

DIETARY INFLUENCES ON URINARY OXALATE AND RISK OF KIDNEY STONES

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1. ABSTRACT

Calcium oxalate is the most common constituent of kidney stones. Increases in urinary oxalate increase risk of calcium oxalate supersaturation more than increases in urinary calcium, as the physiological level of oxalate is about one-fifth to one-tenth that of urinary calcium. Urinary oxalate derives from two sources: endogenous synthesis and diet. Endogenous synthesis is proportional to lean body mass, and cannot be altered by any current treatment. Dietary oxalate is found in all plant foods. A single food may vary 2-15 fold in oxalate content, depending on variety and growth conditions. The salt form of oxalate, whether sodium, potassium, calcium or magnesium is likely to affect absorption, but has been little studied. Absorption of oxalate from food sources typically is 3-8% of its total oxalate in non-stone-forming individuals. Recent research shows that 40-50% of urinary

oxalate comes from the diet of healthy individuals consuming typical diets with 150-250 mg/d dietary oxalate. However, a subpopulation of oxalate "hyperabsorbers" is found in most studies of stoneforming patients. It is likely that all stone formers will benefit from reduction of dietary oxalate, but especially hyperoxaluric stone formers.

2. INTRODUCTION

The amount of oxalate excreted in the urine is an important risk factor in the development of calcium oxalate stone formation in susceptible individuals. As urine normally contains much less oxalate (0.1-0.5 mM) than calcium (1-5 mM), small changes in oxalate concentration have much larger effects on the supersaturation of urine with calcium oxalate than do comparable changes in

calcium concentration (1). When calcium oxalate concentration exceeds its saturation limit, it may precipitate as crystals. The relative precipitability is often expressed as a risk index. One commonly used risk index is the Tiselius Risk Index (2), a formula which relates the hour excretion of four urinary components and volume to AP(CaOx). The formula for using the 24 hour collection period is: $AP(CaOx) = 1.9 \times [Calcium]^{0.84} \times [Oxalate] \times [Magnesium]^{-0.12} \times [Citrate]^{-0.22} \times [Volume]^{-1.03}$

The Tiselius Risk Index of calcium oxalate precipitability not only includes calcium and oxalate, but also includes citrate and magnesium, which act as inhibitors of crystallization. Citrate complexes with calcium, and magnesium complexes with oxalate; both calcium citrate and magnesium oxalate are relatively soluble. Therefore, increasing concentrations of citrate and magnesium reduce the concentrations of calcium and oxalate available for precipitation. Volume is also included as a component of the risk index, as more dilute urine is less likely to form calcium oxalate crystals. A constant of 1.9 is included in the Tiselius Risk Index formula so that the index number 1.0 is the limit of solubility of calcium oxalate salts. Variations on the formula have been published for urine collections of less than 24 hours (2).

Widely varying prevalences of hyperoxaluria in stone formers have been reported from nearly none to 50%. At the high end Baggio *et al* (3) reported that 50% of stone formers had oxalate excretions more than two standard deviations above that of non-stone formers. Hatch (4) found 30% of stone formers were hyperoxaluric. Laminski *et al* (5) found 19% of a series of 207 patients to have mild hyperoxaluria, while Trinchieri *et al* (6) found only 10%. The widely varying prevalences no doubt reflect the influence of both diet choices and genetic susceptibility to dietary influences (7) as presented in this review.

3. SOURCES OF URINARY OXALATE

3.1. Endogenous synthesis

In humans, a substantial part of urinary oxalate results from endogenous synthesis. This is estimated at 10 mg/d based on excretion of oxalate-free diets (8). The organs or tissues synthesizing this oxalate are not known for certain, nor are the pathways (9). The contribution of endogenous synthesis to urinary oxalate is seen in the reported associations between lean body mass and both total urinary oxalate (10), and endogenous oxalate (11). Lemann *et al* (10) found that mean daily urine oxalate was directly related to mean daily urine creatinine in 94 healthy adults. The mathematical prediction of mmol/d urine oxalate was $0.0768 \pm 0.00940 \times \text{urine creatinine (mmol/d)}$. Curhan *et al* (12) found that body size expressed as body mass index (BMI) was related to risk of kidney stone formation in prospective studies of nurses and male health professionals. Both prevalence and incidence increased as BMI increased. Since increased body weight is composed of both lean and fat mass, increased lean mass would be a contributor to the increased urine oxalate and therefore risk. It is not known how weight loss or an increase in muscle mass due to physical activity affects urinary oxalate.

