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Urinary oxalate excretion increases with body size and decreases with increasing dietary calcium intake among healthy adults

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Urinary oxalate excretion increases with body size and decreases with increasing dietary calcium intake among healthy adults. Increasing dietary calcium intake decreases urinary oxalate excretion by increasing intestinal precipitation of dietary oxalate as calcium oxalate. This mechanism was speculated to account for the decreased prospective incidence of kidney stones as estimated dietary calcium intake, adjusted for caloric intake, increased among men in a recent large epidemiological study. To further assess the relationship between estimated diet calcium and urinary oxalate, we studied 94 healthy adults, 50 women and 44 men, ages 20 to 70 years with weights ranging from 47 to 104 kg while they ate their customary diets. Each subject completed a semiquantitative food frequency questionnaire and collected three 24-hour urines preserved with HCl. The urines were collected accurately as judged by a mean intrasubject CV for creatinine excretion of 9.8% and direct relations between urinary creatinine excretion and body wt ($r = 0.62$; $P < 0.0001$), or predicted urine creatinine content for sex, age and weight using the Cockcroft and Gault formulas ($r = 0.76$; $P < 0.0001$). Estimated diet calcium intake ranged from 6.8 to 68 mmol/day (272 to 2720 mg/day) and averaged 29.5 mmol/day (1180 mg/day). Individual mean urinary oxalate excretion ranged from 0.079 to 0.332 mmol/day (7 to 29 mg/day) and averaged 0.198 mmol/day (17 mg/day). Among all subjects, daily oxalate excretion was directly related to creatinine excretion as an estimate of lean body mass ($r = 0.61$; $P < 0.0001$). Thus, oxalate excretion among men averaged 0.228 ± 0.051 SD mmol/day, a value significantly higher than the average among women of 0.173 ± 0.045 mmol/day ($P < 0.001$). Daily urine oxalate excretion/creatinine decreased curvilinearly as estimated dietary Ca intake increased ($r = -0.30$; $P = 0.0035$) and as the ratio of estimated dietary calcium to dietary oxalate increased ($r = -0.39$; $P = 0.0001$). We conclude that body size is the major determinant of urinary oxalate excretion among healthy adults, presumably reflecting variations in endogenous oxalate synthesis with lean body mass. Increasing estimated diet calcium intake, especially up to the range of 15 to 20 mmol/day (600 to 800 mg/day) has an additional effect to decrease urinary oxalate excretion, presumably by limiting intestinal absorption of dietary oxalate.

Calcium oxalate is the major component of about 80% of all kidney stones [1, 2]. Average urinary oxalate concentration, as determined by the daily rate of urinary oxalate excretion relative to urine volume is, therefore, a critical determinant of the relative saturation of the urine with respect to poorly soluble calcium oxalate [3]. Approximately 85% of urinary oxalate is derived from oxalate produced in the body as an end product of metabolism, while the remaining 15% is derived from intestinal absorption of dietary oxalate [4, 5]. Urinary excretion of dietary oxalate is decreased by increasing dietary calcium intake among both healthy adults and calcium-stone formers [6–10] because of precipitation of dietary oxalate with calcium in the gut, thereby reducing intestinal oxalate absorption. The results of a recent large epidemiological study demonstrated that the prospective incidence of kidney stones among 45,000 men without prior stones decreased over a four year follow-up period as calcium intake, assessed by a well standardized diet history, increased [11]. The authors of that study proposed that their observations might be related to a progressive decrease in urinary oxalate excretion, as dietary calcium intake increased among the participants in the study as a consequence of the effect of calcium to reduce intestinal oxalate absorption. The present study was, therefore, primarily undertaken to directly evaluate urinary oxalate excretion rates among healthy adults in relation to the composition of their customary diets, also as assessed by the same diet questionnaire used in the epidemiological study. Also, since previous studies of relatively small numbers of stone formers and of healthy subjects have shown that there appears to be a direct relationship between daily urinary oxalate excretion and body size [7, 12], we wanted to extend evaluation of that relationship to a larger group of subjects.

Methods

We studied 94 healthy adults as out-patients in the Medical College of Wisconsin Clinical Research Center, with their consent, using a protocol approved by the Medical College of Wisconsin Human Research Review Committee. Fifty women and 44 men participated, approximately five women and five men in each of the ten five-year age intervals between 20 and 70 years. None had a personal history of kidney stones. Twelve of the 50 women and 1 of the 44 men were regularly taking a calcium supplement providing $\geq$ 500 mg calcium/day, while 4 of the 50 women and 3 of the 44 men were regularly taking vitamin C $\geq$ 500 mg/day. None was taking diuretics. Each subject was provided a stipend for the collection of three 24-hour urine specimens and for the completion of the dietary questionnaire. A semiquantitative food frequency questionnaire was used to evaluate the diets of the subjects [13–15]. Oxalate-containing foods not on the questionnaire were added to the list [16] as was the quantity of water

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consumed in addition to other listed beverages. Nutritionist IV (N-Squared Computing, Salem, OR, USA) software was used to analyze the nutrient content of the diet for total calories, total water (water, beverage and water content of foods), oxalate, protein, calcium, sodium, potassium, fiber and ascorbic acid. Oxalate values for those foods which have published data were entered into the software data base.

The urines were preserved with 20 ml of 6 N HCl during collection to prevent non-enzymatic conversion of ascorbate to oxalate [12, 17, 18]. Urine volume and the concentrations of creatinine, oxalate, calcium, magnesium, sodium, potassium, ammonium, phosphate, citrate, sulfate and urea nitrogen were measured. Urine volumes were directly measured volumetrically and were not corrected for the 20 ml of HCl added to the collection containers. Creatinine, phosphate, ammonium and urea nitrogen concentrations were measured using an autoanalyzer by methods previously described [19]. Oxalate was measured using immobilized oxalate oxidase [20, 21]. During the time period of the study, the interassay coefficients for low and high oxalate standards in 18 assays averaged 6.9% and 3.2%, respectively, while the average recovery of oxalate added to 106 urine specimens averaged 98.0 ± 4.5 SD %. Calcium and magnesium were measured by atomic absorption spectrophotometry and sodium and potassium by flame emission spectrophotometry. Sulfate was measured turbidometrically [22] and citrate using citrate lyase [23].

