Vitamin C with Metabolites Reduce Oxalate Levels Compared to Ascorbic Acid: A Preliminary and Novel Clinical Urologic Finding

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The incidence and prevalence of kidney stones are notable and are projected to increase over the next decade. Risk factors for kidney stones abound, but a prominent risk factor is hyperoxaluria, which has numerous etiologies, including vitamin C (ascorbic acid) dietary supplement intake. This randomized, double-blind, crossover study examined the effects of two different vitamin C formulations and found that vitamin C with metabolites (Ester-C®) significantly reduced urine oxalate levels compared to ascorbic acid. This is a potential novel finding that requires further clinical evaluation.

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Key Words: Vitamin C, ascorbic acid, Ester-C®, hyperoxaluria, oxalate, nephrolithiasis, kidney stones.

The financial impact of kidney stones on the U.S. health care system alone is approximately $2 billion per year (Clark, Thompson, & Optenberg 1995; Pearle, Calhoun, & Curhan, 2005). The cost, frequency, and recurrence rates highlight the demand for ongoing preventive research and education. The estimated economic savings in preventing kidney stones has been calculated to be $2500 dollars per patient per year (Parks & Coe, 1996).

Four types of kidney stones primarily diagnosed are calcium (calcium oxalate or calcium phosphate), struvite (infection), uric acid, and cystine (Hall, 2002). Approximately 75% to 80% of kidney stones diagnosed consist predominantly of calcium oxalate (Worcester & Coe, 2008). These solutes may precipitate from supersaturated urine and form a stone depending on the risk factors harbored by each individual. Risk factors for calcium stones

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Introduction
The incidence and prevalence of urolithiasis continue to increase. One risk factor, hyperoxaluria, is related to intake of vitamin C supplements. High vitamin C intake (1000 to 2000 mg/day) correlates with higher urinary oxalate levels because a primary byproduct of ascorbic acid catabolism is oxalate. A patented form of vitamin C known as vitamin C with metabolites (Ester-C™), contains several metabolites and is bound to calcium to create a non-acidic formulation.

Objective
To determine if intake of vitamin C with metabolites (Ester-C) has the capacity to reduce urinary oxalate levels when compared to vitamin C (ascorbic acid) in previously non-stone-forming subjects.

Method
A randomized, double-blind, crossover trial of vitamin C with metabolites was compared to ascorbic acid in 50 healthy adults. Subjects (n = 25 in each arm) on a controlled diet ingested 1000 mg/day for 5 days and 2000 mg/day for an additional 5 days, and urine oxalate was measured. After a 7-day washout, participants repeated the same protocol (crossed over) with the alternate form of vitamin C.

Results
There was a significant change in 24-hour urinary oxalate levels among subjects when comparing the two treatments (p = 0.04), with a decrease of urine oxalate levels in the vitamin C with metabolites group and an increase in urine oxalate in the ascorbic acid group. Approximately 25% more subjects experienced a reduction in 24-hour oxalate (59% to 34%) and oxalate concentration (72% to 46%) over the 10-day period when taking vitamin C with metabolites compared to ascorbic acid, despite higher plasma, white blood cell, and urine vitamin C levels in the vitamin C with metabolites group.

Conclusions
Due to the crossover design, it is plausible that vitamin C with metabolites reduces urinary oxalate levels compared to ascorbic acid, which is a novel finding that requires further clinical evaluation.

Level of Evidence – II
(Melnyk & Fineout-Overholt, 2005)

include low fluid intake, low urinary citrate, high salt or protein intake, low calcium intake, high urinary calcium, and higher levels of urinary oxalate (hyperoxaluria) (Hall, 2002; Moe, 2006).