3.3.1. Protein

Increased dietary protein is associated with increased urine lithogenicity due to increases in urinary calcium, uric acid and a decrease in citrate; however, the effect of dietary protein is less well studied. Studies have reported discrepant results: Early studies by Robertson *et al* (13), and Urivetzky *et al* (14) reported increased dietary protein increased urinary oxalate, agreeing with Giannini *et al* (15) who reported that moderate protein restriction reduced urinary oxalate. In contrast, Fellstrom *et al* (16), and Marangella *et al* (17) found no increases with higher protein intake, supported by the studies of Hiatt *et al* (18) and Kok *et al* (19) who found no decreases with reduced protein intakes. Holmes *et al* (20) found that in healthy non-stoneforming subjects, only women had higher urinary oxalate on a high protein diet. Rotily *et al* (21) advised 34 stoneformers to reduce their protein intake in a four month study; there was no decrease in mean urine oxalate, even in the subgroup of 12 who reduced their urea excretion more than 50 mmol/d, indicating compliance with the reduced protein diet. Hypercalciuric and normocalciuric patients responded similarly. A possible explanation for these discrepancies is found in the results of Nguyen *et al* (22). They compared the effect of moderate protein diets (75-84 g/d) with high protein diets (172-201 g/d) in stone formers with and without mild hyperoxaluria (MMO) and healthy controls. Both diets were low in oxalate and vitamin C. Four of the 12 MMO patients, 3 of the eight normo-oxaluric, but none of the controls, had an increase in urinary oxalate on the fifth day of diet. Therefore about one-third of the stoneformers had an increase. Taken together, these results suggest that the variable responses seen in previous studies may be due to a genetic difference in response to dietary protein. As most of these studies were relatively short, it is not known whether continuation of a high protein diet for longer times would lead to a diminution of the hyperoxaluric response in apparently sensitive subjects.

The food source of dietary protein, plant versus animal, will affect the amount of dietary oxalate, and potentially urinary oxalate. Breslau *et al* (23) fed non-stone formers three diets with the same total protein (75 g/d) but differing protein sources: vegetarian, ovo-vegetarian and animal. While urinary calcium was higher on the animal protein diet, urinary oxalate was higher on the vegetarian diet, probably because dietary oxalate in the vegetarian diet was twice as high. These changes offset each other so that urinary crystallization was not different between diets. Massey and Kynast-Gales (24) found similar effects in normocalciuric calcium stone formers. If dietary protein is excessive, reduction of both vegetable and animal protein sources appears appropriate.

3.1.2. Ascorbate

Some ascorbate (vitamin C) is converted in humans to oxalate. Many early reports of the effects of ascorbate supplements found that high doses increased urinary oxalate, though this finding was not universal. However, it is now known that ascorbate can be nonenzymatically converted to oxalate in urine at physiological conditions (25), so unless preservatives were

Table 1. Effect of Ascorbate Supplements on Urinary Oxalate

First Author, Year	Ascorbate (g/day)	Number of subjects	Baseline Oxalate (mg/d)	Supplemented Oxalate (mg/d)	Oxalate Increase (mg/d)
<u>Healthy Non-Stoneformers</u>					
Levine 1996	0.4	7	30	35	+ 5
Levine 1996	1	7 (same persons as above)	30	40	+ 10
Wandzilak 1994	1	21	26.5	31.4	+ 4.9 ¹
Liebman, 1997	2	6	30.0	32.2	+ 2.2 ²
Auer 1998	4	10	17.5	19.2	+ 1.7
<u>Normo-Oxaluric Stoneformers</u>					
Urivetzky 1992	0.5	3	21.6	28.4	+ 6.8
Urivetzky 1992	1	3	26.1	39.8	+ 13.8
Urivetzky 1992	2	3	18.2	36.4	+ 18.2
<u>Hyper-Oxaluric Stoneformers</u>					
No studies					

¹ Wandzilak explained this increase as originating from generation of oxalate from ascorbate during the assay procedures. ² The mean increase was due to a large increase in one of the six individuals, with little or no change in the other five (Liebman, personal communication)

