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Thomas E. Levy, MD, JD

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CHAPTER 4

THE SAFETY OF HIGH DOSES

"Opinions are caught like an infection, and put into practice without examination."

Balzac

Overview

Along with its numerous and substantial clinical benefits, vitamin C is also one of the safest and least toxic therapies that can be administered to a patient, regardless of diagnosis. Everybody needs some vitamin C on a regular basis, and the only potential problems with vitamin C administration arise in a very limited number of clinical situations. Some researchers have voiced their concerns about the proper dosing of vitamin C in these situations, and the validity of these concerns will be addressed in some detail.

Long-Term and High-Dose Supplementation

Intravenous vitamin C has already been demonstrated as a very safe form of vitamin C supplementation. Casciari et al. (2001) reported that "terminal cancer patients" were given 50,000 mg of intravenous vitamin C daily for up to eight weeks. The "blood count and chemistry parameters" revealed no evidence of toxicity or side effects from this administration. Kalokerinos et al. (1982) also reported on the safety of intravenous vitamin C, noting that "in Australia alone, some 100 physicians" have administered as much as 300,000 mg of vitamin C per day to their

patients. These authors go on to mention that "in most cases the results have been spectacular, the only side effect is 'chronic good health.'"

Cathcart (1981), using his method of dosing patients with vitamin C up to "bowel tolerance" (see Chapter 3, in the treatment of AIDS), often gave individual patients more than 200,000 mg of oral vitamin C daily as ascorbic acid. Cathcart (1985) asserted that he had treated over 11,000 patients in the prior 14 years with vitamin C. Regarding doses ranging from 4,000 mg to over 200,000 mg in a 24-hour period, he commented that there was "a remarkable lack of systemic difficulties" with these doses of vitamin C. By 1993, Cathcart's patient count had exceeded 20,000, and no remarkable difficulties with these dosage levels had emerged (Cathcart, 1993). Some of his AIDS patients (Cathcart, 1984) would take anywhere from 25,000 to 125,000 mg of vitamin C daily on a regular basis, only varying the dose depending upon fluctuating bowel tolerance, which generally reflected the activity level of the disease. Cathcart noted that occasional minor complaints of gas, diarrhea, or acid stomach were seen more often in well patients, appearing only rarely in the "very sick" patients. He asserted that even with these high daily doses of vitamin C, he "cannot recall any patient who has been damaged by large doses of ascorbate," except for some dissolving effect on tooth enamel in a few people who swished the vitamin C in their mouths before swallowing.

Cathcart also commented on the incidence of a few possible side effects that some authors feel may be associated with vitamin C therapy. Cathcart noted in the doses of vitamin C that he administered, oxalate kidney stones did not occur, and patients who had them previously tended not to get them again. Cathcart's extensive clinical experience directly contradicts the widespread but mistaken belief that large doses of vitamin C will result in kidney stone formation. Cathcart also noted that "three out of thousands" developed a "light rash" that cleared without discontinuing the vitamin C. Regarding the urinary tract, he noted that "six patients have had mild pain on urination," but that "acute and chronic urinary tract infections" were often eradicated with the vitamin C. A few patients had "discoloration of the skin" under some types of jewelry, possibly because of a detoxification effect of the vitamin C. Cathcart reported that a few patients had small sores in their mouth on lower doses of vitamin C that subsequently cleared when dosing was increased to the bowel tolerance levels. He noted that a few patients with "hidden peptic ulcers" might have had pain, but that others were benefited. Cathcart also commented that he has seen only benefit and no aggravation of gouty arthritis with high doses of vitamin C.