An increased concentration of oxalate can be due to numerous factors, such as endogenous production from the liver (a primary source), increased production from a rare congenital disorder, increased oxalate absorption from inflammatory bowel disease and short bowel syndrome (which interferes with the binding of dietary oxalate to calcium that is already attached to fat molecules, and thus, oxalate is absorbed in the colon), high dietary oxalate intake from foods (such as chocolate, cocoa, draft beer, nuts, rhubarb, and spinach), and a low dietary and/or supplemental calcium intake (allowing for less binding of oxalate). Another often-cited prominent source of hyperoxaluria is vitamin C (ascorbic acid) dietary supplements, where increasing dosages are directly correlated with increases in urinary oxalate because this is one primary metabolite of vitamin C (Hall, 2002; Moe, 2006).

Since ascorbic acid increases oxalate levels, and calcium discourages exogenous oxalate absorption, it is of interest that when combined into one compound (vitamin C with metabolites or Ester-C), the resulting clinical urologic impact has never been adequately researched in humans. This comparative study in urology was needed because of potential safety, educational, and preventive implications, and because of the popularity of vitamin C supplements.

Objective
This randomized, double-blind, crossover trial is the largest to date to evaluate the impact of supplementation with vitamin C with metabolites compared to ascorbic acid with regard to two separate, 10-day oxalate production periods in healthy individuals without a history of kidney stones. The objective of this study was to compare the effect of this buffered vitamin C supplement containing metabolites versus ascorbic acid on numerous health-related endpoints when administered as two increasing doses over 10 days to healthy volunteers. The primary outcome was the impact on gastrointestinal symptoms and quality of life (data submitted elsewhere), whereas a variety of secondary outcomes were assessed, including the impact of these two formulations on urinary oxalate levels. This was a pertinent secondary endpoint because the dosages utilized in this trial are well known for potentially producing hyperoxaluria when ascorbic acid is utilized by itself in stone-forming and non-stone-forming subjects (Baxmann, De Mendonca, & Heilberg, 2003; Massey, Liebman, & Kynast-Gales, 2005; Traxer, Huet, Poindexter, Pak, & Pearle, 2003).

The impact of vitamin C with metabolites on oxalate levels has not been thoroughly quantified, but a past study found the potential for oxalate reduction (Wright, Suen, & Kirk, 1990). Vitamin C is one of the most utilized dietary supplements in the U.S. (Radimer et al., 2004) and around the world (Hirayama, Lee, Binns, Watanabe, & Ogawa, 2008). Thus, due to the overall popularity of vitamin C supplements with the public among all age groups (Gardiner, Buettner, Davis, Phillips, & Kemper, 2008; Picciano et al., 2007; Radimer et al., 2004) and even among health care professionals themselves (Frank, Bendich, & Denniston, 2000; Gardiner, Woods, & Kemper, 2006), it seemed clinically pertinent to investigate this urologic outcome through the utilization of higher doses of these supplements.
Table 1.
Inclusion Criteria Utilized Before Determination of Randomization in the Ester-C Compared to Ascorbic Acid Crossover Dietary Supplement Study

<table>
<thead>
<tr>
<th>Criteria</th>
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<tr>
<td>Male or female, ages 18 to 75 years.</td>
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<td>Females using medically approved birth control or are not of childbearing potential.</td>
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<td>Healthy as determined by laboratory results, medical history, and physical examination, with no major co-morbidities.</td>
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<td>Agrees to avoid foods from list of foods high in vitamin C provided and to maintain their regular diet.</td>
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<td>Known sensitivity to acidic foods.</td>
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<td>Provides voluntary, written, informed consent.</td>
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Table 2.
Exclusion Criteria Utilized Before Determination of Randomization in the Ester-C Compared to Ascorbic Acid Crossover Dietary Supplement Study

<table>
<thead>
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<th>Criteria</th>
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<tr>
<td>Pregnant, breastfeeding, or planning to become pregnant during the trial.</td>
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<td>Use of supplements or prescription or over-the-counter drugs known to contain or interact with vitamin C.</td>
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<td>History of alcohol or drug abuse within the last year.</td>
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<td>History of kidney stones or unstable renal and/or liver disease.</td>
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<tr>
<td>History of any other unstable disease, morbid condition, or abnormal blood test. BMI greater than or equal to 35 kg/m².</td>
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<td>Unstable medications (&lt; 30 days).</td>
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<tr>
<td>Known allergy or sensitivity to test article ingredients.</td>
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<tr>
<td>Any other condition that may adversely affect subject’s safety or ability to complete the study.</td>
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Methods