Since the urines were collected in HCl we could not directly measure urine pH or total CO_2-content. However, we estimated urine pH based upon the measured urinary NH_4/creatinine ratio using the mean for that relationship observed in 734 24-hour urine specimens collected under mineral oil and preserved with thymol and phenylmercuric nitrate by 42 healthy adults [19, 24, 25]: pH = 6.6965 to 1.6195 * log NH_4/creatinine mmol/mmol; $r = 0.78$ (pH range 5.05 to 7.30). Similarly, we estimated urine total CO_2 concentration using estimated pH based on the mean relationship between total CO_2 concentrations and pH measured in 631 24-hour urines having a pH ranging from 5.80 to 7.30 from the same 42 subjects: log [total CO_2-content], mmol/liter = −4.8443 + 0.88814 * pH ($r = 0.91$). In addition, for urines having a pH < 5.80, we assumed that the urine was in equilibrium with the blood pCO_2 = 40 mm Hg. Since the urines were collected in HCl we also could not measure the subject's actual urinary Cl excretion rates. However, we also assumed that urine [Cl] = urine [Na] since most Cl is added to foods during preservation, cooking or at table as NaCl, because dietary Na and Cl in health are almost completely absorbed by the intestine and because among 145 healthy adults (86 eating constant diets in our Clinical Research Center providing < 5 to 275 mmol Na/day and 59 eating their self-selected home diets) we have observed that: urine Cl mmol/day = 3.77 + 0.946 * urine Na mmol/day ($r = 0.97$) [25]. Using these derived data together with the directly measured concentrations of urinary constituents, we estimated the relative saturation of each urine with respect to calcium oxalate monohydrate [$Ca(COO)_2 \cdot H_2O$] and brushite ($CaHPO_4 \cdot 2H_2O$) using the EQUIL program developed by Finlayson and associates [26].

Results are presented as group means ± SD and in some instances ranges. Simple and multiple regression analyses were performed using SAS. These relationships were considered significant if $P \leq 0.01$. For some analyses dietary intake was adjusted for caloric intake as described by Willett and associates [13].

Table 1. Subject Characteristics

	All	Women	Men	Women vs. men *P*
Number	94	50	44	
Age. *years*				
Mean	43.9	44.8	42.8	0.515
Range	19.8–70.4	19.8–70.4	22.2–68.4	
Weight, *kg*				
Mean	72.7	66.8	79.4	<0.001
Range	47.3–103.9	47.3–96.9	57.0–103.9	
Height, *m*				
Mean	1.70	1.64	1.77	<0.001
Range	1.52–1.90	1.52–1.75	1.61–1.90	
Surface area, m^2				
Mean	1.83	1.72	1.96	<0.001
Range	1.44–2.23	1.44–2.08	1.70–2.23	
Body mass index, kg/m^2				
Mean	25.2	24.9	25.4	0.513
Range	18.3–37.1	18.9–37.1	18.3–32.0	

Group differences between men and women were compared by unpaired *t*-test. These comparisons were considered significantly different if $P \leq 0.05$. Some additional aspects of the relationships between measured urine composition and estimated diet composition will be the subject of separate report.

Results

Subjects

The ages and physical characteristics of all 94 subjects and, separately, for the 50 women and the 44 men are shown in Table 1. The ages and body mass indices of the women and the men were similar, but the men, as expected, were heavier, taller and had larger estimated surface areas.

Daily urine composition

The means and ranges of daily urine composition for all of the subjects and separately, for the women and the men are shown in Table 2.

The accuracy of the individual daily urine collections were evaluated based on their creatinine content in relation to body wt and to predicted creatinine content based on sex, age and body wt using the Cockcroft and Gault formulas [27]. The grand mean of the individual coefficients of variation in creatinine content of the three urines averaged 9.6%. As shown in Figure 1, creatinine excretion rates for all urine collections by the 94 subjects was, as expected, significantly correlated to their body weights; $r = 0.62$; $P < 0.0001$ (Fig. 1A) and more closely correlated to predicted urinary creatinine content [27] that also takes account of the lower muscle mass of women and the decline in muscle mass with age; $r = 0.76$; $P < 0.0001$ (Fig. 1B). These data indicate that the subjects collected their urines with reasonable accuracy.

Despite the larger body size of the men, their mean daily urine volumes averaged 1587 ml, a value that was slightly less but not significantly different from the mean of 1685 ml among the women; $P = 0.541$ (Table 2). Otherwise, the mean daily urinary excretion rates of all of the other measured urinary constituents, with the exception of citrate, were significantly greater among the

Table 2. Daily urine composition

	All 94 subjects		50	44	Women vs. men
	Mean	Range	Women	Men	*P*
Volume *ml/day*	1645	593–5697	1685 ± 832[b]	1587 ± 863	0.541
Creatinine *mg/day*	1462	550–2455	1175 ± 245	1789 ± 285	<0.001
Oxalate *mmol/day*	0.198	0.079–0.332	0.173 ± 0.045	0.228 ± 0.051	<0.001
Calcium *mmol/day*	4.50	1.40–10.88	3.92 ± 1.69	5.16 ± 2.20	0.003
Sodium *mmol/day*	156	47–322	143 ± 42	171 ± 51	0.006
Potassium *mmol/day*	67	24–125	60 ± 18	75 ± 22	<0.001
Magnesium *mmol/day*	5.85	1.58–10.05	5.24 ± 1.58	6.54 ± 1.66	<0.001
Phosphate *mmol/day*	29.8	11.9–51.0	25.6 ± 6.7	34.5 ± 7.2	<0.001
Sulfate, *mmol/day*	20.0	4.0–32.1	17.1 ± 5.5	23.2 ± 4.9	<0.001
Citrate *mmol/day*	4.12	0.64–9.52	4.40 ± 1.42	3.80 ± 1.42	0.043
Ammonium *mmol/day*	32.1	10.9–74.3	27.3 ± 7.2	37.4 ± 11.9	<0.001
Urea-N *g/day*	10.15	4.33–19.21	8.84 ± 2.36	11.63 ± 2.68	<0.001
pH[a]	6.06	5.70–6.53	6.02 ± 0.16	6.11 ± 0.06	0.009
Total CO_2 content *mmol/liter*[a]	3.7	1.7–9.3	3.4 ± 1.4	4.1 ± 1.4	0.022
Chloride *mmol/day*[a]	156	47–322	143 ± 42	171 ± 51	0.006
Relative calcium oxalate saturation[a]	3.1	0.4–8.7	2.5 ± 1.6	3.8 ± 1.6	<0.001
Relative brushite saturation[a]	1.1	<0.1–3.8	0.8 ± 0.8	1.5 ± 0.9	0.001

