti OR ‘double-blind method’/exp OR ‘single-blind method’/exp) AND ([adult]/lim OR [aged]/lim) NOT ([animals]/lim NOT [humans]/lim) NOT ([review]/lim OR [meta analysis]/lim) AND [embase]/lim AND [1966-2010]/py

CENTRAL: 723 Publications

((kidney) OR (kidney diseases) OR ((kidney):ti,ab AND (disease*):ti,ab) OR (nephropathy) OR (nephropath*):ti,ab OR (glomerulonephritis) OR (glomerulonephritis):ti,ab OR (renal insufficiency) OR (renal insufficiency):ti,ab OR ((renal):ti,ab AND (insufficiency):ti,ab) OR (gout) OR (gout):ti,ab OR (uricosuria) OR (uricosuria):ti,ab OR (hyperuricosuria) OR (hyperuricosuria):ti,ab OR (hypouricosuria) OR (hypouricosuria):ti,ab OR (hyperuricemia) OR (hyperuricemia):ti,ab OR (hypouricemia) OR (hypouricemia):ti,ab OR (nephrolithiasis) OR (nephrolithiasis):ti,ab OR (uric acid) OR (uric acid):ti,ab OR ((uric):ti,ab AND (acid):ti,ab)) AND ((ascorbic acid) OR ((ascorbic):ti,ab AND (acid):ti,ab) OR (antioxidant) OR (antioxidant*):ti,ab OR (vitamins) OR (vitamin*):ti,ab) NOT (review):pt NOT (meta analysis):pt, from 1966 to 2010 in Clinical Trials

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Significance and Innovation

- Combining the results of thirteen randomized, controlled trials resulted in a significant reduction in SUA of -0.35 mg/dL (95% CI: -0.66, -0.03; $P = 0.032$; SI: -20.8 μmol/L).
- The thirteen trials were very heterogeneous ($I^2 = 77\%$).
- Reductions in SUA were larger among trials administering 500 mg/d or greater of vitamin C, trials administering vitamin C without other interventions, and trials that used a placebo group.

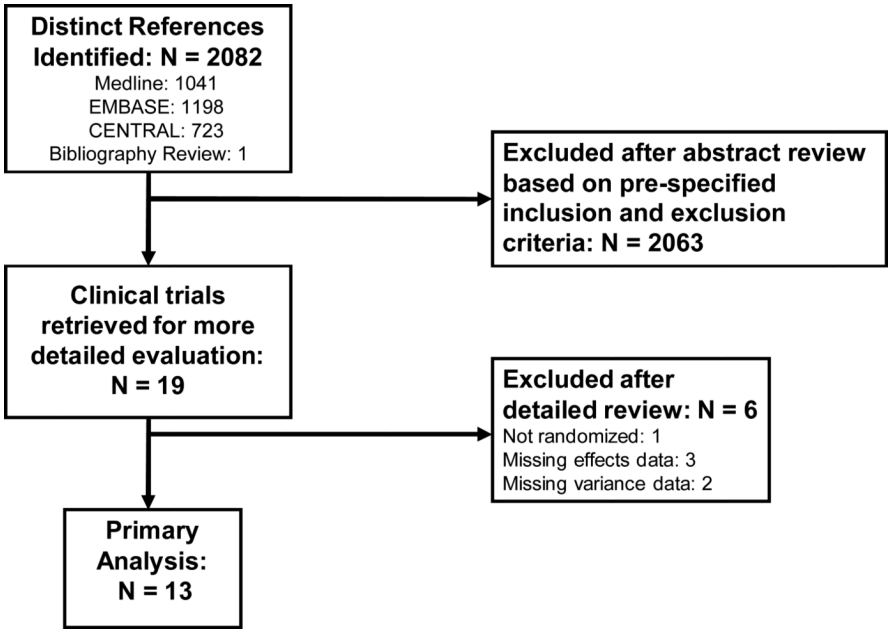

Figure 1. Search Results

Flow diagram of the trial selection process.

