Ascorbate Increases Human Oxaluria and Kidney Stone Risk¹,²

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ABSTRACT  Currently, the recommended upper limit for ascorbic acid (AA) intake is 2000 mg/d. However, because AA is endogenously converted to oxalate and appears to increase the absorption of dietary oxalate, supplementation may increase the risk of kidney stones. The effect of AA supplementation on urinary oxalate was studied in a randomized, crossover, controlled design in which subjects consumed a controlled diet in a university metabolic unit. Stoneformers (n = 29; SF) and age- and gender-matched non-stoneformers (n = 19; NSF) consumed 1000 mg AA twice each day with each morning and evening meal for 6 d (treatment A), and no AA for 6 d (treatment N) in random order. After 5 d of adaptation to a low-oxalate diet, participants lived for 24 h in a metabolic unit, during which they were given 136 mg oxalate, including 18 mg ¹³C₂ oxalic acid, 2 h before breakfast; they then consumed a controlled very low-oxalate diet for 24 h. Of the 48 participants, 19 (12 stoneformers, 7 non-stoneformers) were identified as responders, defined by an increase in 24-h total oxalate excretion > 10% after treatment A compared with N. Responders had a greater 24-h Tiselius Risk Index (TRI) with AA supplementation (1.10 ± 0.66 treatment A vs. 0.76 ± 0.42 treatment N) because of a 31% increase in the percentage of oxalate absorption (10.5 ± 3.2% treatment A vs. 8.0 ± 2.4% treatment N) and a 39% increase in endogenous oxalate synthesis with treatment A than during treatment N (544 ± 131 A vs. 391 ± 71 μmol/d N). The 1000 mg AA twice each day increased urinary oxalate and TRI for calcium oxalate kidney stones in 40% of participants, both stoneformers and non-stoneformers.  J. Nutr. 135: 1673–1677, 2005.

KEY WORDS:  vitamin C  ascorbic acid  hyperoxaluria  nephrolithiasis  oxalate

The current recommended upper limit for ascorbic acid (AA)³ is 2000 mg/d (1). A small percentage (1.5%) of ingested AA is converted in vivo to oxalate (2), which is excreted without further metabolism quantitatively in the urine over 24 h. It is uncertain whether amounts greater than typical intakes from foods increase the risk for kidney stones (1). AA supplementation is widely practiced in the United States; 12.4% of the U.S. adult population (3) and 12–14% of 50–60-year-old stable for 3 mo and was the same for both study treatments. Six of the 8 participants who completed the study were responders, defined by an increase in 24-h total oxalate excretion > 10% after treatment A compared with N. Responders had a greater 24-h Tiselius Risk Index (TRI) with AA supplementation (1.10 ± 0.66 treatment A vs. 0.76 ± 0.42 treatment N) because of a 31% increase in the percentage of oxalate absorption (10.5 ± 3.2% treatment A vs. 8.0 ± 2.4% treatment N) and a 39% increase in endogenous oxalate synthesis with treatment A than during treatment N (544 ± 131 A vs. 391 ± 71 μmol/d N). The 1000 mg AA twice each day increased urinary oxalate and TRI for calcium oxalate kidney stones in 40% of participants, both stoneformers and non-stoneformers. Subjects and Methods

Subjects. Individuals (n = 29) with a self-reported history of calcium oxalate stones and 20 age- and gender-matched non-stoneformers were recruited from participants in previous nephrolithiasis studies, their families, and acquaintances (Table 1). All participants were at least 18 y old and without complicating medical conditions (renal, urinary tract, intestinal, thyroid, parathyroid, skeletal, or nutritional disorders; uncontrolled hypertension or diabetes), or medication or supplement use that affect calcium or oxalate metabolism. Nonprescription aspirin, antacid, and laxative use were prohibited, but prescription medications were allowed if the dosage had been stable for 3 mo and was the same for both study treatments. Six of the 19 responders were stoneformers (SF) and 10 were non-stoneformers (NSF) administered AA (treatment A; 10.7 ± 2.7% compared with 8.5 ± 2.6%). If AA supplements are taken, the increased urinary oxalate may increase the risk of calcium oxalate kidney stones.

Contradictory results from previous research evaluating the effect of AA supplementation on urinary oxalate were attributed primarily to methodology that allowed in vitro degradation of urinary AA to oxalate (6). However, early case studies suggested that genetic differences contributed to the variable response to AA supplements (7). Small sample sizes and insufficient dietary control have limited the identification of a subset of individuals that respond to AA supplementation with increased urinary oxalate.