added, most studies published before 1994 cannot be accurately interpreted because of this technical problem. Recently, 4 studies conducted with appropriate precautions to prevent nonenzymatic conversion of ascorbate have determined the effects of ascorbate doses ranging from 400 mg to 4 g per day in healthy people who do not form stones (Table 1). In 1994, Wandzilak *et al* (26) found that 1, 5, and 10 g per day doses increased urinary oxalate from 34 mg per day to 41, 41, and 48 mg per day, respectively ($P < .05$), in 15 healthy people who did not form stones (9 men and 6 women). In 1996, Levine *et al* (27) reported in a depletion-repletion study that a dose of 400 mg per day ascorbate increased urinary oxalate from 30 to 35 mg per day (ns), whereas a 1,000 mg per day dose increased it to 40 mg per day ($P < .02$), compared with a dose of 200 mg or less in 6 healthy men who did not form stones. However, in 1997, Liebman *et al* (28) found that 2 g per day for 4 days increased mean urinary oxalate only from 30 to 32 mg per day (ns) in 6 healthy subjects (2 men and 4 women). However, the mean increase was due to a large increase in one of the six subjects, with no change in the other five. Similarly, in 1998, Auer *et al* (29) found that 4 g per day for 5 days only increased urinary oxalate from 17.5 to 19.4 mg per day (ns) in 10 healthy men.

Three epidemiological studies have reported no association of supplemental ascorbate use or serum ascorbate levels with increased risk of kidney stones in the population as a whole. Curhan *et al* (30) reported no difference in relative risk of symptomatic kidney stones in a five year prospective study of men over the five quintiles of vitamin C consumption; quintile means ranged from under 250 mg/d for the lowest to more than 1500 mg/d in the highest, which would have included megadose supplement users. Subjects with a history of kidney stones at the beginning of the study were excluded from their analysis. These same investigators (31) found similar results in a large prospective study of women with essentially the same experimental design; women with vitamin C intake over 1500 mg/d had a 1.06 RR compared to women consuming less than 250 mg/d. Simon and Hudes (32) reported that serum ascorbic acid level was not

related to prevalence of kidney stones in men and women surveyed for NHANES II.

The findings of only small effects within the normal range in 2 of the 4 loading studies and no effect in 2 loading studies and 3 epidemiological studies are somewhat reassuring for patients who do not form stones and are taking ascorbate supplements. However, this lack of effect may not be found in people who form calcium oxalate stones. In the only report to date regarding ascorbate loading in normo-oxaluric calcium oxalate stone patients, Urivetzky *et al* (33) found that doses of 500, 1,000, or 2,000 mg per day increased urinary oxalate from 22 to 28, from 26 to 40, and from 18 to 36 mg per day, respectively ($P < .05$). With a dose of 1 g per day ascorbate, the 14 mg per day increase in urinary oxalate in people who form stones was greater than the 7 mg per day increase reported by Wandzilak *et al* (26) or the 10 mg per day by Levine *et al* (27) in people who do not form stones. Because the risk of calcium oxalate precipitation increased with either higher oxalate or calcium concentration, the increased risk of stone recurrence with even small increases in oxalate would be greater in people who form stones because of hypercalciuria or hyperoxaluria. More studies of patients with stones are clearly needed to determine if there is an "ascorbate"-sensitive subpopulation, as has been suggested for protein.

Ascorbate doses greater than 1 g per day confer little additional benefit for those wanting to maintain tissues fully saturated with ascorbate. Levine *et al* (34) reported that 100 mg per day saturated neutrophils, monocytes and lymphocytes. Plasma was saturated at intakes of 1,000 mg per day. This concurs with the predictions of pharmacokinetic analyses (27). In 1999, Carr and Frei (35) reviewed published studies of vitamin C and chronic disease prevention and concluded that an intake of 90 to 100 mg per day is required for optimal disease reduction. Until further evidence is obtained, people who form calcium oxalate stones are probably wise to either avoid ascorbate supplements or at least restrict them to 250 mg per day or less.

3.1.3. Vitamin B6

Vitamin B-6, in the form of pyridoxal phosphate, is a required cofactor for the transamination of glyoxylate to glycine. When vitamin B-6 status is inadequate for full enzyme activity, glyoxylate is converted to oxalate. Acute vitamin B-6 deficiency induced by feeding a vitamin B-6 free formula diet for six weeks increased urinary oxalate in five healthy males (36). The oxalate increases became evident by the third week, and were rapidly reversed by 600 mg/d pyridoxine during the seventh week. Massey *et al* (37) reported the only study of marginal vitamin B-6 status on urinary oxalate in a healthy population. In this study, mild to moderate vitamin B-6 depletion did not increase urinary oxalate. The depletion diet contained 0.46 mg/d B-6. Similar low levels of B-6 intakes in free-living US populations have been reported by Kant and Block (38); their analysis of NHANES II survey data found that 13% of white females, 17% of black females, 4% of white males and 11% of black males consumed less than 0.5 mg/d. No effect of B-6 status on urinary oxalate was seen although higher protein intakes used in this study may have increased vitamin B-6 requirements. Vegetarian diets, which are low in B6, may be high in legumes, fruits and vegetables and thus dietary oxalate; if an increase in urinary oxalate is seen in omnivorous women changing to a vegetarian diet, this increase may be due to the increase in dietary oxalate rather than vitamin B-6 deficiency.