[a] Estimated as described in **Methods**
[b] Variances through the Table are shown as SD.

men, as expected, because of their large body sizes. As shown in Table 2, the mean daily urinary citrate excretion rate among the women averaged 4.4 mmol/day (845 mg/day), a quantity significantly greater ($P = 0.043$) than among the men, which averaged 3.8 mmol/day (730 mg/day), as has been observed by others [28].

Mean daily oxalate excretion for all 94 subjects averaged 0.199 ± 0.055 mmol/day (range 0.079 to 0.332 mmol/day). Figure 2 shows that among all 94 subjects mean daily urinary oxalate excretion rates were directly associated with body wt ($r = 0.52$; $P < 0.0001$), with body surface area ($r = 0.52$; $P < 0.0001$) and, more closely, with lean body mass as reflected by mean daily urinary creatinine excretion ($r = 0.62$; $P < 0.0001$). Thus, the men, because of their greater body weight and muscle mass (Table 1 and Fig. 1), excreted an average of 0.228 ± 0.051 mmol oxalate/day, significantly more than the average oxalate excretion rates among women that averaged 0.173 ± 0.045 mmol/day ($P < 0.0001$).

The urines of the men exhibited relative urinary saturations with respect to calcium oxalate that were significantly higher than among the women by about 50% (Table 2) as consequence of: (a) the greater daily rates of urinary oxalate and calcium excretion among the men and (b) the same or slightly lower urine volumes among the men resulting in higher urinary oxalate and calcium concentrations. Similarly, the average relative saturation of the urines of the men with respect to brushite were significantly higher than those of the women by about 85% (Table 2) because daily urinary calcium and phosphate excretion rates were significantly higher, daily urine volumes slightly lower and estimated urine pH were slightly, but significantly, higher among the men. The urines of the women were, on average, undersaturated with respect to brushite.

Estimated diet composition

Table 3 summarizes the means and ranges of estimated diet composition for the group based on the food frequency questionnaire and, separately, these estimates for women and for men. The estimates for dietary Ca intake shown in Table 3, which averaged 26.2 mmol/day and ranged from 6.2 to 65.6 mmol/day, includes only Ca contained in food and not the additional Ca taken as supplements by some subjects. When the additional Ca taken as supplements by some subject was taken into account, Ca intake for the group averaged 29.5 mmol/day and ranged from 6.8 to 68 mmol/day. Estimated mean daily intakes of total water (in food, including beverages, as well as water), of oxalate and of calcium were similar among the men and the women. The estimated mean daily intakes of potassium among men were slightly but not significantly greater than among the women (Table 3). Total vitamin C intake, including that taken as supplements, also did not differ in men and women (Table 3), although when only vitamin C contained in the basic diets was considered, the diets of the men were estimated to contain 218 mg vitamin C/day as compared to 154 mg/day among the women ($P = 0.011$). The mean daily intakes of the total calories, sodium, phosphate, and of protein and fiber were significantly greater among the men than among the women, as expected, because of the larger body sizes of the men.

Relationships between urinary oxalate excretion and estimated dietary calcium intake

Figure 3 summarizes the principal observed relationships between urinary oxalate excretion and dietary Ca intake as well as the ratio of dietary Ca to dietary oxalate. As shown in Figure 3A, urinary oxalate excretion, divided by creatinine to take account of the relationship between oxalate excretion and lean body size (Fig. 2), was inversely related to the estimated Ca intake of the basic diet, exclusive of Ca supplements: urine oxalate/creatinine μmol/mmol = 18.3 to 0.0945 * diet Ca mmol/day ($r = -0.27$; $P = 0.0077$). This relationship appeared to be curvilinear: urine oxalate/creatinine μmol/mmol = 24.1 − 6.01 * log(basic diet Ca,

