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Ross P. Holmes · Dean G. Assimos
Harold O. Goodman

Genetic and dietary influences on urinary oxalate excretion

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Abstract Several genes contribute to the development of calcium oxalate nephrolithiasis as it is a polygenic disease. To explore the influence of genetic factors on oxalate excretion we have examined the distribution of oxalate excretions in 101 normal individuals who consumed self-selected diets. The distribution was apparently trimodal, consistent with the existence of three classes of oxalate excretors reflecting two allelic genes determining high and low oxalate excretion occurring with frequencies of 0.32 and 0.68 respectively. The pattern of inheritance in eight families was compatible with the expression of a pair of codominant alleles. A comparison of the distribution of excretory classes among the 101 normal individuals with that of 101 calcium oxalate stone formers suggests that high oxalate excretion may be associated with a 4-fold increased risk of stone disease and intermediate excretion with a 1.6-fold increase. Control of dietary factors influencing oxalate excretion apparently improved the discrimination between excretory classes in 17 individuals but the intra-individual variability in oxalate excretion was not reduced in four of nine individuals in whom this parameter was evaluated. More stringent dietary control than that applied in this study may be required before more extensive genotyping of individuals is attempted.

Key words Oxalate · Dictary oxalate · Genetic effects · Urinary excretions · Urolithiasis · Kidney stones

Introduction

The familial occurrence of calcium oxalate stone disease has been reported for over a century. A detailed study of its transmission in a large number of families indicated that the diathesis is due to a polygenic system (two or more gene loci) [18]. The amount of calcium excreted in urine is an inherited trait, indicating that the alleles regulating calcium excretion occur at one of the loci involved in the polygenic system [6]. The data we have obtained were compatible with the hypothesis that a pair of codominant alleles regulate intestinal calcium absorption [6]. Because urinary oxalate excretion directly influences the likelihood of calcium oxalate crystallization and because more hyperoxalurics are observed among stone formers than controls, a pair of alleles influencing oxalate excretion may also exist analogous to those affecting calcium excretion. Compatible with such an influence we have reported that the inter-individual variability in oxalate excretion is 3 times the intra-individual variability in excretion [6]. This criterion has to be fulfilled for a genetic effect to be present. An inherited trait associated with red cell oxalate transport and intestinal oxalate absorption has previously been reported [3] but its relationship to the amount of oxalate excreted in urine is not certain.

In this study we have examined the distribution of the mean oxalate excretion in 101 normal individuals to determine whether it is consistent with the existence of three groups: low, intermediate and high excretors. This distribution was compared with that in 101 oxalate stone formers. We have further studied segregation of oxalate excretion in a small number of families to determine whether it is compatible with the expression of a codominant pair of alleles. To examine whether dietary control improves the discrimination between excretory classes we have also measured oxalate excretion in individuals consuming diets of known oxalate content and controlled in other factors that may modify intestinal oxalate absorption.

Subjects and methods

Subjects

The characteristics of the cohort of 101 normal Caucasian individuals (54 males and 47 females, mean age 29.2 ± 9.4 years)

R. P. Holmes (✉) · D. G. Assimos · H. O. Goodman
Department of Urology, Bowman Gray School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, USA; Tel: +1 (910) 716-4231, fax: +1(910) 716-0174, e-mail: rholmes@bgsm.edu

whose oxalate excretions were examined in this study have been previously reported [10]. For calculations of relative risks, data from this Center on the urinary oxalate excretions of 101 Caucasian stone formers (68 males and 33 females, mean age 45.9 ± 15.1 years) were collated. Selected patients met three criteria: (1) chemical analysis of a stone had indicated calcium oxalate as a major constituent, (2) at least two 24-h urine collections were assayed, and (3) collections were obtained prior to the initiation of drug or dietary therapy. Eight families were also recruited to study the pattern of inheritance of oxalate excretion. Inclusion criteria consisted of at least four family members spanning at least two generations who were willing to collect three 24-h urine collections while consuming self-selected diets. Three families contained a total of six recurrent calcium oxalate stone formers who were not receiving any therapy. Seventeen subjects in apparent good health (12 males and 5 females of mean age 30.8 ± 8.2 years and mean weight 72.0 ± 14 kg) were recruited from within our Center for controlled dietary studies. The first nine individuals (5 females and 4 males) recruited collected four 24-h urines on self-selected diets and consumed a controlled diet for 10 days with urine collections each day. A further eight individuals only collected 24-h urines while consuming the controlled diet for 5 days.

