Discovery is seeing what everybody else has seen, and thinking what nobody else has thought.
- Albert Szent-Gyorgi, discovered vitamin C in 1928

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Part V

Do vitamin C supplements induce kidney stones?

By Bill Sardi

Do vitamin C supplements induce kidney stones? The National Library of Medicine lists 64 reports concerning this topic. Some reports say no, others say yes, there is an increased risk for kidney stones with high-dose vitamin C. Recently, Linda Massey, a researcher at Washington State University, suggested 500 milligrams of vitamin C/day is the maximum *"that would be considered safe"* in regards to vitamin C and kidney stones. The Council for Responsible Nutrition then replied to Massey's letter and concludes any alleged risk for kidney stones from vitamin C consumption would only be in a small group of men. Steve Hickey, PhD, of Manchester, England, then responded to Massey's claim with a letter, which is printed below.

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Letters to the Editor

Safety of vitamin C

Linda Massey
Department of Human Nutrition and Dietetics · Washington State University

Dear Sir:

Hathcock et al (1) cite the 2000 Food and Nutrition Board statement on the lack of evidence that vitamin C increases oxalate formation (2) as confirmation that vitamin C intakes of 2000 mg/d do not increase the risk of kidney stone formation. However, research published since that panel concluded their literature review suggests otherwise. Chai et al (3) reported in 2004 that 2000 mg ascorbic acid (AA)/d increased both oxalate synthesis and absorption. Additional analysis of the responses of 29 calcium stone formers (SFs) and 19 non-stone formers (NSFs) found that consumption of 1000 mg AA twice daily resulted in 2 distinctly different oxaluric responses. Forty percent of the subjects, including both SFs and NSFs, experienced increases of 10% in 24-h urinary oxalate (4). The other 60% of the subjects had essentially no oxaluric response. Examination of individual responses from 3 published studies in which supplements of 1000–2000 mg AA/d were given (5-7) showed that 7 of the 19 total subjects (38%) had similar increases in urinary oxalate of >10%. Genetic susceptibility in the study participants probably accounted for most of the discordance in response to AA that was previously reported; small sample sizes and the lack of a dietary control probably contributed as well.

Three other studies with less rigorous designs also came to similar conclusions about the risk of kidney stone formation related to AA supplements. Baxmann et al (8) reported an increase in urinary oxalate of 61% in SFs after 1000 mg AA/d, 41%

in SFs after 2000 mg AA/d, and 56% in NSFs after 2000 mg AA/d. Chalmers et al (9) studied 17 SFs and 11 NSFs who consumed 2000 mg AA/d. They found that, compared with the NSFs, the SFs excreted 12% more oxalate with no AA supplementation and 22% more with AA supplementation. Traxer et al (10) conducted a similar study with 12 SFs and 12 NSFs who ingested 1000 mg AA with each morning and evening meal. Urinary oxalate excretion increased 33% (10 mg oxalate/d) in the SFs and 20% (6 mg oxalate/d) in the NSFs. As did we, Traxer et al (10) identified responders in both the SFs and the NSFs. Baxmann et al (8) identified increases in the Tiselius Risk Index and in urinary oxalate in 47 SFs and 20 NSFs who were randomly assigned to either 1000 mg AA/d (500 mg ingested twice/d) or 2000 mg AA/d (1000 mg ingested twice/d) for 3 d. Before day 1 and on day 3, a 24-h urine sample was obtained. The increase in the Tiselius Risk Index with 1000 mg AA/d (0.51) was similar to that with 2000 mg AA/d (0.56), which suggests that lower doses of AA may also be lithogenic in genetically susceptible individuals. Because hyperoxaluric responses have been shown at doses of both 1000 and 2000 mg AA/d, current evidence suggests that 500 mg AA/d is the maximum dose that can be considered safe, at least until additional testing at lower doses is done.

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Letters to the editor

Reply to L Massey

John N Hathcock, Balz Frei, Stephen Lawson and Carol Johnston

Council for Responsible Nutrition
Washington, DC 20036

Dear Sir:

Massey cites 5 studies (one in press) on the relation between urinary oxalate and vitamin C published since the Food and Nutrition Board (FNB) revised the dietary reference intakes for vitamin C in 2000 (1). These studies reported that supplemental vitamin C (1000–2000 mg/d) was associated with increases in urinary oxalate ranging from 10% to 61%. Several studies identified 2 subpopulations in oxaluric response to vitamin C among stone formers and non-stone formers in the small groups examined. About 40% of the subjects showed an increase in urinary oxalate of 10%. The FNB reviewed earlier studies, which also found increases in urinary oxalate associated with supplemental vitamin C.