Moertel et al. (1985) conducted a prospective, double-blind study of the effects of 10,000 mg vitamin C daily versus placebo on 100 patients with

advanced colorectal cancer. Except for a few patients having slightly more heartburn with vitamin C than placebo (a difference the authors determined to be "not statistically significant"), no "clear evidence of a specific toxicity of vitamin C" was detected in any of the patients. However, ascorbic acid was likely the form of vitamin C administered. Had the vitamin C been given as sodium ascorbate, no heartburn at all would be anticipated. The median time of vitamin C administration was 2.5 months, with the longest duration being 15.6 months. Even though the subjects were sick patients who would be expected to be especially sensitive to any agent with even mild toxicity, the daily 10,000 mg dose was very well-tolerated with no significant side effects observed. Earlier, Creagan et al. (1979) had administered either 10,000 mg daily of vitamin C as ascorbic acid or placebo to 123 advanced cancer patients who were felt to be "unsuitable" for chemotherapy. These patients were very ill, with a median survival time of seven weeks. Nevertheless, the vitamin C was very well-tolerated, producing only mild nausea and vomiting with the same frequency as the lactose placebo pills. The authors also specifically noted that no kidney stones were produced by this therapy, even though some patients received the vitamin C for over six months.

Bendich and Langseth (1995) compiled a good review article that also addressed the safety of chronic vitamin C supplementation. In addition to the reports noted above, a host of other therapeutic trials with vitamin C have also reported no adverse effects with dosages of vitamin C considered by most researchers and clinicians to be in the "mega-dose" range. In five double-blind studies giving either vitamin C or placebo, the doses of vitamin C ranged from 400 to 4,000 mg daily, and the durations of therapy ranged from one to 24 months (Ludvigsson et al., 1979; Bussey et al., 1982; McKeown-Eyssen et al., 1988; Taylor et al., 1991; Osilesi et al., 1991). In six other clinical trials that were not double-blinded and had no placebo given, long-term vitamin C administration did not result in any side effects. The vitamin C doses ranged from 500 to 5,000 mg daily, and the durations of therapy ranged from one to 30 months (Lux and May, 1983; Melethil et al., 1986; Brox et al., 1988; Godeau and Bierling, 1990; Reaven et al., 1993; Sharma and Mathur, 1995). In an article reviewing a large number of vitamin C studies, Hanck (1982) also confirmed the remarkable safety of long-term supplementation. Bass et al. (1998), in a double-blind study, found that vitamin C administration was very safe even for premature infants.

It can certainly be concluded that vitamin C is an exceptionally safe supplement, which has already been given in very large doses for extended periods of time with no significant problems occurring. There are few, if any, prescription or non-prescription medicines or supplements that are as free of side effects as vitamin C. This is in spite of the fact that vitamin C has one of the widest flexibilities in dose amount of any ingestible substance. The mild gastrointestinal effect of slight heartburn or

stomach upset is limited to the ascorbic acid form of vitamin C. Vitamin C is equally effective in its sodium ascorbate form, and there is no stomach upset with this preparation.

Does Vitamin C Cause Kidney Stones?

Vitamin C as ascorbic acid is first metabolized to oxidized ascorbic acid, or dehydroascorbic acid (DHAA). Whenever vitamin C first contributes two electrons to another compound while performing its major responsibility as an antioxidant, DHAA is immediately produced. Other antioxidants and some enzymes can promptly regenerate DHAA back to the potent, unoxidized ascorbic acid (Long and Carson, 1961; Basu et al., 1979; Rose and Bode, 1992; Bode et al., 1993). However, when this regeneration does not occur, further metabolic breakdown of vitamin C can take place. **The primary metabolic pathway of vitamin C** is as follows (Davies et al., 1991):

- 1. Vitamin C (ascorbic acid) to DHAA**
- 2. DHAA to diketogulonic acid**
- 3. Diketogulonic acid to lyxonic acid, xylose, threonic acid, or oxalic acid (oxalate)**

Oxalate, or oxalic acid, is a major metabolite of vitamin C after it is utilized and fully broken down in the body. Oxalate is considered a true metabolic "end product" because there is no evidence that mammalian tissues further utilize it or break it down any further (Hagler and Herman, 1973).

Since the primary constituent in most kidney stones is calcium oxalate (Jayanthi et al., 1994), many conventional doctors have simply concluded that significant vitamin C supplementation will lead to kidney stones.

For this reason alone, it would seem that many patients are still warned by their physicians that vitamin C supplementation "might" cause problems and increase their chance of developing a kidney stone. However, there exists a large amount of literature from respected research centers that indicates otherwise.