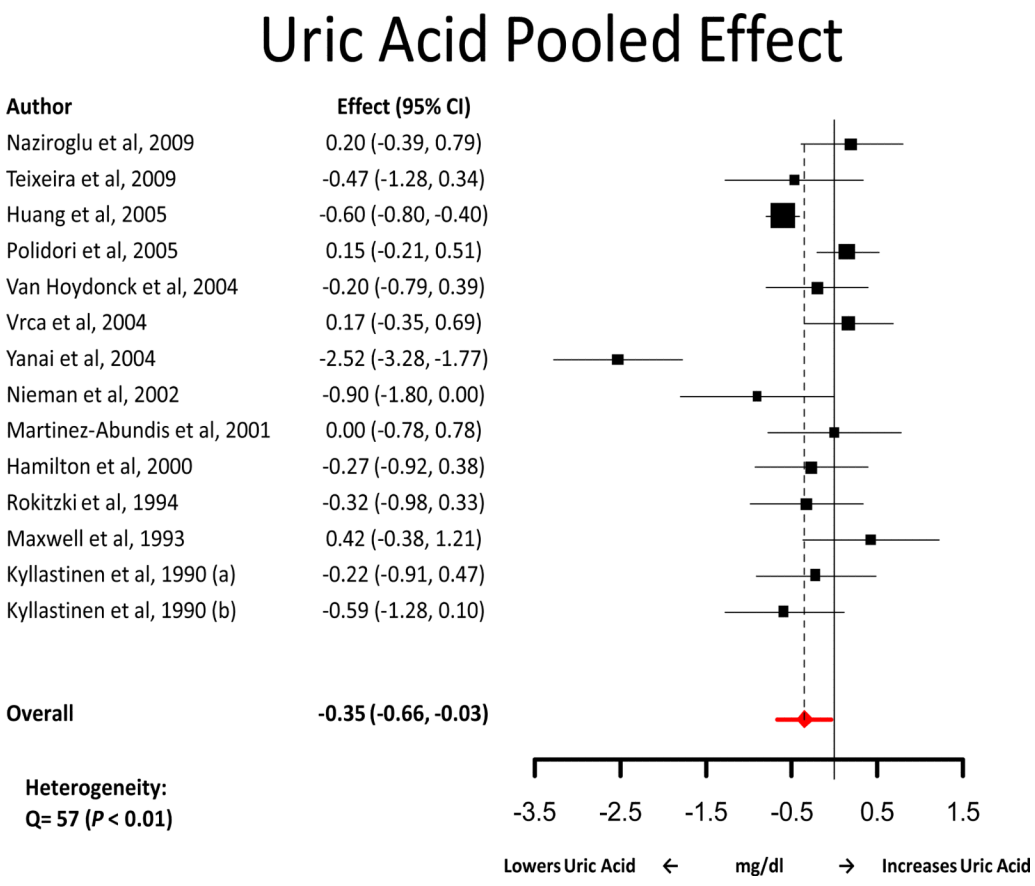

Figure 2. Forest Plot of the Pooled Effect of Vitamin C Supplementation on Serum Uric Acid

Net change in each individual study for serum uric acid in randomized controlled trials of vitamin C supplementation and overall pooled result. The area of each square is proportional to the study weight in the analysis. Horizontal lines represent 95% confidence intervals (CIs). The red diamond represents the pooled estimate and the 95% CI obtained from inverse-variance weighted random-effects models.