This study examined the effect of a divided dose of 2000 mg/d AA on oxalate excretion, absorption, and endogenous synthesis, as well as the Tiselius Risk Index (TRI) for calcium oxalate precipitability. The study design included strict control of dietary AA and oxalate. Both SF and NSF were studied for ascorbate-induced changes in risk; subjects were also characterized as responders or nonresponders.
29 SF and 3 of the 20 NSF habitually consumed ≥500 mg of AA supplements several times each week; they were asked to discontinue AA at least 1 wk before study participation because previous studies showed that 3 d abstinence was sufficient to eliminate the effects of AA on urinary ascorbate and oxalate (8). Calcium supplements were restricted to ≤100 mg/d, and other habitual nutrient supplements were limited to ≤100% of the Recommended Dietary Allowance during the study. All participants were screened for normal fasting urinary calcium:creatinine ratio and normal calcium absorption determined by 4-h urinary calcium excretion after a 1000-mg oral calcium load [1 package Carnation French Vanilla Instant Breakfast (Nestle Food Company), 240 mL 2% low-fat milk, and 22 mL calcium gluconate syrup (Calciquid, Breckenridge Pharmaceutical)]. Lean body mass was determined by air displacement plethysmography (Bod Pod Body Composition System, Life Measurement) or bioelectrical impedance (Model BES 200Z, Bioelectrical Sciences) and used for the determination of completeness of daily urinary collections by comparing expected creatinine with actual creatinine. Procedures were approved by the Human Subjects Review Committee at Washington State University and written informed consent was obtained from participants.

Metabolic study design. A randomized crossover design was employed, with each volunteer participating in two 6-d experimental periods. Figure 1 depicts the experimental design. During one experimental period (treatment A), they consumed 1000 mg AA supplement (Nature Made Nutritional Products; no detectible oxalate by direct assay) with the morning and evening meals during adaptation, and with the oxalate load at 0700 h and the evening meal at 1800 h in the metabolic unit. The alternate 6-d period (treatment N) was exactly the same but without AA supplementation. Because the oxaluric effect of AA reaches a plateau after 3 d (8), and urinary composition stabilizes by d 4 and 5 of consuming a controlled diet (9,10), 5 d of adaptation were considered sufficient. Each 6-d experimental period included 2 d of free-living adaptation with consumption of a self-selected, self-recorded low-oxalate diet (excluding the 10 highest known oxalate-containing foods: spinach, rhubarb, beets, tea, chocolate, nuts, wheat bran, berries, parsley, beans, and other legumes), followed by an additional 3 d free-living adaptation to a controlled low-oxalate diet (37–43 mg oxalate/d provided by the investigators, and concluded with 24 h in a metabolic unit consuming a controlled low-oxalate diet (6–7 mg oxalate/d) (Table 2).

Urinary AA levels were determined to verify AA supplement compliance. In the metabolic unit, a staff member observed meals and confirmed food, oxalate load, and AA supplement consumption by participants. All foods were purchased from the same suppliers and lots, and were provided to participants in weighed portions. The oxalate content of all plant foods was measured directly by oxalate oxidase assay (Trinity Biotech) after acid extraction (11). Caffeinated or decaffeinated coffee was provided in regulated quantities because the oxalate content was determined to be low, and caffeine does not affect oxalate excretion (12). Very low oxalate varieties of herbal tea, but not regular tea, were also allowed in controlled amounts. Diets were designed at both 8784 and 10,458 kJ/d to better accommodate individual energy requirements. The nutrient composition of study diets was determined by computerized diet analysis using Nutritionist Pro software (version 1.3, 2002, N-Squared Computing).

At 0700 h on the morning of the metabolic unit stay, after a 12-h fast, participants were given a 136-mg oxalate load [18 mg $^{13}$C$_2$-oxalic acid (Cambridge Isotope Laboratories) plus 118 mg nonlabeled oxalate contained in a gel capsule] with 175 g of unsweetened 100% of the Recommended Dietary Allowance. All participants consumed the same amount of food during the 2 treatments, whichever was most appropriate for their energy expenditure.