In patients with known kidney disease, some reasonable cautions are in order. However, a healthy person who avoids dehydration and ingests even very large amounts of vitamin C does not need to have any concern about kidney stone formation. In fact, there is a strong suggestion in some studies that regular supplementation of vitamin C actually decreases the chances of kidney stone development. Two recent and extensive studies at Harvard have clearly demonstrated that vitamin C is not a factor in the development of kidney stones in healthy adults. Curhan et al.

(1999) looked at a group of 85,557 women with no history of kidney stones. Over a follow-up period of 14 years, 1,078 cases of kidney stones developed in this group. Vitamin C intake had no statistical association with any increased risk of stone development. A bit earlier, Curhan et al. (1996) looked at a group of 45,251 men with no history of kidney stones. They also found that vitamin C was not a risk factor for stone formation over their six years of follow-up, and it did not matter whether the men were consuming 250 mg or 1,500 mg of vitamin C daily. Gerster (1997) noted that a statistical study revealed that individuals with the highest vitamin C intake actually had a lower risk of kidney stones compared to individuals taking the least vitamin C. Analyzing the relationship more precisely, Simon and Hudes (1999) found that every 1.0 mg/dL increase in blood vitamin C levels was "independently associated" with approximately a 28% decrease in the prevalence of kidney stones in men. Gaker and Butcher (1986) reported that an 81-year-old woman successfully dissolved her very large kidney stone over an eight-week period with only diuretics, antibiotics, and vitamin C.

In veterinary work, Belfield and Zucker (1993) reported two cases in which vitamin C administration dissolved documented bladder stones. A 10-year-old female terrier was found to have bladder stones. Since the owner did not want an operation for only that reason, the dog was placed on 500 mg of vitamin C daily. After six months the animal had unrelated uterine surgery, and an operative examination of the bladder revealed that the stones were gone. In another case, a veterinarian gave a small-breed dog 8,000 mg of vitamin C as ascorbic acid daily for four months. This successfully dissolved a large bladder stone.

Many factors are involved in the precipitation of calcium oxalate out of the urine, leading to stone formation, and increased vitamin C supplementation is but one of these factors. It is important to realize that a given risk factor can only produce a given medical condition when other surrounding circumstances favor the development of that condition as well. These risk factors, with appropriate references, include the following:

1. Increased urinary oxalate (Hagler and Herman, 1973b; Ogawa et al., 2000)
2. Increased vitamin C supplementation (Pru et al., 1985; Urivetzky et al., 1992; Auer et al., 1998)
3. Calcium ascorbate as the type of supplemental vitamin C (Kalokerinos et al., 1981; Tsugawa et al., 1999)
4. Presence and concentration of other dissolved substances (solutes) in the urine (Oke, 1969; Lawton et al., 1985)
5. Presence of heavy metal chelation agents, such as DMPS, DMSA, and EDTA, which have their own independent kidney toxicities, due to increased urinary solute load and toxin damage to the kidneys (Oke, 1969)
6. Increased urinary calcium (Noe, 2000; Kinder et al., 2002; Bushinsky et al., 2002; Borghi et al., 2002)