Diets

Controlled diets were prepared in the metabolic kitchen associated with our General Clinical Research Center. Caloric requirements were calculated based on the individual's age, sex, height, weight, and level of activity. A 2-day menu cycle was used on 10-day protocols and a single menu on 5-day protocols. Diets contained, per 2500 kcal: 112 ± 11 (SD) g protein, 62.2 ± 12.1 mg oxalate, 1241 ± 128 mg phosphorus, 288 ± 48 mg magnesium, 1000 mg calcium, 142 ± 23 mmol sodium, 86 ± 14 mmol potassium, 9.2 ± 1.2 g fiber, and 17.9 ± 2.5 g acid ash. All diets provided the same proportions of calories from protein (19.0% ± 1.7%) fat (24.1% ± 2.9%), and carbohydrate (60.5% ± 4.0%). The nutrient content of foods was calculated using software based on USDA tables except for oxalate, which was measured directly as described below. The diet contained 344 ± 36 mg Ca^{2+}/2500 kcal and supplemental Ca^{2+} to adjust the level to 1000 mg was provided in apple juice as calcium glubionate (Sandoz) and was consumed in divided portions with meals.

Assays

The oxalate content of acidified urine samples was measured by a modification of Sigma's 591 oxalate oxidase assay as previously described [10]. The creatinine content of urine samples was assayed on an Abbott Spectrum analyzer using a kinetic picric acid technique with a kit supplied by the manufacturer. The oxalate content of food was assayed by preparing a 10% (w/v) homogenate in 1 M H_3PO_4 using a Polytron (Brinkmann Instruments) homogenizer. Particulate matter was removed by a 2-min centrifugation at maximum speed in a microfuge followed by filtration of the supernatant through a 0.2-μm nylon filter. An aliquot of the filtrate was diluted 100-fold in pure H_2O (>18 megaohms) for oxalate analysis by capillary electrophoresis [7, 8]. Foods with a low oxalate content were homogenized in 0.1 M H_3PO_4 and diluted 10-fold for analysis.

Data analysis

The mean of three excretions was used to diminish the effects of intra-individual variability on the distributions. Excretions of oxalate were expressed relative to creatinine to partially correct for differences in body size between individuals [13] and to partially compensate for errors in collection. The relative risk and its significance level for high excretors were calculated using a standard method [14]. The same method was used for calculating the relative risk for intermediates but omitting the high excretors from both the control and stone forming groups. The proportions of low, intermediate and high oxalate excretors among the normal subjects were tested for compatibility with the Hardy-Weinberg equilibrium [14] on the hypothesis that these three phenotypes were produced by a pair of codominant alleles. Urinary excretions on controlled and self-selected diets were compared by a paired, two-tailed Student's *t*-test. Results are presented as means ± standard deviations.

Results

The distribution of the mean of three 24-h oxalate excretions relative to creatinine (Cr) for 101 normal individuals is shown in Fig. 1. The distribution is skewed to the right, which is consistent with the presence of a small hyperoxaluric class. The presence of small numbers of hyperoxaluric individuals in normal populations has previously been reported by others (e.g., [20]). Subjects with values ≥36 mg/g Cr (45 mmol/mol) were classified as hyperoxaluric to be consistent with commonly used criteria [16]. This division between high and intermediate oxalate excretors formed one antimode to divide the distribution. This group comprised 9% of the normal group and 28% of the stone formers. Near the group mean, which was 23.2 ± 9.0 mg/g for the non-stone-forming individuals, a near maximal frequency of individuals would be expected in a normal distribution. Two low frequencies at 20 and 22 mg/g suggested, however, that the distribution of values below 36 mg/g could be divided into at least two excretory classes of individuals. An arbitrary antimode separating low and intermediate excretors was set at 21 mg/g, which is close to the middle of the range of values obtained for the low and intermediate excretors. This division of the distribution resulted in a low excretory class with a mean oxalate excretion of 15.9 ± 3.2 mg/g, an intermediate excretory class with a mean excretion of 25.9 ± 4.3 mg/g, and a