Setting and Sample Population

This single-center, randomized, double-blind, two-arm crossover study was conducted at a clinical site in the Midwest (KGK Synergize, Inc., London, Ontario, Canada). Fifty adults with sensitivity to acidic foods were recruited for this study via advertisement or from the clinic database. At screening, medical history was reviewed, including concomitant therapies and inclusion/exclusion criteria (see Tables 1 and 2). Anthropologic measurements, routine blood tests, and a urine pregnancy test (where applicable) were also performed.

Two groups of 25 subjects were randomly and blindly assigned to one of two treatment sequences. The two groups were matched, and there were no significant differences in their baseline characteristics (for both groups: mean age = 44 years; clinic recorded weight = 75 kg; body mass index (BMI) = 27; waist-to-hip ratio = approximately 0.88). Approximately 80% of the participants were past smokers or never smoked, 78% were female, and 100% were Caucasian.

Procedure

Subject treatment diaries were dispensed and reviewed at each visit to record test article use, changes in concomitant therapies, and any adverse events. Additionally, subjects returned the original container with remaining tablets at each visit to determine compliance. To minimize potential baseline differences in plasma, white blood cell (WBC), and urinary vitamin C and oxalate, subjects were instructed to avoid consuming foods and beverages from a list of items with high vitamin C content. A 3-day food diary was dispensed at screening, with instructions to fill it out on 2 weekdays and 1 weekend day prior to randomization. Subjects were instructed to refrain from taking supplements, including vitamin C, for 2 weeks prior and throughout the duration of the study. Use of any prescription or over-the-counter products known to interact with vitamin C, such as iron, aspirin, and analgesics, within 4 weeks of randomization and during the study was not allowed. Other stable medications (at least 90 days prior to randomization) were allowed.

Treatment

Subjects took two different preparations of vitamin C at escalating doses divided over 10 days and separated by a 7-day washout period. The two preparations were plain ascorbic acid and a buffered vitamin C blend containing calcium ascorbate dihydrate and vitamin C metabolites (Ester-C manufactured by NBTY, Inc. Boca Raton, FL), referred to as “vitamin C with metabolites.” The two preparations were administered in the form of tablets, each containing 500 mg vitamin C, as confirmed by ultra performance liquid chromatography (Agilent, Wilmington, DE). The interventions were matched in terms of size and appearance.

Subjects took their medications in the morning on an empty stomach with water at least 90 minutes before breakfast. They took two pills per day on days 1 through 5, and 4 pills per day on days 6 through 10, for a total of 10 consecutive days of treatment. The subjects took no vitamin C supplements during the minimum 7-day washout period, and then repeated the schedule with the second preparation according to their assigned intervention sequence.

Protection of Human Subjects

The study protocol was approved by Health Canada’s Natural
Health Products Directorate (NHPD) and Institutional Review Board Services (IRB Services) of Aurora, Ontario, Canada. The study was conducted in accordance with ICH-GCP guidelines and governmental regulations following the ethical principles, which have their origins in the Declaration of Helsinki. Informed consent was obtained from each study subject prior to any study-related procedures.

**Biological Measurements**

Subject urine was collected and analyzed for oxalate, furanone (a metabolite in the patented formula), and vitamin C levels at baseline and after 10 days of treatment with each preparation. Patients were instructed to combine all collected urine in a Unisafe 24-Hour Urine Container (VWR International, Mississauga, Ontario) with preservative and store under refrigeration. Oxalate analysis was performed according to the oxalate oxidase procedure, using an Abbott Architect c8000 chemistry analyzer (Abbott Laboratories, Ltd., Saint-Laurent, QC). Urine furanone was analyzed by high-performance liquid chromatography (HPLC) (Varian, Lake Forest, CA) with PDA detection.