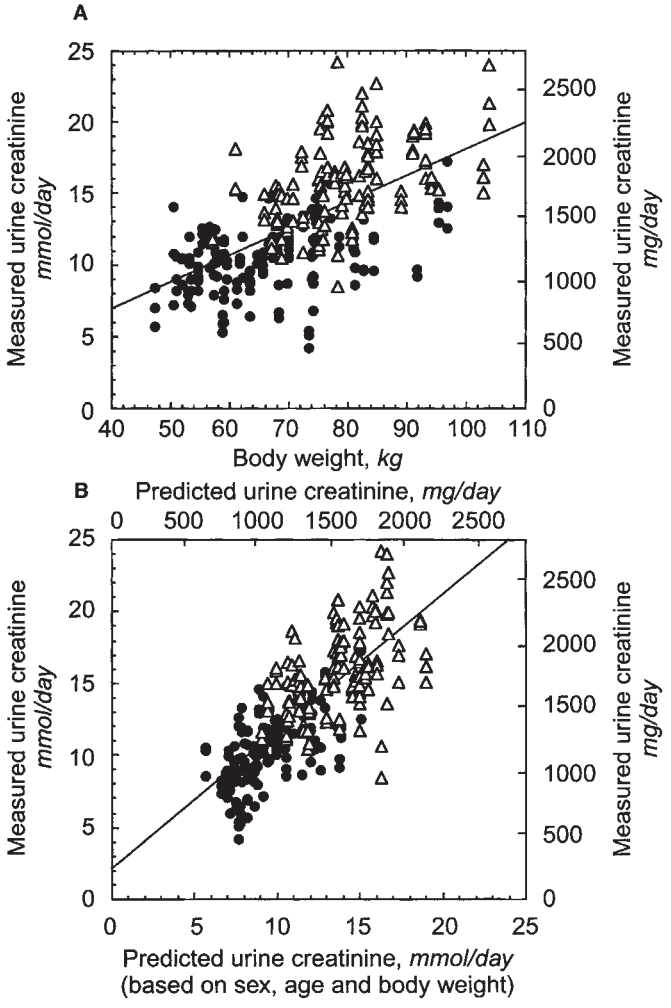

Fig. 1. A. *Daily urine creatinine excretion for all 3 urine collections by each of the 94 subjects in relation to body wt: measured creatinine mmol/day = −0.619 + 0.187 * weight kg (r = 0.62; P < 0.0001).* The left vertical axis gives creatinine in molar units and the right vertical axis gives creatinine in equivalent mass units. Symbols are: (●) women; (△) men. **B.** Daily urine creatinine excretion for all urine collections by each subject in relation to predicted creatinine excretion based on the Cockcroft and Gault formulas: measured creatinine mmol/day = 2.11 + 0.984 * predicted urine creatinine mmol/day ($r = 0.76$; $P < 0.0001$). The superior horizontal axis and right vertical axis give creatinine in mass units.

mmol/day); $r = -0.30$; $P = 0.0035$. Thus, urinary oxalate/creatinine appeared to decrease to an approximate plateau when dietary Ca intake exceeded about 20 mmol/day (800 mg/day). When urinary oxalate/creatinine was evaluated in relation to total Ca intake that also included the Ca contained in supplements taken by some of the subjects, an inverse relationship was no longer detectable ($r = -0.10$; $P = 0.3096$). As shown in Figure 3B, there was a similar trend for urinary oxalate/creatinine to decrease as the basic dietary Ca intake/kg body wt increased, although these relationships was not significant: urine oxalate/creatinine μmol/mmol = 17.6 − 4.81 * diet Ca/body wt mmol/kg ($r = -0.20$; $P = 0.0458$); urine oxalate/creatinine = 13.97 − 3.92 * log(diet Ca/body wt mmol/kg); $r = -0.20$; $P = 0.0471$. More significantly, as shown in Figure 3C, urinary oxalate/creatinine was inversely

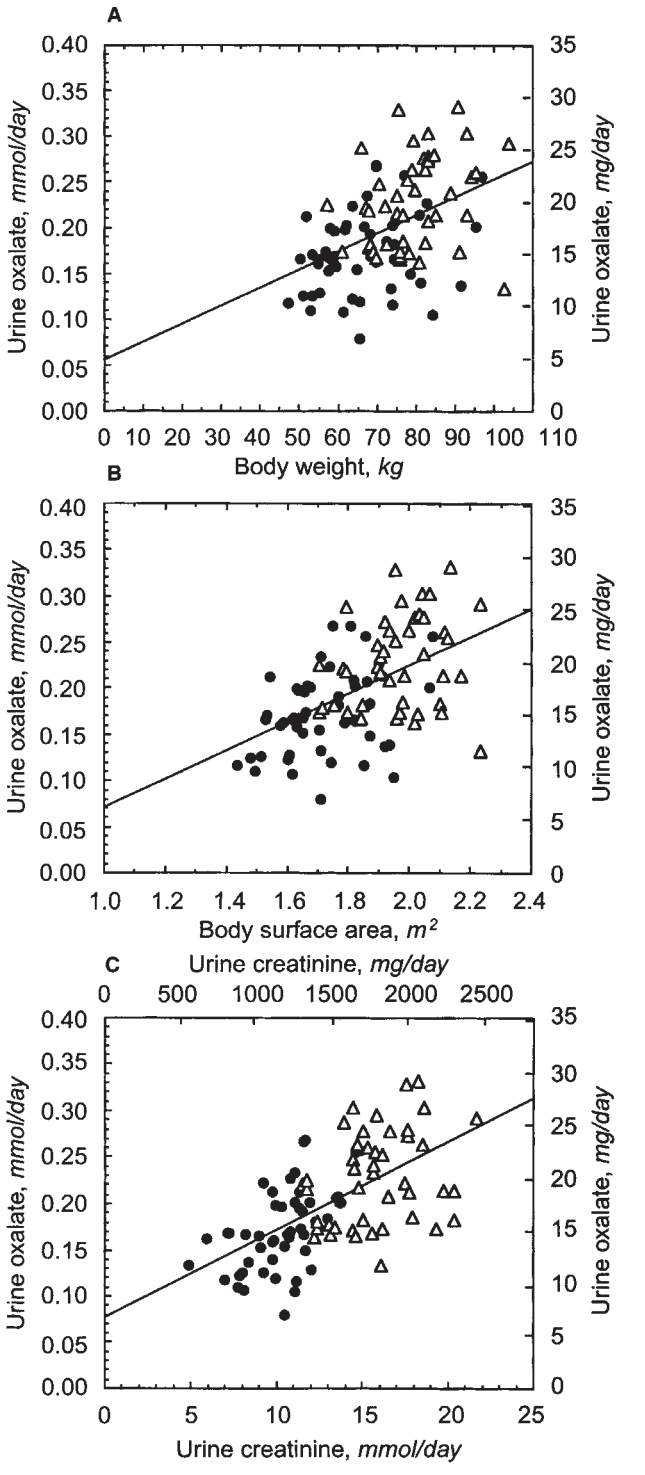

Fig. 2. *Mean daily urine oxalate excretion for each of the 94 subjects in relation to estimates of body size.* **A.** Mean daily urine oxalate in relation to body wt: urine oxalate mmol/day = 0.0552 + 0.00197 * weight kg (r = +0.46; $P < 0.0001$). **B.** Mean daily urine oxalate in relation to body surface area: urine oxalate mmol/day = −0.0844 + 0.154 * surface area, m^2 ($r = 0.52$; $P < 0.0001$). **C.** Mean daily urine oxalate in relation to mean daily urine creatinine excretion as an estimate of lean body mass: urine oxalate mmol/day = 0.0768 + 0.00940 * urine creatinine mmol/day ($r = 0.61$; $P < 0.0001$). In each panel, the right vertical axis gives oxalate in mass units. In (C) the superior horizontal axis gives creatinine in mass units.