### TABLE 1
Participant characteristics at screening

<table>
<thead>
<tr>
<th></th>
<th>Stoneformers</th>
<th>Non-stoneformers</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>Gender</td>
<td>19 M, 10 F</td>
<td>8 M, 11 F</td>
</tr>
<tr>
<td>Age, y</td>
<td>49.8 ± 14</td>
<td>50.8 ± 14.3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>88.8 ± 17.2</td>
<td>79.4 ± 16.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.5 ± 5.7</td>
<td>29.8 ± 6.7</td>
</tr>
<tr>
<td>Urinary calcium, mg/d</td>
<td>217 ± 118</td>
<td>164 ± 78</td>
</tr>
<tr>
<td>Urinary oxalate, mg/d</td>
<td>35 ± 8</td>
<td>33 ± 12</td>
</tr>
<tr>
<td>NRI</td>
<td>1.3 ± 0.6</td>
<td>0.9 ± 0.5</td>
</tr>
</tbody>
</table>

1 Values are means ± SD.

### TABLE 2
Composition of daily study diets at 2 energy levels

<table>
<thead>
<tr>
<th></th>
<th>Adaptation diet</th>
<th>Metabolic unit diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 20</td>
<td>n = 28</td>
</tr>
<tr>
<td></td>
<td>n = 20</td>
<td>n = 28</td>
</tr>
<tr>
<td>Energy, kJ</td>
<td>8837</td>
<td>10,460</td>
</tr>
<tr>
<td>Protein, g</td>
<td>60</td>
<td>67</td>
</tr>
<tr>
<td>Ascorbic acid, mg</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Calcium, mg</td>
<td>740</td>
<td>795</td>
</tr>
<tr>
<td>Magnesium, mg</td>
<td>124</td>
<td>148</td>
</tr>
<tr>
<td>Oxalate, mg</td>
<td>37</td>
<td>43</td>
</tr>
<tr>
<td>Sodium, mg</td>
<td>2969</td>
<td>3315</td>
</tr>
</tbody>
</table>

1 All participants consumed the same amount of food during the 2 treatments, whichever was most appropriate for their energy expenditure.
applesauce and 240 mL of deionized water. Meals in the metabolic unit were served at 0900, 1300, and 1800 h. The low-oxalate breakfast consisted of a plain bagel, grape jam, cream cheese, yogurt, and apple juice. Liberal deionized water intake was encouraged to promote a 24-h urine volume of ~2.5 L.

During the 5-d adaptation, urine was collected in calibrated jugs containing 100 mL of 3 mmol/L hydrochloric acid over 24-h periods. In the metabolic unit, urine was collected and pooled at 2-h intervals for 8 h after the labeled oxalate load, then at two 3-h intervals, and finally after 10 h overnight for a total of 24 h. All urine collected in the metabolic unit was immediately acidified to pH < 2.0 by the addition of 20 mL of 3 mmol/L HCl at each collection interval to prevent in vitro AA degradation to oxalate. Urine volumes were recorded, urine was filtered (#2 paper, Whatman) and aliquots were quickly frozen at −20°C until assay.

Biochemical analyses. Urine composition was determined as follows: AA by the dinitrophenylhydrazine method (13); 13C2-oxalic acid by GC-MS (Metabolic Solutions); oxalate, citrate, and creatinine by the microplate colorimetric oxalate oxidase (Sigma-Aldrich), citrate lyase (14), and picric acid (15) methods, respectively, using a Sunrise light absorbency microplate reader (Tecan); and calcium, magnesium, and sodium by inductively coupled plasma optical emission spectrophotography (Optima 2000 DV, Perkin Elmer Instruments). Oxalate absorption from the administered oxalate loads was determined by recovery of administered 13C2-oxalic acid as described previously (3). Endogenous oxalate synthesis for urine samples collected postoxalate loading was approximated by subtracting the oxalate absorbed (recovered 13C-oxalic acid/administered 13C2-oxalic acid) × oxalate ingested at 0700 h (via the oxalate load) from the total urinary oxalate excretion over the specified time period. TRI for 24-h urine collections was calculated using the formula by Tiselius (16), which relates the excretion in mmol of 4 urinary components and urine volume in L as follows:

\[
\text{AP(CaOx)} = 1.9 \times [\text{Calcium}]^{0.84} \times [\text{Oxalate}] \times [\text{Magnesium}]^{0.12} \\
\times [\text{Citrate}]^{-0.25} \times [\text{Volume}]^{-1.03}
\]

The TRI is a measure of calcium oxalate saturation, which predicts the risk of its precipitation.