Plasma and WBC ascorbic acid levels were measured at baseline and after 5 and 10 days of treatment with each product dose. A 6 ml sodium heparin tube (BD Vacutainer, Mississauga, Ontario) was filled, and the tube was centrifuged at 3000 rpm to separate the plasma from the WBC. Both the plasma and WBC samples were prepared by standard methods and analyzed by HPLC with UV detection.

**Statistical Analysis**

Fifty subjects were required to detect a clinically relevant difference of 0.50 in the primary endpoint with 80% power at the 5% level of significance (two-sided), assuming a standard deviation of 0.85 and a correlation of 0.1 between pairs of observations, allowing for 15% loss to follow-up. Other endpoints had to achieve a 0.05 level in order to achieve significance, and both between and within group analysis was conducted on all endpoints because of the crossover design.

Repeated measures ANOVA was used to compare vitamin C with metabolites to ascorbic acid with respect to these endpoints. In a test for carry-over that was significant at the 0.10 level, between-group comparisons were limited to the first period, and comparisons were conducted using unpaired t-tests. Within product (group) comparisons were made using paired t-tests.

The total number of adverse events during each of the two treatments was recorded and summarized using frequencies and percentages. Between-group comparisons were made using the techniques described by Jones and Kenward (1989) for analyzing dichotomous outcomes in a crossover study. With the exception of tests for carry-over, probability values less than 0.05 were again considered statistically significant.

The SAS statistical program (version 9.1) was used to perform the analysis. The proportion of patients experiencing adverse events that were probably or possibly related to study product was compared using McNemar’s Chi-square test (assuming no carryover). Compliance was great enough that between product comparisons were not warranted.

**Table 3. Mean Plasma and 24-Hour Urine Oxalate at Various Intervals**

<table>
<thead>
<tr>
<th></th>
<th>Ester-C</th>
<th>+/- SD</th>
<th>Ascorbic Acid</th>
<th>+/- SD</th>
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<tbody>
<tr>
<td><strong>Mean Plasma Vitamin C (uM)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>48</td>
<td>37</td>
<td>42</td>
<td>28</td>
</tr>
<tr>
<td>5 days</td>
<td>147</td>
<td>57</td>
<td>151</td>
<td>62</td>
</tr>
<tr>
<td>10 days</td>
<td>152</td>
<td>72</td>
<td>145</td>
<td>66</td>
</tr>
<tr>
<td><strong>24-Hour Urine Oxalate (umol/day)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>305</td>
<td>144</td>
<td>300</td>
<td>103</td>
</tr>
<tr>
<td>10 days</td>
<td>282</td>
<td>102</td>
<td>315</td>
<td>123</td>
</tr>
</tbody>
</table>

**Results**

Both groups were well matched, and a variety of other parameters were also analyzed, including cardiovascular health, and no differences were found. For example, the systolic, diastolic blood pressure and mean heart rate for the entire group was 115, 74, 70, and combined with the other parameters exemplifies the excellent overall health of this study population.

Mean plasma vitamin C levels increased between baseline and 5 days after both treatments and also increased over the period from 5 to 10 days in the vitamin C with metabolites group. However, mean plasma vitamin C decreased between 5 and 10 days with ascorbic acid (see Table 3). Mean WBC vitamin C concentrations increased significantly over all periods for both treatments but was only highly significant (p < 0.001) over all time intervals for vitamin C with metabolites.

Urine vitamin C levels increased over the period from baseline to 10 days with both treatments and no differences between products. Urine furanone levels from baseline to 10 days after treatment also increased, and there was a significant within-group (p < 0.04) increase in the vitamin C with metabolites group. No significant differences occurred in urine creatinine or 24-hour urine volume.