Table 3. Daily diet composition

	All 94 subjects		50	44	Women vs. men
	Mean	Range	Women	Men	*P*
Water *ml/day*	2750	1040–5320	2700 ± 880[a]	2810 ± 890	0.542
Calories *kcal/day*	2190	780–4530	1936 ± 695	2474 ± 803	0.001
Oxalate *mmol/day*	6.6	1.3–39.7	6.6 ± 3.7	6.6 ± 6.5	0.985
Calcium *mmol/day*[b]	26.2	6.2–65.6	24.7 ± 10.6	27.8 ± 12.4	0.193
Phosphate *mmol/day*	50	13.7–102	45.4 ± 14.5	55.1 ± 19.4	0.006
Sodium *mmol/day*	114	28–239	102 ± 41	129 ± 47	0.005
Potassium *mmol/day*	94	37–213	89 ± 25	101 ± 38	0.076
Protein *g/day*	95	27–206	85 ± 25	106 ± 34	0.001
Protein-N *g/day*	15.2	4.3–33.0	13.7 ± 4.0	16.9 ± 5.5	
Fiber *g/day*	22.9	6.9–83.4	20.7 ± 7.6	25.5 ± 14.4	0.041
Vitamin C *mg/day*[c]	262	41–1512	242 ± 292	286 ± 287	0.465

[a] Variances throughout the Table are shown as SD
[b] Estimated calcium in diet; does not include Ca supplements (see text)
[c] Includes vitamin C in supplements

related to the ratio of estimated dietary Ca to dietary oxalate: urine oxalate/creatinine μmol/mmol = 17.8 − 0.354 * basic diet Ca/oxalate mmol/mmol ($r = -0.37$; $P = 0.0003$). This inverse relationship also appeared to be curvilinear: urine oxalate/creatinine μmol/mmol = 19.0 − 4.96 * log(diet Ca/oxalate mmol/mmol); $r = -0.39$; $P = 0.0001$. Thus, urinary oxalate/creatinine appeared to decrease to an approximate plateau when the ratio of dietary Ca/oxalate reached about 5 mmol/mmol or between 2 and 3 mg/mg. When total Ca intake, including the Ca contained in supplements by some subjects, was used to estimate the dietary Ca/oxalate ratio, the linear inverse relationship between urinary oxalate/creatinine and dietary total Ca/oxalate was somewhat less close: $r = -0.27$; $P = 0.0089$. For all 94 subjects, no significant relationships could be detected between daily urinary oxalate excretion and dietary Ca intake, either as estimated basal dietary Ca intake ($P = 0.9906$), energy adjusted [13] basal dietary Ca intake ($P = 0.1466$), total Ca intake that included the Ca supplements taken by some subjects ($P = 0.6046$) or energy adjusted total Ca intake ($P = 0.1519$). Similarly, urinary oxalate excretion divided by creatinine was not related to energy adjusted basal Ca intake/kg ($P = 0.326$), total Ca intake/kg ($P = 0.7104$) or to energy adjusted total Ca intake/kg ($P = 0.7048$). There were trends for urinary oxalate/creatinine to increase as either estimated dietary oxalate intake/kg intake ($P = 0.0824$) or energy adjusted dietary oxalate intake/kg increased ($P = 0.0454$), but these relationships were not significant.

There were no detectable relationships between individual mean daily urinary oxalate excretion rates and the estimated daily intakes of total calories, protein, vitamin C or fiber.

Discussion

Increasing dietary calcium intake as well as the oral administration of calcium supplements have been shown to reduce urinary oxalate excretion rates in healthy subjects and in patients with calcium kidney stones, due to the precipitation of dietary oxalate within the intestine thereby limiting intestinal oxalate absorption. Our observation that urinary oxalate excretion/creatinine declined as the estimated ratio of dietary calcium to oxalate increased among healthy adults eating self-selected diets subjects is consistent with those observations.

Several factors may, however, have limited the sensitivity of our study to assess this relationship. First of all, we have no way of validating the precision of the estimates of dietary composition based on the food frequency questionnaire. We did not ask the subjects who participated in the study to keep dietary diaries on the day before and the day of each of their urine collections that could possibly have provided more accurate estimates of their individual dietary calcium and oxalate intakes. Moreover, the oxalate content of many foods are not accurately known and, in addition, the partition of oxalate within a given food between free oxalic acid that could be precipitated by calcium contained in other foods and calcium oxalate that presumably would not be so affected is not well known. Second, previous studies of the effects of calcium intake on urinary oxalate excretion [6–10] have, almost exclusively, compared urinary oxalate excretion rates in subjects eating diets containing ≤ 10 mmol Ca/day (≤ 400 mg Ca/day) to oxalate excretion rates when dietary calcium intake was ≥ 25 mmol/day (1000 mg Ca/day). Only 3 of our 94 subjects living in Wisconsin, "America's Dairyland," had estimated Ca intakes less than 10 mmol/day. Moreover, we did not specifically recruit subjects known to consume diets providing only small amounts of calcium, nor did we arrange to have a subset of subjects follow a calcium restricted diet for several weeks before collecting their urine. We also did not specifically recruit subjects who ate diets high in oxalate as well as low in calcium that are prevalent among populations with a high incidence of kidney stones. Thus, the capacity of the study to detect higher rates of urinary oxalate excretion when the ratio of dietary Ca to dietary oxalate was low (< about 2 mmol/mmol) was limited.