Statistical analyses. Statistical significance of differences between treatment A and treatment N, SF and NSF, and between responders (participants with higher oxalate excretion with AA) and nonresponders, was determined by paired or 2-sample Student’s t test using Excel software (version 10.3207.3131, 2002, Microsoft). Repeated measures ANOVA was conducted using Number Cruncher (2001). Differences were considered significant when \( P \leq 0.05 \). Values are presented as means ± SD.

RESULTS

All 49 volunteers completed the metabolic study. Data from 1 NSF participant was dropped from the analysis due to emesis after the combined oxalate and AA load, leaving 29 SF and 19 NSF (Table 1) for the final analyses. Study diets (Table 2) were consumed per protocol as validated by sodium excretion for free-living adaptation days. Sodium excretion was 102 ± 6% of calculated dietary intake during adaptation days and metabolic unit study, and did not differ between treatments A and N (data not shown). Urinary creatinine excretions during treatments A and N were 105 and 109% (during adaptation), and 102 and 103% (during the metabolic study) of expected urinary creatinine based on lean body mass, supporting the completeness of the urine collections. Urine volumes did not differ between treatments A and N, between SF and NSF, or between responders and nonresponders during adaptation or the metabolic study.

Ascorbate excretion decreased progressively over adaptation d 1, 3, and 5 for subjects administered treatment N, and progressively increased over adaptation d 1, 3, and 5 for those administered treatment A for all subjects (data not shown). Urinary ascorbate did not differ between SF and NSF, or between responders and nonresponders administered the same treatment. Oxalate excretion decreased progressively over adaptation d 3–5 in subjects administered both treatments, and similarly for both SF and NSF (data not shown). Dietary oxalate was only 40 mg/d during adaptation, less than typical intakes of 150 mg/d (17).

In SF, but not NSF, 24-h urinary oxalate was higher during treatment A compared with treatment N (Table 3). When SF were categorized as clinically hyperoxaluric (mean total oxalate ≥ 450 μmol for the 2 screening days) or normoxaluric, the hyperoxaluric SF had significantly higher oxalate absorption and endogenous synthesis than normoxaluric individuals during treatment N (Table 4). However, they were nonresponsive to the effects of AA on endogenous synthesis and absorption, in that ascorbate-induced increases in these values were observed only in the normoxaluric group.

Nineteen of 48 participants were identified as responders, defined by increased 24-h oxalate excretion >10% after AA compared with N administration during the metabolic unit study; 12 responders were SF and 7 were NSF. Responders were slightly older than nonresponders (56 ± 13 compared to 47 ± 13 y, \( P = 0.02 \)). Gender was not related to oxaluric response to AA. Responders had higher 24-h TRI with treatment A compared with N (Table 5). The higher total oxalate excretion in responders with AA supplementation could be attributed to a combination of higher oxalate absorption and higher endogenous oxalate (Table 5).

### TABLE 3

Biochemistry of 24-h urine and the risk index of stoneformers and non-stoneformers when they were (A) or were not (N) administered AA during the metabolic unit study

<table>
<thead>
<tr>
<th></th>
<th>Stoneformers (n = 29)</th>
<th>Non-stoneformers (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>Volume, L</td>
<td>2.18 ± 0.66</td>
<td>2.13 ± 0.60</td>
</tr>
<tr>
<td>Ca, mmol</td>
<td>3.82 ± 1.63</td>
<td>3.79 ± 1.80</td>
</tr>
<tr>
<td>Citrate, mmol</td>
<td>5.85 ± 2.26</td>
<td>5.60 ± 2.23</td>
</tr>
<tr>
<td>Mg, mmol</td>
<td>3.81 ± 1.15</td>
<td>3.75 ± 1.21</td>
</tr>
<tr>
<td>Oxalate, μmol</td>
<td>566 ± 103†</td>
<td>659 ± 139†</td>
</tr>
<tr>
<td>TRI</td>
<td>0.94 ± 0.45</td>
<td>1.10 ± 0.60</td>
</tr>
</tbody>
</table>