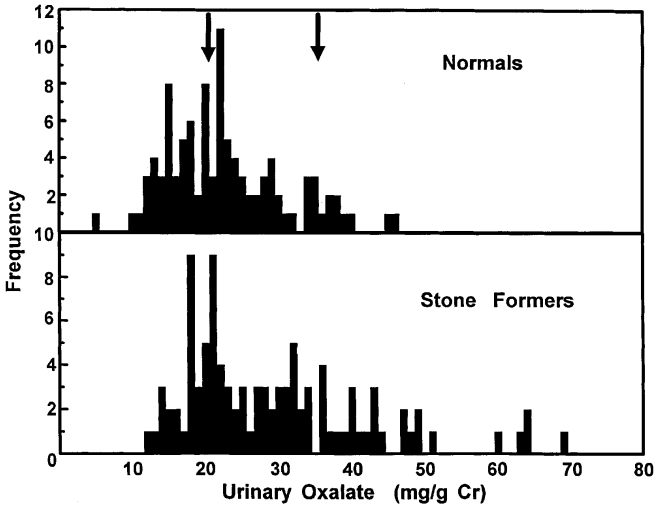

Fig. 1 Distribution of mean oxalate excretions in 101 normal individuals and 101 calcium oxalate stone formers. *Arrows* identify the values (antimodes) separating excretory classes

high excretory class with a mean excretion of 39.6 ± 3.6 mg/g. The differences between the means of these three groups suggest that the genic effects are additive. The division points for these three classes are only tentative as it is clear that considerable overlap occurs between the excretory classes, presumably due to the lack of control of environmental factors influencing oxalate excretion. Furthermore, if these division points are nonsensical they may depart from the Hardy-Weinberg equilibrium and numerous exceptions in segregation within families should become apparent.

The numbers of normal individuals assigned to low, intermediate and high excretory classes were 45, 47 and 9 respectively. The numbers of excretors in the three classes are compatible with a population at equilibrium ($\chi^2 = 0.421$, $df = 1$, $P > 0.3$) and the existence of a pair of codominant alleles responsible for these excretory classes. The estimated frequencies of the alleles for low and high excretion are 0.68 and 0.32, respectively. The antimodes from the normal distribution were used to subdivide oxalate excretions in 101 stone formers. This subdivision indicated that there were 27% low excretors, 46% intermediate excretors and 28% high excretors.

Three 24-h urines were obtained from eight families and the members classified using the antimode values assigned for normal individuals in Fig. 1. The pedigrees are shown in Fig. 2. All pedigrees are compatible with a two-allele system exhibiting codominance. The number of families is too small for rigorous genetic analysis.

As described above, our observations on urinary oxalate excretion have satisfied three of the primary criteria for a genetic trait contributing to the polygenic complex responsible for susceptibility to oxalate stone disease. However, a more complete discrimination between excretory classes is required for selecting genetically homogeneous subjects for more rigorous biochemical and genetic studies of oxalate excretion. This need provided the impetus for studying whether dietary control would suppress any diet-associated variability in intestinal oxalate absorption and endogenous oxalate synthesis. To determine the efficacy of dietary control, normal individuals consumed a diet with known contents of calcium, magnesium, sodium, potassium, phosphorus, oxalate, fiber and protein. The oxalate content of all dietary constituents used in the controlled diets was measured by capillary electrophoresis and is reported in Table 1. Participants in the study consumed 55.3 ± 11.7 (SD) mg oxalate/2500 kcal. As an index of whether the dietary control was affecting the variability in urinary oxalate excretion, changes in the intra-individual coefficients of variation (CV) in oxalate excretion on self-selected diets and on controlled diets were examined (Table 2). The first nine individuals consumed the controlled diet for 10 days and collected four 24-h urines prior to commencing the study. The effectiveness of the dietary control was evident in significant reductions in the CVs for calcium, sodium, potassium and urea-N. Notably, mean oxalate excretions and the CVs of these excretions were not significantly different on the two diets. No consistent change in oxalate excretion with time occurred on the controlled diet ($P = 0.47$ by ANOVA), indicating that adaptive changes in factors influencing the variability in oxalate excretion (changes in intestinal flora, absorption, or endogenous metabolism) were not apparent. In five of

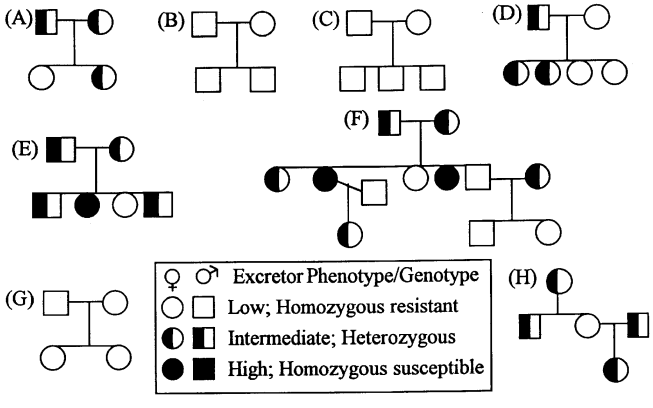

Fig. 2 Pedigrees of low, intermediate and high oxalate excretors in eight families