Vitamin B-6 intakes reported in the NHANES II survey indicated that only 23-29 % of adult males and 6-11 % of females met the 1980 Recommended Dietary Allowance (RDA) for vitamin B-6 intake (39). Of more concern, 24-39 % of males and 39-67% of females consumed less than 50% of the 1989 RDA, which is 2.0 mg/d for males and 1.6 mg/d for females. No population surveys of vitamin B-6 status assessed by biochemical measures have been reported, but it is probable that marginal vitamin B-6 status occurs in apparently healthy populations. This appears to be more likely in those individuals who have little or no consumption of muscle foods or dairy products, which are good sources of vitamin B-6.

If marginal vitamin B-6 status does increase urinary oxalate, the population incidence from this cause appears to be low. Curhan *et al* (31) found no association between vitamin B-6 intakes and kidney stones in a five-year prospective study of males. However the intakes of the reference group with lowest intakes included B-6 intakes up to 3 mg/d, 150% of the RDA. This pooling of males with deficient and adequate intakes would mask effects in the deficient subgroup, which would be expected to be only about 10% of the population (38). Vitamin B-6 supplements of 2 or 10 mg/d (39, 40, 41) reduced urinary oxalate in a few patients with calcium oxalate stones, suggesting that marginal vitamin B-6 status may contribute to excessive oxalate excretion in some individuals. Overall the data support the conclusion that marginal vitamin B-6 status

is not likely to be a significant cause of increased urinary oxalate in a healthy population.

There is some evidence that a few patients with primary hyperoxaluria might benefit from large amounts of pyridoxine supplements. Milliner *et al* (42) summarized the clinical experiences of 25 primary hyperoxaluric patients and concluded that 2.6-3.4 mg/kg pyridoxine combined with orthophosphate treatment reduced calcium oxalate crystallization and appeared to preserve renal function. Mitwalli *et al* (43) that 250-500 mg/d pyridoxine reduced urinary oxalate and stone recurrence in 12 men with mild hyperoxaluria on a low oxalate diet. In contrast, Edwards *et al* (44) reported an increase in urinary oxalate in hypercalcuric stoneformers with mild hyperoxaluria with a 200 mg/d dose. Although large doses of B6 appear to benefit some patients, the potential increase in urinary oxalate requires that patients taking high doses be carefully monitored for potential adverse effects.

3.2. Dietary oxalate versus endogenous contributions in non-stoneformers

The classic paradigm has been that only 10-15% of urinary oxalate originates from the diet, so dietary restriction will not be very effective. However a carefully done study by Holmes *et al* (8) has challenged this assumption. The urinary oxalate of healthy non-stoneformers fed an oxalate-free formula diet fell from 17 to 9 mg/d or to about 10 mg/g creatinine. When dietary oxalate was added back at varying levels from 10 to 250 mg, urinary oxalate increased from to 14 mg/g at 10 mg to 17 mg/g at 180 mg, a typical intake for these individuals. The dietary contribution to urinary oxalate ranged from 24 % at 10 mg/d to 40% at 180 or 250 mg. At these typical intakes, about 6% of dietary oxalate was absorbed. In a therapeutic situation, reduction of dietary oxalate from 250 to 50 mg/d would reduce urinary oxalate by 40%; if urinary oxalate was 50 mg/d, a decrease in 30 mg/d would be expected if the patient was absorbing oxalate at normal levels. It is likely that some stone patients absorb more than 10% of dietary oxalate (see section 5.1), so a dietary oxalate reduction in patients with higher absorption would not have to be as strict to have considerable benefit.

3.3. Dietary oxalate

3.3.1. Mechanisms of absorption.

Oxalate absorption has been found in all segments of the gastrointestinal tract (45, 46, 47). Both active and passive absorption has been reported. An untested assumption is that only free oxalate form is absorbed. Since only the potassium and sodium salts are soluble at physiological conditions, these would be the dietary forms absorbed. Since calcium and magnesium salts are insoluble at gut conditions, it has been assumed that these salts were not absorbed. However, Hanes *et al* (48) reported that dual labeled calcium oxalate appeared to be absorbed intact in rats. About 2% of the load was absorbed. Confirmation of absorption of intact calcium oxalate in humans has not been tested. Adding calcium or magnesium to oxalate loads reduces urinary oxalate absorption (see section 4.1).