7. Decreased urinary magnesium (Schwartz et al., 2001)
8. Decreased urinary citrate (Alvarez et al., 1992; Tekin et al., 2000; Yagisawa et al., 2001)
9. Decreased urinary potassium (Kinder et al., 2002)
10. Increased urinary cystine (Martins et al., 2002)
11. Increased urinary phosphorus (Prie et al., 2001)
12. Increased urinary uric acid (Koide, 1996; Yagisawa et al., 1999)
13. Increased urinary lipids and cholesterol (Khan et al., 1988; Khan and Glenton, 1996)
14. Increased age, with age-associated decrease in glomerular filtration rate (Mousson et al., 1993)
15. Intake of hard water (Bellizzi et al., 1999)
16. Overall state of hydration (Sakhaee et al., 1987; Borghi et al., 1996)
17. Decreased daily volume of urine flow and formation (Riobo et al., 1998; Borghi et al., 1999a)
18. Urinary pH (Wall and Tiselius, 1990; Hokama et al., 2000; Murayama et al., 2001; Kinder et al., 2002; Hsu et al., 2002)
19. Low dietary calcium (Curhan et al., 1997a)
20. Supplemental calcium (Curhan et al., 1997a); supplemental calcium causing calcium gallstones (Powell, 1985)
21. Vitamin D supplementation (Black, 1945; Hodgkinson and Zarembski, 1968; Broadus et al., 1980; Ichioka et al., 2002)
22. Low intake of magnesium and vitamins (Williams and Smith, 1968)
23. Preexisting calcium deposits throughout the body, especially in the vascular system
24. Presence of preexisting kidney insufficiency or failure; being on hemodialysis (Oren et al., 1984; Chen et al., 1990; Daudon et al., 1992)
25. Any injury to the cells lining those parts of the urinary system susceptible to stone formation (Khan and Thamilselvan, 2000)
26. Intake of oxalate stone-generating or oxalate-containing foods (Hagler and Herman, 1973a; Bakane et al., 1999; Massey et al., 2001)
27. Intake of oxalate stone-generating or oxalate-containing beverages (McKay et al., 1995; Curhan et al., 1996a; Terris et al., 2001)
28. Intake of oxalate stone-generating or oxalate-containing supplements and medicines (Shields and Simmons, 1976; Fleisch, 1978; Ettinger et al., 1980; Wolf et al., 1985; Ahlstrand and Tiselius, 1987; Daudon et al., 1987; Michelacci et al., 1992; Kohan et al., 1999; Sundaram and Saltzman, 1999; Gonzalez et al., 2000; Wu and Stoller, 2000)
29. Intake of oxalate stone-generating toxins (Hagler and Herman, 1973c; Conyers et al., 1990; Muthukumar and Selvam, 1998)
30. Receiving total parenteral nutrition (Friedman et al., 1983; Swartz et al., 1984)
31. Deficiency of pyridoxine [vitamin B6] (Gershoff et al., 1959; Faber et al., 1963; Gershoff, 1964; Mitwalli et al., 1988; Alkhunaizi and Chan, 1996; Curhan et al., 1999)
32. Deficiency of thiamine [vitamin B1] (Buckle, 1963; Alkhunaizi and Chan, 1996)
33. Having had intestinal bypass or resection surgery, or small bowel

- malabsorption from any cause (Gregory et al., 1977; Drenick et al., 1978; Nightingale, 1999; Nightingale, 2001)
34. Urinary tract infection, or presence of bacteria (Trinchieri et al., 1996; Dewan et al., 1997; Daskalova et al., 1998; Hokama et al., 2000; Sohshang et al., 2000; Kim et al., 2001)
 35. Presence of increased oxidative stress in the urinary tract (Scheid et al., 1996; Muthukumar and Selvam, 1998)
 36. Primary hyperoxaluria, a hereditary disorder (Daudon et al., 1998)
 37. Hyperparathyroidism (Ralph-Edwards et al., 1992; Yamaguchi et al., 2001)
 38. Urinary stasis, or incomplete voiding (Nikakhtar et al., 1981; Sarkissian et al., 2001)
 39. Obstructive urinary disease (Kim et al., 2001)
 40. Polycystic kidney disease (Torres et al., 1988; Torres et al., 1993)
 41. Cirrhosis (Hagler and Herman, 1973c)
 42. Diabetes (Hagler and Herman, 1973c)
 43. Congestive heart failure (Hagler and Herman, 1973c)
 44. Crohn's disease (Shiraishi et al., 1998; Buno et al., 2001; McConnell et al., 2002)
 45. Cystic fibrosis (Turner et al., 2000; Perez-Brayfield et al., 2002)
 46. Renal tubular acidosis (Hagler and Herman, 1973c)
 47. Sarcoidosis (Sharma, 1996; Rodman and Mahler, 2000)
 48. Klinefelter's syndrome (Hagler and Herman, 1973c)
 49. Parasitic diseases, including amebiasis, schistosomiasis, giardiasis, and ascariasis (Hagler and Herman, 1973c)
 50. Antibiotic therapy (Bohles et al., 2002)
 51. Increased fluoride intake (Singh et al., 2001)
 52. Prolonged bedrest (Hwang et al., 1988)
 53. Kidney transplantation (Torrecilla et al., 2001)
 54. Hypertension (Borghetti et al., 1999; Hall et al., 2001)
 55. Increased alcohol intake (Hughes and Norman, 1992)
 56. Increased glucose intake (Burns et al., 1951; Nguyen et al., 1989)
 57. Pregnancy (Hildebrandt and Shanklin, 1962; Maikranz et al., 1989)
 58. Methoxyflurane anesthesia (Mazze et al., 1971; Mazze et al., 1971a; Silverberg et al., 1971)
 59. Ketogenic diet (Furth et al., 2000)
 60. Space travel (Whitson et al., 1997; Whitson et al., 1999)