When we took account of Ca contained in supplements taken by some of the subjects of the study, an inverse relationship between urinary oxalate/creatinine and total dietary Ca intake was no longer detectable, and the inverse relationship between urinary oxalate/creatinine and total dietary Ca/oxalate was less close. Presumably these observations reflect the lesser effects of higher Ca intakes to reduce urinary oxalate excretion relative to creatinine (Fig. 3). It is also possible that some subjects took their Ca supplements at times separate from meals so that the additional Ca was not simultaneously available with dietary oxalate to cause calcium oxalate precipitation in the intestine.

Nevertheless, the results of the present study are consistent with the results of the epidemiological study that demonstrated that the prospective incidence of kidney stones among men declined with increasing dietary Ca intake, an effect attributed to the effect

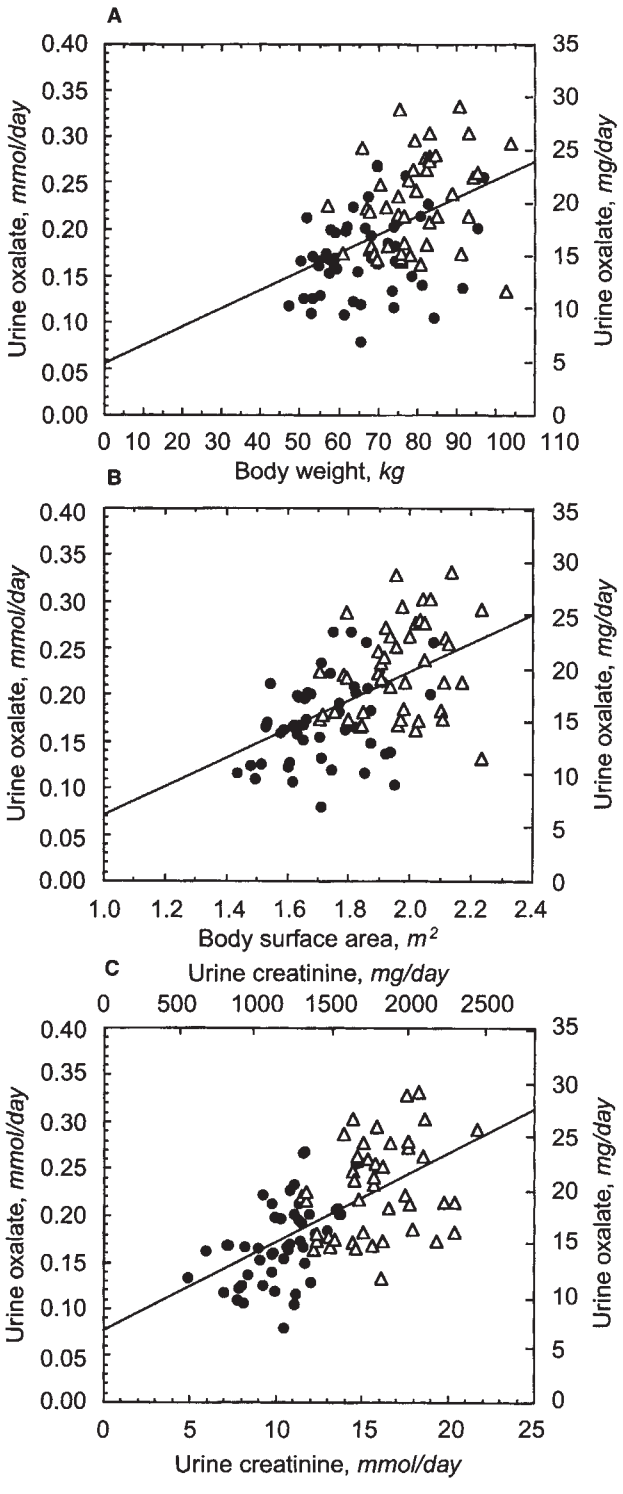

Fig. 3. A. *Individual mean daily urine oxalate/creatinine excretion in relation to estimated basic dietary Ca intake/day (exclusive of Ca supplements): urine oxalate/creatinine μmol/mmol = 18.3 − 0.0945 * diet Ca mmol/day (r = −0.27; P = 0.0077); or urine oxalate/creatinine μmol/mmol = 24.1 − 6.01 * log(diet Ca, mmol/day); r = −0.30; P = 0.0035.* **B.** Individual mean daily urine oxalate/creatinine excretion in relation to basic dietary Ca intake/day/kg body wt: urine oxalate/creatinine μmol/mmol = 17.6 − 4.81 * diet Ca/body wt mmol/kg ($r = -0.20$; $P = 0.0458$), or urine oxalate/creatinine = 13.97 − 3.92 * log(diet Ca/body wt, mmol/kg); $r = -0.20$; $P = 0.0471$. C. Individual mean daily urine oxalate/creatinine excretion in relation to the ratio of individual estimated basal dietary calcium intake to dietary oxalate intake: urine oxalate/creatinine μmol/mmol = 17.8 − 0.354 * diet Ca/oxalate mmol/mmol ($r = -0.37$; $P = 0.0003$), or urine oxalate/creatinine μmol/mmol = 19.0 − 4.96 * log(diet Ca/oxalate mmol/mmol); $r = -0.39$; $P = 0.0001$. In each panel, the inferior horizontal axis and left vertical axis give molar units and the superior horizontal axis and right vertical axis give mass units. Symbols are: (●) women; (△) men.