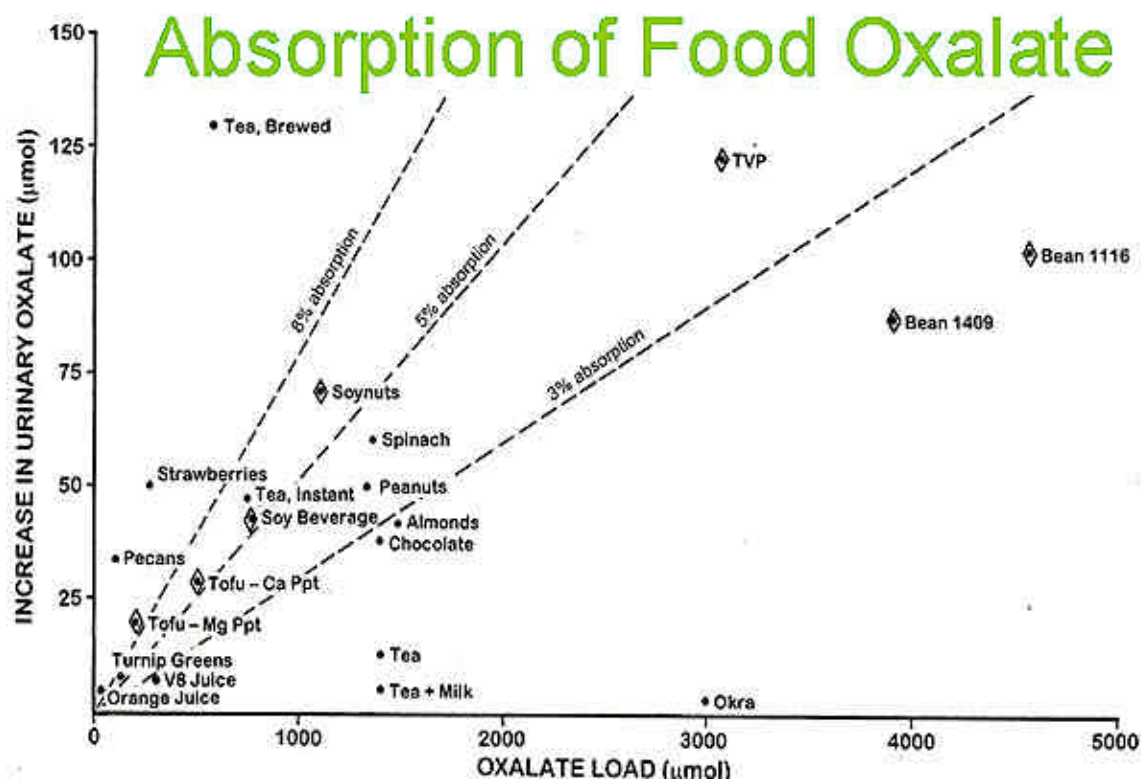


Figure 1. Relationship between oxalate load and urinary oxalate excretion in humans

3.3.2. Oxalate absorption from foods in healthy individuals

Oxalate absorption from foods has been studied using the increase in urinary oxalate after consumption of a known oxalate load as a food. Most of the studies where urinary excretion was determined have found that 3-8% of the food oxalate was absorbed (49, 50, 51, 52, figure 1). A few outliers are seen, specifically brewed tea and soybean seeds. The soybean seeds are high in both calcium and oxalate, and the lower absorption is likely due to both the relative unavailability of the calcium oxalate complex and the high loads, which may exceed the capacity of the gut to absorb oxalate.

4. OTHER DIETARY FACTORS POTENTIALLY AFFECTING URINARY OXALATE

4.1. Calcium and magnesium

Oxalate binds with calcium and magnesium to form insoluble salts. In 1978, Barilla *et al* (53) demonstrated that adding either 2.8 mmol of calcium or magnesium to a 5 mmol sodium oxalate load containing 2.2 mmol each of calcium and magnesium reduced the 8 hr post-load oxalate excretion by 50% and 42% respectively, in eight ileal disease patients. Similar findings were seen in stone patients with 65% and 57% reductions respectively. Berg *et al* (54) found that adding 200 mg magnesium as the carbonate salt to meals containing 22.5 mmol oxalate (2027 mg), 14 mmol calcium and 14.4 mg magnesium reduced 32 hour oxalate excretion by 51% in ten healthy subjects. In a two week trial, adding 5 mmol magnesium as either the citrate or oxide to self-selected meals reduced 24 hour

urinary oxalate by 16%. Increasing calcium from 1211 mg/d to 3828 mg/d by increasing dairy products and adding a calcium-rich mineral water to a high oxalate diet (2220 mg) reduced urinary oxalate 59% in healthy non-stoneforming men (55). On the lower calcium intake, all 14 subjects were hyperoxaluric, and increasing the calcium brought all urinary oxalate values to within a normal range.