One of the primary reasons why the vitamin C/kidney stone connection continues to generate concern is because vitamin C does increase the urinary concentration of oxalate. Therefore, it just seems logical to assume that more and prolonged vitamin C administration will continue to increase this concentration until calcium oxalate stones begin to form.

However, research proves that this is not the case, although vitamin C is one of many risk factors (see above) for increased oxalate formation and the subsequent formation of calcium oxalate stones. Schmidt et al.

(1981) determined that there was actually a leveling off of oxalate production even though the vitamin C dosing was continued.

The researchers noted that a significant amount of the vitamin C does not even get metabolized to oxalate and is excreted unchanged in the urine.

When very high doses of vitamin C are administered for any significant medical condition, the active, non-oxidized form of vitamin C is much more readily regenerated from the oxidized vitamin C that is initially generated. This process further prevents the irreversible metabolism of vitamin C to the oxalate end product.

Takenouchi et al. (1966) noted that about 80% of vitamin C administered to human subjects was eliminated as dehydroascorbic acid, the oxidized form of vitamin C. They concluded that the metabolic breakdown of vitamin C in humans does not necessarily have to follow the entire sequence down to oxalate. They also noted that as the vitamin C dose is increased, urinary excretion of diketogulonic acid increased. This is a clear indication that further oxidative breakdown of the diketogulonic acid to oxalate does not have to occur for a metabolic breakdown product of vitamin C to be excreted.

In healthy men, Lamden and Chrystowski (1954) showed that vitamin C doses of 4,000 mg or less "produced no significant increase in oxalate excretion" over non-supplementers. Fituri et al. (1983) found that the ingestion of 8,000 mg of vitamin C daily for seven days by eight normal subjects did not "significantly alter urinary or plasma oxalate during or after ingestion."

Other investigators have found that vitamin C administration will raise urinary oxalate levels (Tiselius and Almgard, 1977; Hatch et al., 1980; Hughes et al, 1981). As noted in the list above, vitamin C is only one of many risk factors that can affect whether calcium oxalate stones are ultimately formed. Unfortunately, many of the research studies examining this issue have not even looked for most of the other risk factors itemized above, resulting in conflicting findings on the ability of vitamin C to increase urinary oxalate. Fituri et al. even noted that some studies have used a tablet form of vitamin C, and they suggested that the tartaric acid and sucrose present in some tablets could convert to oxalate in the body. The amounts of such additional agents in pills can be significant, as Wilk (1976) noted that 100 mg vitamin C pills weighed 400 mg, with the additional 300 mg due to fillers. Auer et al. (1998a) also showed that urine specimens not preserved with EDTA registered erroneously high oxalate levels in their testing, possibly indicating a reason for some of the higher oxalate levels noted in other urine studies of vitamin C supplementers.

Logically, there have to be multiple other ways to metabolize and excrete vitamin C rather than by urinary oxalate. Casciari et al., (2001) showed that 50,000 mg daily doses of intravenous vitamin C have already been given to cancer patients for eight-week periods without problem. If urinary oxalate was the only excreted metabolic product of vitamin C, such doses would cause such a supersaturation of oxalate in the urine that crystal deposition and eventual stone formation would have to occur. Yet, this does not occur.