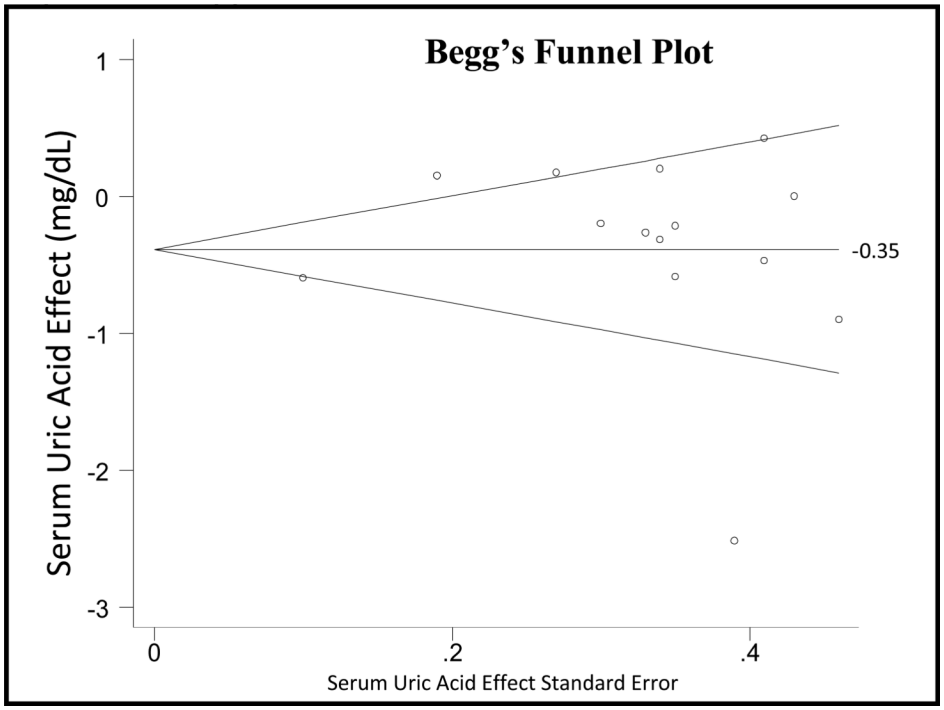

Figure 3. Begg's Funnel Plot with Pseudo 95% Confidence Limits

Begg's funnel plot with pseudo 95% confidence limits (sloped lines). Serum uric acid effect (mg/dL) is plotted on the y-axis, and the standard error is plotted on the x-axis. The vertical line represents the overall pooled effect (-0.35 mg/dL). Circles represent the SUA effect and standard error of each trial.

Table 1

Clinical trials examining the effect of vitamin C supplementation upon serum uric acid, ordered by year of study.

Source (year)	Country	Population	Size	Mean Age, y (SD)	% Male	Study Design††	Study Duration, d*	Intervention (per day)	Control	Baseline Uric Acid (mg/dL)**	Pretreatment Plasma Ascorbic Acid (μmol/L)***	Uric Acid Measurement	Completing Trial (%)
Naziroglu *et al*(25), 2009†	Turkey	Postmenopausal & Diabetic Women	40	51 (45 - 65)	0	PO	42	Vit C 1000mg, Vit E 600mg, Estradiol 0.625mg, Medroxyprogesterone 5mg	Estradiol 0.625mg, Medroxyprogesterone 5mg	3.6 (1.1)	-	Routine kits, autoanalyzer	100
Teixeira *et al*(26), 2009	Portugal	Athletes	20	19.7 (3.6)	70	PD	28	Vit C 400mg, Vit E 272mg, β-carotene 30mg, Lutein 2mg, Selenium 400μg, Zinc 30mg, Magnesium 600mg	Placebo	4.9 (1.0)	56.2 (24.0)	Enzymatic method at 550 nm using commercial kit (Horiba ABX A11A01670)	100
Huang *et al*(10), 2005†	USA	Adult Nonsmokers	184	58.2 (13.7)	45	FPT	60	Vit C 500mg	Placebo	5.2 (1.5)	62.2 (15.5)	Hitachi 917 autoanalyzer Roche Diagnostics; uricase-peroxidase method with ascorbate oxidase incubation	92
Polidori *et al*(27), 2005	Italy	Acute Ischemic Stroke	59	77.0 (7.2)	53	PO	90	Vit C 200mg, Aspirin 300mg	Aspirin 300mg	2.9 (0.9)	27.0 (4.5)	High performance liquid chromatography with Supelco columns	100
Van Hoydonck *et al*(28), 2004	Belgium	Healthy Male Smokers	42	52 (12)	100	XD	28	Vit C 500mg	Placebo	-	45 (20)	Enzyme-linked calorimetric assay (Roche, Basel, Switzerland)	81
Vrca *et al*(29), 2004†	Croatia	Patients with Graves' Disease	57	-	9	PO	28	Vit C 200mg, β-carotene 6mg, Vit E 36mg, Selenium 60μg, Methimazole at varying doses	Methimazole at varying doses	3.5+	-	Olympus AU500 Analyser	100
Yanai *et al*(30), 2004	Japan	Healthy, Nonsmoking male athletes	8	20.4 (1.6)	100	PS	21	Vit C 1000mg	Placebo	5.2 (0.8)	-	Uricase calorimetric method	100
Nieman *et al*(31), 2002†	USA	Ultramarath on Runners	29	47.7 (12.1)	-	PD	7	Vit C 1500mg	Placebo	-	-	Hematology Laboratory	97
Martinez-Abundis *et al*(32), 2001	Mexico	Obese male volunteers	16	26.5 (6.3)	100	PD	28	Vit C 1000mg	Placebo	7.0 (1.2)	-	Enzymatic methods	100
Hamilton *et al*(33), 2000†	UK	Healthy Adults	32	35 (9)	50	XD	42	Vit C 500mg	Vit E 73.5mg as placebo	4.4 (0.9)	63.6 (12.5)	Commercial kits on a Cobas Fara (Roche Dianostic Systems)	94
Rokitzki *et al*(34), 1994	Germany	Male Athletes	24	38.5 (8.5)	100	PD	31.5	Vit C 200mg, Vit E 400 IU	Placebo	5.9 (1.0)	46.3 (12.8)	Enzymatic test	92