There was an overall non-sig-
significant decrease in 24-hour urine oxalate from baseline to 10 days after treatment in the vitamin C with metabolites group and an overall non-significant increase in the ascorbic acid group (see Table 3). Approximately 25% more subjects experienced a reduction in 24-hour oxalate (59% to 34%; \( p = 0.04 \)) and oxalate concentration (72% to 46%; \( p = 0.04 \)) over the 10-day period when taking vitamin C with metabolites compared to ascorbic acid. Overall, 6% fewer directly and indirectly related adverse events were reported for vitamin C with metabolites compared to ascorbic acid.

Discussion

Hyperoxaluria, regardless of etiology (Khan, 2005), promotes kidney injury, and laboratory data exist in which kidney damage also occurs via the induction of hyperoxaluria (Khan, 1997). Thus, the question of whether or not vitamin C supplements cause kidney stone formation due to the increase in oxalate concentration is only a portion of the larger discourse. Hyperoxaluria is an abnormal metabolic consequence that should be generally discouraged and prevented.

Previous clinical trials have consistently demonstrated the large increases in oxalate with greater vitamin C intake from dietary supplements (Baxmann et al., 2003; Massey et al., 2005; Traxter et al., 2003). This occurred in previous stone formers and in subjects with no history of kidney stones—similar to this study’s population. This pertinent finding needs reiteration because numerous healthy men and women produce large quantities of urinary oxalate, regardless of stone risk status, when ingesting larger doses of concentrated ascorbic acid from dietary supplements. For example, a previous clinical trial of calcium oxalate stone formers ingesting 1000 mg (group 1) or 2000 mg (group 2) per day of vitamin C, and non-stone formers ingesting 1000 mg (group 3) for a total of only 3 days found that all three groups experienced significant increases in oxalate excretion: 61% increase in oxalate in group 1, 41% in group 2, and 56% in group 3 (Baxmann et al., 2003). A significant increase in calcium oxalate urinary super-saturation, as measured by the Tiselius risk index, also occurred in all three groups. The Tiselius index is a measure of a variety of urine parameters, including \( \text{pH} \), that ultimately measures calcium oxalate saturation, where increasing values represent a greater potential risk of precipitation or stone formation (Tiselius, 1991). However, urinary \( \text{pH} \) did not change after vitamin C was ingested in any of the groups in the Baxmann et al. (2003) study.

Another clinical trial published in the same year used a crossover design (Traxter et al., 2003), similarly to this study’s design. Calcium oxalate stone formers and non-stone formers were assigned to a controlled metabolic diet for two 6-day intervals. During one interval, participants were given 1000 mg of vitamin C, and a placebo was given during the other interval. Twenty-four-hour urine specimens were obtained on days 5 and 6 of each interval. There were no changes in urinary \( \text{pH} \), but a significant increase in urinary oxalate occurred again in stone-formers (33%) and non-stone formers (20%). Therefore, it seems that changes in urinary \( \text{pH} \) may not be directly correlated with vitamin C and the risk of hyperoxaluria.

A third and more recent crossover trial of stone and non-stone formers consuming 2000 mg of ascorbic acid compared to no intake for 6-day intervals found similar results to the other trials (Massey et al., 2005). A total of 40% of both the stone and non-stone formers experienced increases in the Tiselius index and 24-hour urinary oxalate concentrations of greater than or equal to 10%. The other 60% experienced no change in their oxalate concentrations. The authors of this study advise caution in ingesting high-doses of ascorbic acid in individuals with or without a history of kidney stones because an individual’s (compared to a population’s) response to vitamin C supplements in regard to potential hyperoxaluria is not consistently predictable from this and previous trials. In other words, it is currently accepted that hyperoxaluria occurs with higher doses of ascorbic acid (1000 to 2000 mg/day), but some individuals are able to metabolically escape this response for an unknown intrinsic or extrinsic reason, regardless of previous stone history.

Notably, past trials consistently indicate that a large percentage of individuals, regardless of kidney stone history, age, gender, and race, ingesting 1000 to 2000 mg of ascorbic acid for only short periods experience hyperoxaluria to some degree, and a clinical implication needs to be derived from this observation. Results from this study mirror past studies of ascorbic acid, at least when comparing the crossover group results while taking this supplement. Approximately 66% of subjects on ascorbic acid experienced an increase in 24-hour oxalate after 10 days, and there was an overall mean increase (+5%) in oxalate in this entire group.