† Values are means ± SD. * Different from stoneformers administered the same treatment; † different from those not administered AA within each group.
reported. for most of the discordance in response to AA previously
Genetic susceptibility in study participants probably accounts
supplementation, SF may not necessarily be responders to AA.
responders would be at increased risk to form stones with AA
identified responders in both SF and NSF. Although
20% (6 mg oxalate/d) in NSF. As in our study, Traxer et al.
oxalate excretion increased 33% (10 mg oxalate/d) in SF and
1000 mg AA with each morning and evening meal. Urinary
NSF without AA and 22% more with AA. Traxer et al. (23)
2000 mg AA. They found SF excreted 12% more oxalate than
Chalmers et al. (22) studied 17 SF and 11 NSF consuming
urinary oxalate increase in SF after 1000 mg AA/d, 41% after
AA supplementation. Baxmann et al. (21) reported a 61%
demonstrating mean increases in total oxalate excretion with
AA supplementation. Baxmann et al. (21) reported a 61%
urinary oxalate increase in SF after 1000 mg AA/d, 41% after
2000 mg AA/d in SF, and 56% after 2000 mg AA/d in NSF.
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2000 mg AA. They found SF excreted 12% more oxalate than
NSF without AA and 22% more with AA. Traxer et al. (23)
conducted a similar study with 12 SF and 12 NSF ingesting
1000 mg AA with each morning and evening meal. Urinary
oxalate excretion increased 33% (10 mg oxalate/d) in SF and
20% (6 mg oxalate/d) in NSF. As in our study, Traxer et al.
(23) identified responders in both SF and NSF. Although
responders would be at increased risk to form stones with AA
supplementation, SF may not necessarily be responders to AA.
Genetic susceptibility in study participants probably accounts
for most of the discordance in response to AA previously
reported.

RESULTS

Consumption of 1000 mg AA twice each day resulted in 2
distinctly different oxaluric responses: 40% of individuals,
including both SF and NSF, had increases in 24-h urinary
oxalate ≳ 10%. The other 60% had essentially no oxaluric
response. It is not known what portion of a larger population
would have an AA-induced increase in urinary oxalate; the
actual proportion could be more or less than 40% when careful
sampling is done. In an early report, Briggs (7) found only 3 of
67 individuals tested had an increase in urinary oxalate.
Examination of individual responses from 3 published studies
in which 1000–200 mg AA supplements were given (18–20)
showed that 7 of the total 19 subjects (38%) had a >10%
increase in urinary oxalate, a proportion similar to ours.
Results of this study concur with those of previous studies in
demonstrating mean increases in total oxalate excretion with
AA supplementation. Baxmann et al. (21) reported a 61%
urinary oxalate increase in SF after 1000 mg AA/d, 41% after
2000 mg AA/d in SF, and 56% after 2000 mg AA/d in NSF.
Chalmers et al. (22) studied 17 SF and 11 NSF consuming
2000 mg AA. They found SF excreted 12% more oxalate than
NSF without AA and 22% more with AA. Traxer et al. (23)
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1000 mg AA with each morning and evening meal. Urinary
oxalate excretion increased 33% (10 mg oxalate/d) in SF and
20% (6 mg oxalate/d) in NSF. As in our study, Traxer et al.
(23) identified responders in both SF and NSF. Although
responders would be at increased risk to form stones with AA
supplementation, SF may not necessarily be responders to AA.
Genetic susceptibility in study participants probably accounts
for most of the discordance in response to AA previously
reported.

In our study, 79% of the AA-induced increase in total
urinary oxalate in responders was attributed to increased endo-
genous synthesis, and 21% to increased oxalate absorption.
Hatch (24) postulated the existence of 2 kinds of abnor-
malities leading to increased risk of kidney stones, i.e., increased
endothelial increase and increased oxalate absorp-
tion. In our study population, both seemed to occur together in
many individuals.

Of interest was the finding that normooxaluric SF, but not
hyperoxaluric SF, exhibited increases in endogenous oxalate
synthesis and oxalate absorption in association with AA sup-
plementation. This was an unexpected finding because of the
supposition that stoneformers with higher urinary oxalate lev-
els consuming their usual diets would be more sensitive to
AA-induced increases in urinary oxalate. However, a partial
explanation may relate to the fact that by virtue of being
normooxaluric, there is more potential for a physiologic effect
of AA on endogenous oxalate synthesis and/or oxalate absorp-
tion to be clinically observed as an increase in oxaluria.