Source (year)	Country	Population	Size	Mean Age, y (SD)	% Male	Study Design††	Study Duration, d*	Intervention (per day)	Control	Baseline Uric Acid (mg/dL)**	Pretreatment Plasma Ascorbic Acid (µmol/L)***	Uric Acid Measurement	Completing Trial (%)
Maxwell *et al*(35), 1993	UK	Healthy Students	16	19.6 (1.5)	67	PO	21	Vit C 400mg	Vit E 400mg	4.8 (1.0)	77.7 (19.3)	Automated uricase-peroxidase system	100
Kyllastinen *et al*(36) (a), 1990	Finland	Long-stay Hospital Patients	29	81+ (68 - 93)	0	XD	42	Vit C 200mg	Placebo	-	-	Routine laboratory methods	93
Kyllastinen *et al*(36) (b), 1990†	Finland	Long-stay Hospital Patients	29	81+ (68 - 93)	0	XD	42	Vit C 2000mg	Placebo	-	-	Routine laboratory methods	93

†**Trials reporting significant baseline reductions in Uric Acid**

††**F is factorial; P is parallel; X is crossover; T is triple blind; D is double blind; S is single blind; O is open**

*__1 Month = 30 days__

**__Uric acid converted from µmol/L to mg/dL by dividing by 59.48__

***__Vitamin C converted from mg/dL to µmol/L by multiplying by 56.776__

+__Median value.__

Table 2

Subgroup analyses consisting of the pooled effect sizes of vitamin C supplementation on serum uric acid level, stratified by trial and subject characteristics.

	Change in serum uric acid (mg/dL)					
Sub-group	**N**[§]	**Effect**	**95% CI**		I^2	**P**[*]
			LL	**UL**		
Dose						
<500 mg/d	6	0.02	-0.21	0.26	0.0%	0.10
≥500 mg/d	8	-0.59	-1.05	-0.13	79.9%	
Duration						
<30 days	7	-0.49	-1.20	0.22	85.2%	0.52
≥30 days	7	-0.25	-0.56	0.06	63.0%	
Baseline Serum Ascorbic Acid						
<56.2 μmol/L	3	-0.02	-0.30	0.27	0.0%	0.20
≥56.2 μmol/L	4	-0.33	-0.75	0.09	53.7%	
Mean Age						
<47.7	6	-0.53	-1.32	0.27	85.3%	0.55
≥47.7	7	-0.29	-0.61	0.04	66.1%	
%Male						
<53	6	-0.26	-0.59	0.07	58.5%	0.66
≥53	7	-0.41	-1.06	0.24	85.6%	
Baseline Serum Uric Acid						
<4.85 mg/dL	5	0.13	-0.12	0.37	0.0%	0.03
≥4.85 mg/dL	5	-0.78	-1.46	-0.09	85.0%	
Trial Design						
Parallel	10	-0.37	-0.80	0.07	83.8%	0.91
Crossover	4	-0.31	-0.63	0.02	0.0%	
Vit C Only Intervention						
Yes	9	-0.54	-0.96	-0.11	78.1%	0.16
No	5	0.04	-0.20	0.29	0.0%	
Placebo Use						