of increasing dietary Ca to reduce oxalate absorption and thus urinary oxalate excretion [11]. In that study the prospective incidence of stones decreased curvilinearly as Ca intake rose, most strikingly from 4.35 stones/1000 men/year in the lowest quintile of energy adjusted estimated dietary calcium intake in which mean calcium intake was 12.9 mmol/day (516 mg/day) to 3.1 stones/1000 men/year in the second quintile of energy adjusted calcium intake in which mean calcium intake averaged 16.6 mmol/day (664 mg/day). Prospective stone incidence then declined much less steeply to 2.79, 2.66 and 2.43 stones/1000 men/year as mean calcium intake rose in the three sequentially higher quintiles of intake to means of 19.6 mmol/day (783 mg/day), 23.4 mmol/day (937 mg/day) and 33.2 mmol/day (1326 mg/day), respectively. Our observations that the urinary oxalate/creatinine ratio decreased in a roughly similar curvilinear manner as dietary Ca or the ratio of Ca to oxalate in the diet increased provides direct support for the view that increasing dietary Ca, especially increases from very low to moderate intakes, reduces urinary oxalate excretion and could thereby reduce stone formation. We have compared these results of the epidemiological study and a comparable analysis of our data in the three panels of Figure 4. The data suggest that for an 80 kg man excreting 15.9 mmol creatinine/day (1800 mg/day), an increase in dietary Ca intake from 10 mmol/day (400 mg/day) to 25 mmol/day (1000 mg/day) would reduce oxalate excretion from about 0.30 mmol/day to about 0.25 mmol/day. This decrement in oxalate excretion as Ca intake is increased by 15 mmol/day is slightly less than previously estimated decrements of −0.06 to −0.12 mmol/day for an equivalent increase in dietary Ca intake over the same range [5, 9]. It also should be noted that when intestinal Ca absorption is enhanced, as occurs among stone-formers with idiopathic hypercalciuria, relatively less Ca would be available in the intestine to precipitate dietary oxalate. Thus, speculatively, somewhat higher Ca intakes might be necessary among such patients to minimize absorption of dietary oxalate, bearing in mind the off-setting effect of a consequent increase in urinary Ca to increase the relative supersaturation of the urine with respect to calcium oxalate.

Additionally, the results of prospective epidemiological study of stone incidence in relation to diet composition [11] showed that stone incidence also fell progressively and essentially linearly as estimated dietary potassium intake increased and as estimated fluid intake increased (from 4.3 to 1.8 and from 3.7 to 1.9 stones/100 men/year from the lowest to the highest quintiles of K and of fluid intake, respectively) in contrast to the apparent near threshold effect of dietary calcium intake. Whether there may have been interrelationships between estimates of dietary calcium intake and intakes of either potassium or fluid in that study is not fully clear. In the present study, estimates of dietary K and of dietary fluid were related to estimates of the Ca content of the basic diet ($r = 0.70$; $P < 0.0001$ and $r = 0.56$; $P < 0.0001$,

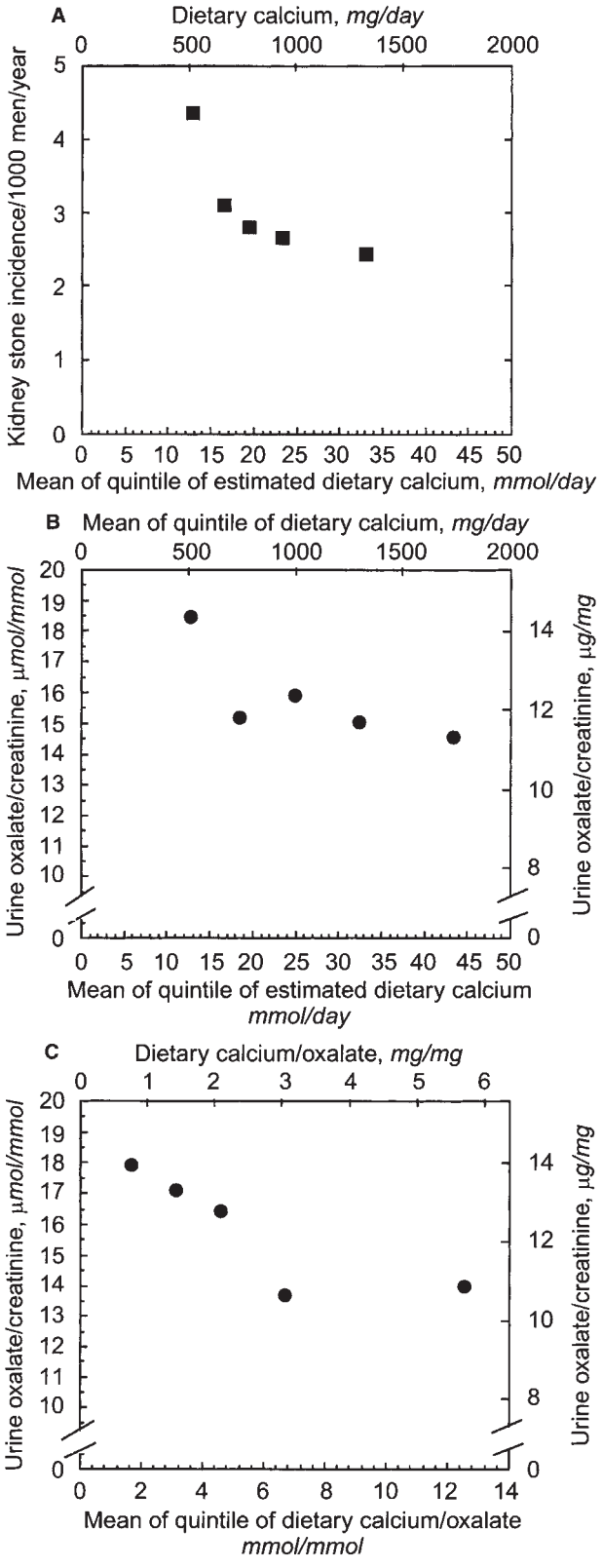

Fig. 4. *Comparison of results of epidemiological study showing a decrease in prospective stone incidence with increasing dietary Ca intake to data from the present study.* **A.** Prospective incidence of kidney stones in relation to means of quintiles of dietary Ca intake. Adapted from data published in [11]. **B.** Mean urinary oxalate/creatinine in relation to mean of quintiles of dietary Ca intake in the present study. **C.** Means of urinary oxalate/creatinine ratios in relation to quintiles of ratios dietary calcium to dietary oxalate among the subjects of the present study. For (B) and (C) the inferior horizontal axis and left vertical axis give molar units and the superior horizontal axis and right vertical axis give mass units.