However, unlike previous studies, the vitamin C with metabolites group, which were the same subjects who also ingested ascorbic acid at a different time interval (crossover), actually experienced a mean overall reduction (-8%) in oxalate. Only 41% of subjects on vitamin C with metabolites experienced an increase in 24-hour oxalate, which is 25% fewer compared to ascorbic acid. A 10% increase in an individual’s 24-hour oxalate has been used as a subjective clinical benchmark in past studies of oxalate inducers, and only 28% of those taking vitamin C with metabolites compared to 51% on ascorbic acid experienced this endpoint.

Strengths

Chance is a possible explanation with novel findings in any clinical trial. However, the randomized, double-blind, cross-
over design; consistent observation in favor of oxalate reduction for vitamin C with metabolites; and the calcium and metabolite content of this supplement make these researchers. The crossover design should have eliminated individual variability to oxalate production that occurred in previous trials. Control of vitamin C intake and high compliance rates in this study also substantially reduce the implication that lifestyle changes or compliance issues favored the metabolite formulation. Plasma vitamin C did not reach saturation over the 10-day period in the vitamin C with metabolites group but did begin to decrease over time with ascorbic acid. This may explain the higher WBC and urine vitamin C levels, as well as higher urinary furanone increases, all in favor of vitamin C with metabolites compared to ascorbic acid.

Previous studies have indicated that tolerability or compliance may be more favorable over the long-term when taking vitamin C with metabolites; fewer adverse effects are experienced compared to ascorbic acid because it is a non-acidic form of vitamin C (Gruenwald, Graubaum, Busch, & Bentley, 2006). Thus, it is theoretically plausible that results of this current study actually underestimate the oxalate differences because subjects found it more difficult to ingest ascorbic acid and had more adverse events and gastrointestinal issues in the past and current studies. Another potential explanation for the lower oxalate levels is the greater resistance to rapid degradation of vitamin C with a longer potential half-life, as has been observed in a past study (Moyad et al., 2008).

Regardless, the potential for oxalate reduction can be explained via multiple potential mechanisms, including decreased absorption via binding of free dietary oxalate by calcium, a lower rate of production or secretion from metabolic resistance, or greater half-life and reduced degradation over time with this form of vitamin C with metabolites. Finally, the enormous financial cost to investigate the primary and multiple secondary end-points in this trial are testimonials of the desire of the scientific team and the manufacturer to establish a paradigm in the dietary supplement industry and to determine the true clinical impact of what this form of vitamin C offers compared to ascorbic acid.

**Limitations**

The limitations of this study should also be emphasized. A more extensive 24-hour urine component analysis, including calcium, phosphate, uric acid, sodium, citrate, magnesium, and potassium, for example, could have been accomplished. Although the crossover design controls for most of these variables, these ancillary tests would have provided more useful information on this issue for future studies and preventive education. Some practical cost-control measures had to be applied, but at least enough information was gleaned from this trial to provide useful clinical information for other trials and for patients who may be concerned about hyperoxaluria and kidney stone formation.

Arguably, this clinical trial could have been of a longer duration if cost had not been an issue, but it is still one of the longest randomized, double-blind, crossover trials in medicine to address this issue. It is also interesting that it supports the results of the landmark 5-year randomized trial of stone prevention conducted in Parma, Italy (Borghi et al., 2002). Despite differences in trial design, intervention, and duration, subjects in the Italian trial who benefited experienced significant oxalate reductions in the first week, which were similar to the oxalate changes after 5 years. Subjects who did not benefit experienced non-significant oxalate increases in the first week, which were also similar to their oxalate changes after 5 years.

Racial diversity was also a limitation of the trial; however, it was more a limitation of the geographical area utilized for the trial and the population that resides near the clinic, rather than a lack of widespread recruiting methods in these researchers’ opinions. Generalizing these results to males and females is an easier task, but applicability to different racial groups and to previous stone former needs more investigation.