	Change in serum uric acid (mg/dL)					
Sub-group	**N**[§]	**Effect**	**95% CI**		I^2	**P**[*]
			LL	**UL**		
Yes	10	-0.59	-0.95	-0.24	71.2%	0.01
No	4	0.19	-0.07	0.45	0.0%	
Allocation Concealment						
Yes	4	-0.31	-0.75	0.13	76.5%	0.89
Not Reported	10	-0.37	-0.86	0.11	79.1%	
Double-blind Design						
Yes	9	-0.50	-0.66	-0.35	0.0%	0.75
No	5	-0.30	-1.17	0.58	90.8%	
Trial Reported Compliance						
Yes	5	-0.35	-0.75	0.05	71.1%	0.92
No	9	-0.34	-0.87	0.18	0.0%	
Healthy Trial Population						
Yes	7	-0.60	-1.26	0.06	82.5%	0.20
No	7	-0.15	-0.49	0.20	71.1%	
Trial Size						
<29	5	-0.58	-1.58	0.41	87.9%	0.37
≥29	9	-0.23	-0.51	0.05	63.4%	

[*] P-values represent comparison of effects between subgroups. Category bounds were determined by the median of abstracted values.

[§] N represents the number of trials. The number of trials may not always add to 13 due to the treatment of one trial as two groups (Kyllastinen et al, 1990) and due to the varying availability of subgroup data in each trial.

Table 3

Trial Quality Design Features

	Allocation Concealment	Randomization Method	Intention-to-Treat Analysis	Blinding of Participants	Blinding of Providers	Blinding of Outcome Assessor	Description of Subject Compliance	Evaluation of Treatment-Specific Losses to Follow-up
Naziroglu *et al*(25), 2009	Not Reported	Not Reported	Not Reported	No	No	No	No	-
Teixeira *et al*(26), 2009	Not Reported	Not Reported	Not Reported	Yes	Yes	No	Yes	-
Huang *et al*(10), 2005	Yes	Not Reported	Yes	Yes	Yes	Yes	Yes	Yes
Polidori *et al*(27), 2005	Yes	Not Reported	Not Reported	No	No	No	Yes	-
Van Hoydonck *et al*(28), 2004	Not Reported	Not Reported	No	Yes	Yes	No	Yes	No
Vrca *et al*(29), 2004	Not Reported	Not Reported	Not Reported	No	No	No	No	-
Yanai *et al*(30), 2004	Not Reported	Not Reported	No	Yes	No	No	No	-
Nieman *et al*(31), 2002	Not Reported	Not Reported	Not Reported	Yes	Yes	No	Yes	No
Martinez-Abundis *et al*(32), 2001	Not Reported	Not Reported	No	Yes	Yes	No	No	-
Hamilton *et al*(33), 2000	Not Reported	Not Reported	No	Yes	Yes	No	No	No
Rokitzki *et al*(34), 1994	Not Reported	Not Reported	Not Reported	Yes	Yes	No	No	No
Maxwell *et al*(35), 1993	Not Reported	Not Reported	No	No	No	No	No	-
Kyllastinen *et al*(36), 1990	Yes	Not Reported	No	Yes	Yes	No	No	No

Summary of design characteristics reported by trials included in our meta-analysis. Trials that reported no loss to follow up did not receive a “yes” or “no” designation.