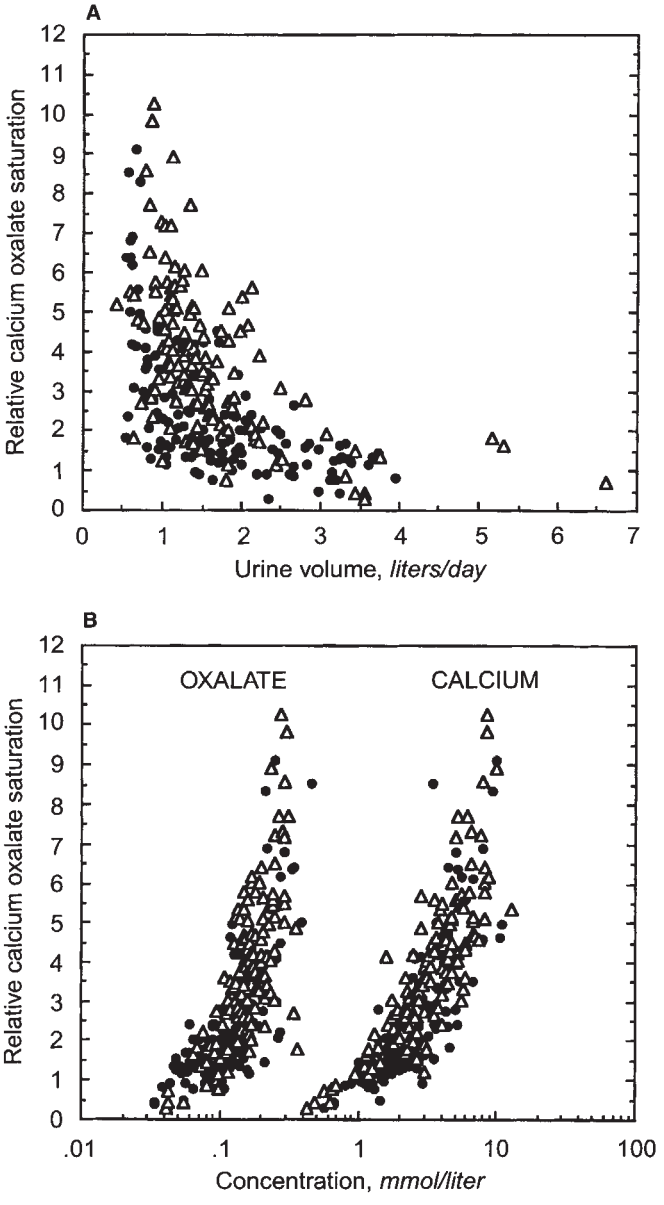

Fig. 5. *The relative saturation with respect to calcium oxalate of each of the 3 urines collected by the 94 healthy adults in relation to daily urine volume* **(A)** *and to urinary oxalate and to urinary calcium concentrations* **(B;** *note log scale on abscissa).* Symbols are: (●) women; (△) men.

respectively). Estimates of fluid intake were significantly related to estimates of dietary K intake ($r = 0.65$; $P < 0.0001$), and urinary volume was also related to urinary K excretion ($r = 0.54$; $P < 0.0001$). Moreover, urinary volume, ml/kg/day, was related to urinary K excretion, mmol/mmol creatinine/day ($r = 0.64$; $P < 0.0001$). These relationships suggest a possible interaction of

increasing dietary intake of water and of K to reduce the incidence of kidney stones.

Additionally, our observations confirm that increasing daily urinary oxalate excretion rates among healthy adults are associated with increasing body weight and with increasing lean body mass as reflected by daily urinary creatinine excretion. Such a relationship has been observed previously [7, 12], but has not been emphasized in studies and in reviews of the role of oxalate in the formation of calcium oxalate kidney stones. Further studies are obviously needed to determine whether urinary oxalate excretion increases with body size among patients with calcium oxalate kidney stones and whether individuals of large body size are over-represented among populations of calcium oxalate stone formers.

Urinary calcium excretion is also well known to increase with body size and such a trend was again observed in our study: urine Ca mmol/day = 1.481 + 0.239 * urine creatinine mmol/day (r = 0.42; $P < 0.0001$). To further explore the importance of these observations among our healthy subjects, we examined the relationships between the relative saturation of their urines with respect to calcium oxalate in relation to urine volume, urinary calcium concentration and urinary oxalate concentration as illustrated in the panels of Figure 5. Most urines from all subjects were supersaturated with respect to calcium oxalate, thus re-emphasizing the potential importance of other normal inhibitors of calcium oxalate crystal nucleation and crystal growth such as osteopontin (uropontin [31, 32]) and nephrocalcin [33] in preventing kidney stones among healthy adults. At any given urine volume, the urines of men were relatively more saturated with respect to calcium oxalate than the urines of women because of the higher daily rates of oxalate and of calcium excretion (Table 2), and thus oxalate and calcium concentrations among the men. The relative saturation of the urines with respect to calcium oxalate rose progressively as urinary oxalate and calcium concentrations increased (Fig. 5B), and more markedly as the oxalate concentrations increased in comparison to increases in calcium concentrations, as emphasized repeatedly by Finlayson [3]. Presumably, these features of urine composition, as well as the higher citrate excretion rates among women, contribute to the well-known greater incidence of kidney stones in men as compared to women (men ~ 3: women 1). Figure 5A also shows the progressively steep increase in the relative saturation of the urines with respect to calcium oxalate as daily urine volumes decrease below 1.5 liter/day among healthy subjects and the decrease in relative calcium oxalate saturation to a near plateau as urine volumes reach 2.5 liter/day or greater. This observation also re-emphasizes the importance of greater fluid intakes and thus higher urine volumes to minimize the relative saturation of the urine with respect to calcium oxalate.

In summary, our data show that body size is a major determinant of urinary oxalate excretion, and also provide further support for the view that diets restricted in Ca increase urinary oxalate excretion. When dietary oxalate varies over ranges generally consumed in the United States, diets providing 15 to 20 mmol Ca/day (600 to 800 mg/day) would appear to provide nearly maximum benefit to reduce urinary oxalate excretion.

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