Since oxalate is a primary component of so many kidney stones, it is also very important to know about **the many other potential sources of increased oxalate concentration in the urine**. In addition to vitamin C, glyoxylate and glycolate are the primary substances that can be metabolized to oxalate (Ogawa et al., 2000). Also, there are numerous other lesser precursors to oxalate, including gelatin, certain amino acids (such as tryptophan, phenylalanine, aspartic acid, tyrosine, threonine, and asparagine), creatinine, purines, glucose, other carbohydrates, and probably several unidentified substances (Hagler and Herman, 1973). A lesser precursor can assume a great deal of importance in the generation of oxalate when one has a peculiar diet rich in the precursor, such as occurs in the regular excessive ingestion of aspartame-containing diet drinks and other diet foods. Aspartame is primarily a combination of phenylalanine and aspartic acid, two of the amino acids that can lead to oxalate. Also, if a patient is receiving hyperalimentation with a high concentration of amino acids, increased oxalate formation can result. Glycine, the simplest of the amino acids, is likely the major source of glyoxylate, which is a major immediate precursor to oxalate (Hagler and Herman, 1973).

Important dietary sources of oxalate include spinach, rhubarb, parsley, citrus fruits, and tea. Tea is probably the most important source of oxalate in the average English diet (Zarembski and Hodgkinson, 1962). Other significant dietary sources of oxalate include Swiss chard, cocoa, chocolate, beet tops, peppers, wheat germ, pecans, peanuts, okra, chocolate, refried beans, lentils, and lime peel. Various soy-based foods can also contain large amounts of oxalate (Massey et al., 2001). High-purine foods, such as sardines and herring roes, also substantially increase oxalate excretion (Zarembski and Hodgkinson, 1969). Oxalate poisoning has been reported in the literature secondary to an excessive intake of rhubarb (Tallquist and Vaananen, 1960; Kalliala and Kauste, 1964). Clearly, a detailed dietary history is critical in the proper management of any patient with kidney stone risk or disease, and merely lessening or discontinuing vitamin C intake as the only significant intervention is not in the patient's best interests. Eliminating one or several of the patient's favorite oxalate-containing foods should always

take precedence over lessening or eliminating any regular supplementation of vitamin C.

Calcium also plays several roles in the propensity for calcium oxalate stone formation. Reducing the dietary (not supplemental) intake of calcium increases the intestinal absorption of oxalate (Hodgkinson, 1958). Conversely, in a study on 45,619 men Curhan et al. (1993) found that a high dietary intake of calcium decreased the risk of symptomatic kidney stones. In looking at 91,731 women, Curhan et al. (1997) again found that the high dietary intake of calcium decreased the risk of symptomatic kidney stones, "whereas intake of supplemental calcium may increase risk." It was also found that vitamin D supplementation increased the excretion of oxalate in humans (Hodgkinson and Zarembski, 1968). Some researchers have actually demonstrated that vitamin C probably lessens the likelihood of kidney stone formation in those individuals who already have a history of stone formation, indicating a possible therapeutic role for vitamin C in the treatment of kidney stone disease. Schwille et al. (2000) found that vitamin C actually inhibited the development of calcium oxalate crystals in these individuals. Not surprisingly, they also concluded that vitamin C does not play a role in helping the formation of kidney stones "under normal conditions." Grases et al. (1998) were able to demonstrate that free radical-damaged cells in an experimental model using living epithelial cells tended to produce a "favorable environment" for the development of calcium oxalate crystals. They found the vitamin C "exerted the most remarkable effects" in preventing the formation of calcium oxalate crystals. Selvam (2002) found that "antioxidant therapy prevented calcium oxalate precipitation in the rat kidney and reduced oxalate excretion in stone patients." Gotz et al. (1986) showed that another antioxidant, lipoic acid, helped prevent the precipitation of calcium oxalate crystals in dogs. Jayanthi et al. (1994) also showed that lipoic acid was effective in lowering oxalate levels in the kidneys and urine of rats. As a powerful antioxidant, vitamin C may well have the same effects as lipoic acid. Certainly, vitamin C also quenches free radicals, prevents oxidant-induced damage, and facilitates tissue healing after such damage has been inflicted. Perhaps eliminating focal areas of such tissue damage makes it that much more difficult to initiate an abnormal deposit of calcium oxalate. This may be one significant way in which vitamin C can reduce kidney stone formation. McCormick (1946) long ago asserted that his research on vitamin C indicated that a vitamin C deficiency was "the basic etiological factor" for stone formation anywhere in the body.