Liebman and Costa (11) used an isotopic method to distinguish between the effects of calcium and magnesium on endogenous versus exogenously derived (dietary) urinary oxalate. When 300 mg calcium as carbonate or magnesium as oxide was added to an oxalate load of 198 mg, oxalate absorption was reduced from 13.5% to 5.1% and 7.6%, respectively. Since Liebman and Chai (56) found that 200 mg calcium maximized the effect with a 200 mg oxalate load, Massey and Kynast-Gales (57) increased dietary calcium by substituting milk for apple juice. Increased calcium was supplied as 120 mL milk (150 mg calcium) with each of the three meals containing about 100 mg oxalate in a study of the 23 normocalciuric calcium oxalate stone formers. Increasing calcium from 354 to 772 mg/d reduced urinary oxalate from 510 to 420 micromol/d, an 18% decrease.

4.2. Sweeteners, Caffeine, and Beverages

4.2.1. Sweeteners

Nguyen and several co-investigators have tested several sweeteners for oxaluric effects in healthy nonstoneformers. Glucose and fructose both increased oxalate (58). 250 mg of the sugar substitute aspartame increased urinary calcium but not oxalate (59). In

Table 2. Percentage of dietary oxalate absorbed in stone-forming (SF) and non-stone-forming (NSF) populations

	% NSF (n)	% over 10%	% SF (n)	% over 10%	Comments
Tiselius <i>et al</i> (1981)	13.6 (15)		14.4 (21)		
Maragella <i>et al</i> (1982)	14.4 (17)		16.5 (63)		All SF
			13.2 (34)		Normocalciuric SF
			19.9 [†] (29)		Hypercalciuric SF
Schwille <i>et al</i> (1984)	9.0 (12)		5.1 [†] (54)		All SF
			5.3 (12)		Normocalciuric SF
			5.0 (42)		Hypercalciuric SF
Lindsjo <i>et al</i> (1989)	6.2 (20)	15%	11.0 [†] (12)	58%	
Berg <i>et al</i> (1990)	8.3 (19)	31%	14.6 [†] (20)	60%	
Hesse <i>et al</i> (1999)	6.7 (50)	18%	9.2 (70)	35%	
Von Unruh <i>et al</i> (2000)	7.5 (86)	23%	9.8 (102)	41%	

[†] Significantly different from nonstoneformers

comparison, 75 g glucose raised urinary oxalate by 27%, mostly within the first two hours. This same group tested 20 g doses of four sugar alcohols used as sugar substitutes: sorbitol, xylitol, Lycasin and Maltisorb. Only xylitol increased urinary oxalate, from 1.9 to 3.0 mmol/mmol Cr. In this study, 20 g glucose did not raise oxalate significantly. Similar loading studies have not been reported in stone formers.

4.2.2. Soft drinks

Because of the effects of glucose and fructose on increasing urinary oxalate, it is not surprising that Rodgers (60) report that drinking 2.0 L of regular [non-diet] cola beverage increased urinary oxalate. Mean oxalate increased from 220 to 280 micromol in 14 males and 190 to 250 micromol in 31 females. In an earlier study, 3 quarts of cola increased urinary oxalate by 8.3 mg/d (61). Cola has been reported to contain some oxalate. Shuster *et al* (62) found that stone patients randomized to abstain from soft drinks had a 7 % reduced incidence of stone recurrence compared to those who continued their usual soft drink consumption. Most of the benefit was seen in individuals who formerly drank non-diet soft drinks.

4.2.3. Citrus juices

Because urinary citrate is an inhibitor of calcium oxalate formation, increased consumption of citric fruit beverages has been tested. Goldfarb and Asplin (63) reported that drinking 240 mL of grapefruit juice three times day increased urinary oxalate from 41 to 52 mg/d, while citrate increased from 505 to 591 mg/d. They concluded that the increase in oxalate offset the beneficial increase in citrate, so there was no change in urine lithogenicity, either positive or negative. Similarly, orange juice increased oxalate by 35% (28, 64). However, lemonade made with 4 oz of lemon juice diluted to a total volume of 2 L slightly decreased oxalate (65).