Although the increase in oxalate observed in some studies may be attributable to the ex vivo conversion of urinary vitamin C to its metabolic product oxalic acid (2), supplemental vitamin C may indeed increase the urinary excretion of oxalic acid, especially in genetically susceptible individuals. Several large-scale, long-term prospective studies have investigated the clinical significance of these findings. In the Health Professionals Follow-Up Study (HPFS), Curhan et al (3) followed 45 251 men with no history of kidney stones for 6 y and found a lower age-adjusted relative risk (RR) of kidney stone formation of 0.78 (*P* for trend = 0.11) in the cohort that consumed 1500 mg vitamin C/d than in the cohort whose intake was <250 mg vitamin C/d. In the Nurses' Health Study, a prospective study of 85 557 women followed for 14 y, Curhan et al (4) found no statistically significant difference in the age-adjusted RR for stone formation between subjects with vitamin C intakes of 1500 and subjects with vitamin C intakes of <250 mg/d. However, in a 14-y follow-up of 45 619 men from the HPFS, in which the referent intake of vitamin C was lowered, Taylor et al (5) found that the multivariate RR for stone formation was 1.41 (*P* for trend = 0.01) in men whose total intake (dietary and supplemental) of vitamin C was 1000 mg/d compared with men whose total intake was <90 mg/d (the recommended dietary allowance). The difference in age-adjusted RR between these quintiles was not statistically significant. The multivariate RR for stone

formation between men with a total intake <90 mg vitamin C/d and men with a total intake <250 mg vitamin C/d was 1.22. The increased risk associated with vitamin C emerged only after dietary potassium, which was inversely associated with stone formation, was included in the multivariate analysis. The multivariate RR for stone formation in men who consumed 1000 mg supplemental vitamin C/d was 1.16 (*P* for trend = 0.01).

Routine restriction of vitamin C in the general population to prevent renal calculi is unwarranted based on the results of the few prospective studies that have been conducted (3–5). According to the recent follow-up to the HPFS (5), which is the only prospective study that has shown a positive association between total vitamin C intake and nephrolithiasis, prophylaxis in men would require restriction of vitamin C to intakes that are less than the recommended dietary allowance and may adversely affect health. As indicated above, the HPFS follow-up found a modestly increased risk at an intake of 90–249 mg vitamin C/d, which would easily be provided by following the recommendation of the US Department of Agriculture to consume 9 daily servings of fruit and vegetables to reduce the risk of cardiovascular disease, certain cancers, type 2 diabetes, and obesity. The observed risk associated with vitamin C in the HPFS follow-up largely occurred at dietary intakes, and high supplemental doses only slightly increased the risk. The Tolerable Upper Intake Level (2000 mg/d) is the highest intake of vitamin C that poses no risk of serious adverse effects for almost all individuals in the general population. The FNB concluded that restriction of vitamin C is warranted in certain subpopulations, such as those who have a glucose-6-phosphate dehydrogenase deficiency or renal disease. The limited data support the restriction of supplemental vitamin C to prevent stone formation only in men who have a propensity for oxalate nephrolithiasis.

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Subject: Stones from Vitamin C?
Date: 8/21/2005

Dear Dr Massey,

I am receiving emails about your recent publications in which you suggest that vitamin C causes oxalate stones. I am currently finding it necessary to refute your suggestions, which appear to be based on an indirect extrapolation from increased oxalate production/excretion.

Could you please provide me with any direct evidence of stone formation from ascorbic acid consumption? I am not aware that such evidence exists.

You appear to be relying on the Tiselius Risk Index for your evaluation. Are you aware that this risk index does NOT include the ascorbate molecule? Can you please explain how the presence of ascorbate ions does not reduce the risk of oxalate stone formation? What happens to the computed risk index (TRI) when ascorbate is included in the calculation? (Look at the derivation and form of the TRI equation. Surely, ascorbate should be included in this equation when the levels are high. For example, the results from Schwille et al, referenced in your paper, agree with this and appear to contradict your extrapolation?)

To put the position simply: ascorbate binds calcium. When there is a large amount of ascorbate, it will compete with oxalate for calcium. To suggest that, in the presence of a large increase in ascorbate, a small increase in oxalate will preferentially bind calcium requires hard evidence.

As far as I am aware, the available evidence shows no risk of stone formation from high intakes of ascorbate. Your paper did not include reference to the direct studies of stone incidence. Indeed the direct evidence refutes the suggestion.

With the greatest of respect, I find your suggestion that vitamin C causes stones unconvincing.

Dr Steve Hickey