If endogenous synthesis of oxalate from AA is ≲1.5% of
supplemental loads (2), increased urinary oxalate from endog-
ogenous synthesis from two 1000-mg doses would be 30 mg of
341 μmol. The actual mean increase in total oxalate observed
was 72 μmol for the study group as a whole, 194 μmol in
responders and −9 μmol in nonresponders. The increase is
likely to be limited by saturation of AA absorption and/or
tissue uptake at doses lower than the 2000 mg/d used in this
study. This assertion is supported by Baxmann et al. (21) who
reported that the increase in urinary oxalate was no greater
with 2000 than with 1000 mg/d in SF. If no more total AA was
absorbed from 2000 than from 1000 mg/d, the 194 μmol
response in responders is close to the 170 μmol increase

### TABLE 4
Biochemistry of 24-h urine of hyperoxaluric and normooxaluric stoneformers when they were (A) or were not (N) administered AA during the metabolic unit study

<table>
<thead>
<tr>
<th></th>
<th>Hyperoxaluric (n = 8)</th>
<th>Normoxaluric (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>Total oxalate, μmol</td>
<td>643 ± 90</td>
<td>669 ± 125</td>
</tr>
<tr>
<td>Endogenous oxalate, μmol</td>
<td>43 ± 5</td>
<td>44 ± 10</td>
</tr>
<tr>
<td>Oxalate absorption, %</td>
<td>10.9 ± 3.1</td>
<td>11.2 ± 3.3</td>
</tr>
<tr>
<td>TRI</td>
<td>1.11 ± 0.54</td>
<td>1.21 ± 0.90</td>
</tr>
</tbody>
</table>

<sup>1</sup> Values are means ± SD. * Different from hyperoxaluric stoneformers administered the same treatment; † different from those not administered AA within each group.

### TABLE 5
Biochemistry of 24-h urine of responders and nonresponders when they were (A) or were not (N) administered AA during the metabolic unit study

<table>
<thead>
<tr>
<th></th>
<th>Responders (n = 19)</th>
<th>Nonresponders (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>Total oxalate, μmol</td>
<td>513 ± 97</td>
<td>707 ± 165&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Endogenous oxalate, μmol</td>
<td>391 ± 71</td>
<td>544 ± 131&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Oxalate absorption, %</td>
<td>8.0 ± 2.4</td>
<td>10.5 ± 3.2&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>TRI</td>
<td>0.76 ± 0.42</td>
<td>1.11 ± 0.67&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> Values are means ± SD. * Different from those not administered AA within each group; † different from the responder administered the same treatment.
predicted from a 1.5% conversion rate. The remaining increase in urinary oxalate, 24 μmol, would be from increased absorption. The oxaluric effect of 500 mg AA/d could be roughly extrapolated from previously reported data from 6 individuals to be ~40% less than that from a 1000-mg dose (25). Because the health benefits of AA supplementation in doses > 500 mg/d are not substantiated (25), 500 mg/d may be considered the maximum dose for individuals at risk for calcium oxalate kidney stones until further research on lower doses is completed.

The increase in TRI associated with AA supplementation in this study was mediated primarily through increased urinary oxalate excretion, with no effect on urinary calcium, magnesium, or citrate. Baxmann et al. (21) identified increases in TRI and urinary oxalate in 47 SF and 20 NSF randomly assigned to either 1000 mg AA (500 mg ingested 2 times/d) or 2000 mg AA (1000 mg ingested 2 times/d) for 3 d. Before d 1 and on d 3, a 24-h urine sample was obtained. The increase in TRI with administration of 1000 mg AA (0.51) was similar to that for 2000 mg AA (0.56), suggesting that lower doses of AA than used in the present study may also be lithogenic.

Although urinary oxalate was shown to increase with AA supplementation, a direct association of AA supplementation with stone incidence is not clear. Taylor et al. (26) recently reported that ≥1000 mg/d of supplemental vitamin C was associated with a 16% increase in the 14-y incidence of kidney stones in the Health Professionals Follow-up Study. In contrast, an earlier report on the women in the Nurses’ Health Study found no association (27). Because supplementation is often sporadic (3), supplementation data collected at 1 dietary survey may not reflect the intake during the whole time the individuals were followed for kidney stone occurrence. Also, our data show that only 40% of our population had an oxaluric response, which would also obscure the risk in a subset of genetically susceptible people. In our study, 21% of SF and 16% of NSF reported taking AA supplements before participation. If only 12–20% of the genetically susceptible 40% were taking supplements, it would be difficult to see an association in an epidemiologic study.

In summary, because an individual’s response to AA supplementation is not predictable, high-dose AA supplementation should be considered cautiously, even for those individuals without a history of stone formation.

LITERATURE CITED