4.2.4. Tea

Regular tea, both black and green, contains substantial amounts of oxalate, from 300-1500 micromol/L (66). Loading studies have found greatly varying oxalate absorption from tea, ranging from less than 1% to over 20%. Herbal teas have much lower oxalate contents, from 31-75 umol/L and are an acceptable alternative (67).

4.2.5. Caffeine

Although caffeine increases urinary calcium significantly, it has no effect on urinary oxalate (68).

Curhan *et al* (69, 70) looked at association of beverage consumption with risk of kidney stones in two prospective studies of male health professionals and females nurses respectively. Only high grapefruit juice consumption was associated with increased risk in both men and women. In contrast, higher consumption of lemonade, cola, other soft drinks, coffee, tea, beer, wine and liquor were not associated with increased risk in men or women. In fact higher consumption of coffee, tea, and wine was associated with slightly decreased risk. The reasons for these findings are not readily apparent. In both studies, increased volume intake was associated with reduced risk.

4.3. Bran

Several types of bran have been tested as a dietary treatment to reduce calcium absorption and thus urinary calcium. The effectiveness of bran has been attributed mainly to its phytate content, which accounts for 70-82% of calcium binding (71). A possible explanation is that when the bran binds calcium, less calcium is available to bind to oxalate, and its absorption is increased. However, brans also contain oxalate, which may increase urinary oxalate, therefore offsetting the benefits of calcium reduction. Most studies have reported an increase in urinary oxalate after bran supplementation. Ebisuno *et al* (72) had stone patients consume 10 g rice bran twice daily. Urinary oxalate increased from 48.7 mg/d at baseline in 164 patients to 57.7 mg/d in the 44 remaining patients. Similar results with rice bran were reported by Jahn *et al* (73). All three studies with wheat bran supplementation have found an increase in urinary oxalate (73, 74, 75). It seems prudent to restrict the amount of concentrated brans in the diet of stone formers as a precautionary measure, especially in hyperoxaluric patients.

5. OXALATE ABSORPTION IN DISEASE

5.1. Stoneformers - genetic effects on the oxalate absorption

Some calcium oxalate stone formers may have higher urinary oxalates, not because they eat more high oxalate foods, but because they absorb more of the dietary oxalate they consume (4). Although gastrointestinal disease = increases oxalate absorption (76), most hyperoxaluric stone formers don't have conditions predisposing to oxalate overabsorption. Several investigators have tested for the possibility of genetically increased oxalate absorption by

Table 3. Variability of oxalate in foods

	Mean (mg/100g food)	Range (mg/100g food)
Rhubarb		24-300
Soybean seeds	1650	670-3500
Chocolate bar	58	50-67
Sweet potato	29	0.2-87
French fries	22	20-23
Tomato	6	3-13
Whole wheat bread	27	25-29

loading healthy stoneformers with labeled oxalate. Although the early investigations by Tiselius (77) and Schuille (78) found no difference in the mean % oxalate absorbed, other more recent studies have reported higher rates in at least hypercalciuric stoneformers (79, 80, 81, 82, Table 2). In all studies, investigators fed food containing labeled oxalate, then collected urine for 24 hours. Most non-stone formers absorb between 3-10% of an oxalate load, so absorption over 10% was considered to be high. Overall, the studies support the concept that at least one-third of the stone-forming population absorb more than 10% of dietary oxalate. For these individuals, dietary counseling to reduce oxalate consumption should be especially beneficial.

5.2. Degradation by gut microbes such as *Oxalobacter formigenes*

Although no human tissues are known to catabolize oxalate, some individuals apparently have gut microbes that do degrade oxalate (83). *Oxalobacter formigenes* is an oxalate-degrading bacterium found in some humans. Doane *et al* (84) reported that the amount of dietary oxalate recovered in feces was associated with the presence of oxalate-degrading bacteria. Its absence has been associated with an increased risk of hyperoxaluria and/or kidney stone formation (85). A therapeutic treatment based on gut recolonization with selected strains is being developed, but not yet available (86).

5.3. Gastrointestinal disease

Hyperoxaluric stone formation is a common complication of enteric disease resulting from increased absorption of dietary oxalate (87). Several mechanisms have been proposed. First, because more calcium is bound to free fatty acids, less is available to bind oxalate, thereby increasing oxalate absorption. Second, the colon may be more permeable due to increased delivery of bile salts. Finally, there may be fewer *Oxalobacter formigenes* or other oxalate-degrading bacteria in the disease state. Few studies have been done on dietary treatments, but dietary oxalate restriction and calcium supplementation give some limited success (76).