**Oxalate and Stone Risk?**

It must be reiterated that despite known consistent urinary oxalate increases with ascorbic acid, a direct correlation with stone incidence has not been established. The large prospective epidemiologic Health Professionals Follow-up Study (HPFS) found a 16% increase in the 14-year incidence of stones with 1000 mg or greater of daily supplemental vitamin C intake (Taylor, Stampfer, & Curhan, 2004). However, an earlier report from the Nurses’ Health Study (NHS) found no relationship between vitamin C and stone risk (Curhan, Willett, Speizer, & Stampfer, 1999). The most comprehensive report from the same institution and perhaps one of the largest studies on 24-hour urinary oxalate places this argument in the proper perspective. A cross-sectional investigation of 3348 stone and non-stone formers from men in the HPFS, and women in the NHS, and the Nurses Health Study II (NHS II) was recently published (Taylor & Curhan, 2008). Median urinary oxalate levels were below 40 mg, and the relation between dietary and urinary oxalate levels was similar regardless of nephrolithiasis history. Individuals consuming 1000 mg/d or more of vitamin C compared to less than 90 mg/day had significantly (p < 0.001) more (6.8 mg/day) urinary oxalate. BMI, total fructose intake, and 24-hour urinary magnesium, potassium, and phosphorus levels were also positively correlated with urinary oxalate levels, and age and calcium intake were inversely correlated with urinary oxalate. The authors of this study concluded that
dietary oxalate from most foods minimally contributes to urinary oxalate, but vitamin C supplementation, with its direct correlation, and increased calcium supplement, with its inverse correlation, are potentially more significant contributors to oxalate levels. This would only espouse this current study’s findings utilizing a vitamin C with metabolites formulation that is also bound to calcium. Again, stone risk is only one relevant clinical endpoint, but hyperoxaluria also represents a clinical observation of inadequate kidney and urologic function, and should be deemed just as critical for investigation.

Conclusion

Nephrolithiasis risk is complex and challenging to predict clinically; however, a consistent theme in past and recent small and large investigations is that ascorbic acid supplementation increases oxalate excretion (Assimos & Holmes, 2000; Rivers, Shetty, & Menon, 2000). Finding a method to reduce these levels should be of immediate clinical importance. Some may argue that reducing supplemental intake is the most logical approach, but is this a realistic and science-based approach? In some cases, reduction or elimination of vitamin C should occur, for example, in patients with hemochromatosis (Herbert, 1999); however, this is not an immediate realistic or even best option for others.

Vitamin C has and continues to be one of the most popular dietary supplements, not just with the general public, but also with health care professionals (Frank et al., 2000; Gardiner et al., 2008; Hirayama et al., 2008; Picciano et al., 2007; Radimer et al., 2004). Despite a lack of efficacy of vitamin C for certain conditions (Gaziano et al., 2009), other specific conditions critically rely on adequate or even larger doses of vitamin C supplements. For example, vitamin C is used to enhance iron absorption in general, during pregnancy, or with hemodialysis to prevent anemia (Handelman, 2007; Insel, Turner, & Ross, 2002); to potentially reduce the incidence of lung infections (Hemila & Louhila, 2007); to decrease the risk of reflex pain syndrome that is common after bone fracture and treatment (Zollinger, Tinebreijer, Brederfeld, & Kreis, 2007); after weight loss surgery that may result in amplification of oxalate levels and a potential higher risk of inadequate vitamin C status (Asplin & Coe, 2007; Patel et al., 2009; Riess, Farnen, Lambert, Mathiason, & Kothari, 2009); or as part of a combination product to prevent vision loss in patients with moderate to severe macular degeneration (Age-Related Eye Disease Study Research Group, 2001). Therefore, if additional confirmation of these preliminary novel findings occurs from future clinical research, another method of reducing oxalate concentration and enhancing the safety of vitamin C could result from a calcium ascorbate mixture with metabolites, such as the one utilized in this trial.

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Additional Readings