6. DIETARY RECOMMENDATIONS FOR STONEFORMERS

6.1. Dietary counseling and stone recurrence

Do dietary changes reduce incidence of kidney stones? Only four studies have examined that hypothesis, only one of them specifically targeted at reducing urinary oxalate. Laminstki *et al* (5) found that 18 of 40 mildly hyperoxaluric patients had normal oxalate excretion after a low oxalate diet, with a mean decrease from 421 to 261 micromol/d. Nomura *et al* (88) studied stone patients after

dietary counseling to avoid high oxalate foods and follow the Japanese dietary guidelines for protein, fat and carbohydrate intakes. After six months, urinary oxalate was 30.3 mg/d in the diet group versus 37.4 in the control group. Over the four years of follow-up, the stone recurrence was only 20 % in the diet group, compared to 80% in the control group. In the Czech republic, Kocvara *et al* (89) tested dietary counseling targeted to the specific biochemical urinary abnormality of each patient. Hyperoxaluric patients were advised to restrict dietary oxalate, and consume dairy products with the main meal. The diet group had a 13% recurrence in 3 years, while the control group had a 42 % rate. Finally Borgi *et al* (90) reported a benefit effect of a lower animal protein, higher calcium, lower salt diet. Although animal protein consumption only dropped 10%, dietary calcium increased and salt intake decreased by half. Comparing these changes with published effects of the amount of change of each component on urinary composition in other studies, the main effect was mediated by the change in salt.

6.2. Oxalate content of foods

6.2.1. Variability of oxalate levels in foods.

Unfortunately planning an oxalate-restricted diet has two inherent problems: lack of data on food oxalate content and variability of oxalate levels in foods. The amount of oxalate synthesized by a plant depends not only on its genetic programming as seen by differences in varieties, but also factors such as growing conditions such as soil nutrients, watering conditions etc. Even the amount of variability ranges widely (Table 3). There is also the possibility of analytical error. As mentioned above, ascorbate is converted to oxalate in alkaline conditions, a factor which may account for the higher values seen in the earlier studies which used an enzymatic method to determine oxalate values. Food values determined by HPLC or ion electrophoresis are more accurate and only values determined this way should be used.

How much oxalate is found in common diets? Holmes *et al* (91) reported that analysis of 3 days diet of 5 individuals found dietary oxalate was 152 + 83 mg/d with a range of 44 to 351 mg/d. Massey and Kynast-Gales (57) found a study diet based on the Food Guide Pyramid emphasizing more fruits, vegetables, whole grains and the substitution of nuts and legumes for meat contained 304 mg/d.

6.2.2. Ten “forbidden” foods

The ten foods highest in oxalate are spinach, rhubarb, beets (both leaves and roots), nuts, chocolate, concentrated brans, legumes (beans, including soy), regular tea, parsley and berries. Because counting mg oxalate is difficult and uncertain, a simpler dietary prescription is required for longer-term compliance. A simple initial approach is to advise the avoidance of these ten high oxalate foods. Simultaneous consumption of a high calcium food in sufficient quantities will reduce oxalate absorption from the more moderate oxalate foods in that meal (see section 6.3).

6.2.3. Look for dietary excesses

In the author's experience, about one-quarter of idiopathic stoneformers have an excessive intake of one of

the ten foods discussed in the section above. Excessive intakes of any of the high oxalate foods can be discovered by specifically asking the patient about these ten foods.

6.3. Simultaneous consumption of high calcium food

Massey and Kynast-Gales (57) found that increasing calcium intake from 400 to 800 mg by adding milk to each meal reduced urinary oxalate by 18%. Other high calcium foods, such as cheese, yogurt, puddings and milk-based gravies should also be effective. Each meal should contain 150 mg calcium in order to bind an estimated 100 mg of oxalate in each meal.

6.4. Should normo-oxaluric patients be advised to restrict oxalate?

Dietary counseling is likely to be more effective in individuals with high intakes of high oxalate foods, and individuals with urinary oxalate over 30 mg/day [350 micromol] on self-selected diets. Patients with urinary oxalate under 30 mg/d and no high oxalate foods on days of urine collection should be given precautionary advice to avoid adding these foods to their diet.

7. CONCLUSIONS

1. Dietary oxalate contributes 40-50% of urinary oxalate when typical diets are consumed. 2. Possibly one-third or more of stoneformers have an oxalate absorption that is higher than 10%, the upper limit considered as normal. 3. Dietary restriction of oxalate should be effective in reducing urinary oxalate, and therefore stone recurrence in some stoneformers.

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Key Words: Diet, Oxalate, Protein, Ascorbate, Vitamin B6, Calcium, Citrate, Nephrolithiasis, Review

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