Table 1 The oxalate content of foods consumed (*ND* none detected (< 0.2 mg/100 g)

Food	Oxalate content (mg/100 g)
Apple, raw	0.5[a]
Apple juice	0.4
Bagel	11.7
Banana	3.2
Beef, ground	ND
Broccoli, steamed	1.8
Carrot, raw	5.7
Cream cheese	ND
Dressing, non-fat ranch	3.7
Egg	ND
Graham crackers	23.6
Grape jelly	1.5
Ham, cured	ND
Lettuce, Iceberg	0.6
Macaroni, boiled	6.6
Margarine	ND
Mayonnaise	0.3
Mustard	23.1
Orange	2.2
Orange juice	0.4
Peaches canned in juice	0.8
Pears canned in juice	0.6
Peas, steamed	0.4
Radish	9.3
Rice, white, steamed	2.1
Soda crackers	23.0
Soup, vegetable beef, canned	2.0
Tomato sauce, canned	15.0
Turkey	ND
Vanilla wafer	7.3
White bread	19.4

[a] The oxalate content of foods represents the mean of assays of two different samples)

Table 2 The effect of dietary control on urinary excretions. Values are the mean ± SD (*CV* coefficient of variation)

	Self-selected diets (4 days)	Controlled diets (days 7–10)	*P* value
Oxalate (mg/day)	25.9 ± 6.7	24.7 ± 5.6	0.69
Creatinine (mg/day)	1401 ± 333	1466 ± 310	0.67
Calcium (mg/day)	191 ± 88	165 ± 38	0.44
Sodium (mmol/day)	144 ± 12.5	110 ± 11.2	0.047
Oxalate/creatinine (mg/g)	18.6 ± 4.2	17.5 ± 4.9	0.62
CV oxalate (%)	22.0 ± 10.2	22.9 ± 14.4	0.88
CV creatinine (%)	13.3 ± 7.2	7.5 ± 6.6	0.09
CV calcium (%)	30.0 ± 10.6	12.2 ± 5.5	< 0.001
CV sodium (%)	28.3 ± 14.1	14.5 ± 4.5	0.019
CV potassium (%)	28.1 ± 7.2	12.4 ± 4.7	< 0.001
CV urea-N (%)	20.9 ± 10.9	9.0 ± 4.8	0.009
CV oxalate/creatinine (%)	24.6 ± 7.0	21.1 ± 15.9	0.84
CV responders (%) (n = 5)	26.6 ± 7.8	10.2 ± 2.6	0.002

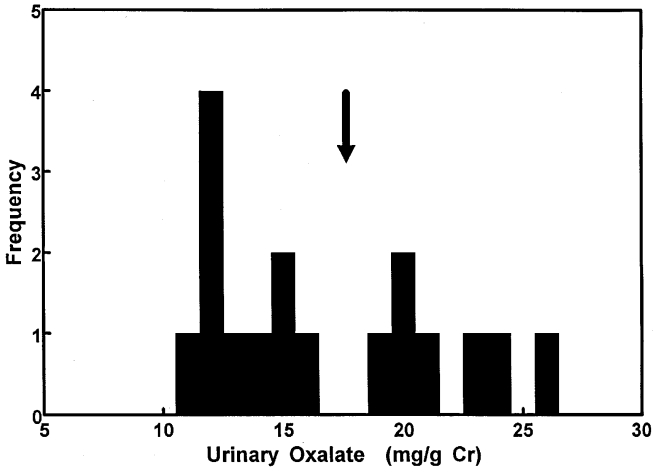

Fig. 3 Distribution of mean oxalate excretions in 17 individuals consuming a controlled diet. *Arrow* designates separation between low and intermediate excretors

the nine individuals there was a significant reduction (P = 0.002) in the variability in oxalate excretion relative to creatinine on days 7–10 of the controlled diet (CV = 10.2% ± 2.6%) compared with that on self-selected diets (CV = 26.6% ± 7.8%). With the other four individuals the CV was unchanged in one and increased in three.

Because of the lack of time-dependent changes in urinary oxalate excretion a further eight individuals consumed the controlled diet for only 5 days. The distribution in oxalate excretion was examined in these eight individuals together with the nine individuals discussed above by an analysis of the mean oxalate excretion of each individual in collections obtained on days 3–5 of the diet. Figure 3 shows that the 17 individuals appeared to separate into two groups with a division at 17–18 mg/g. With this division there were ten low excretors and seven intermediate excretors. These proportions are not significantly different from those observed for assigned excretory classes in the 101 normal individuals. Only 1.7 high excretors would be expected and none being observed is not a significant departure. With the dietary control applied the range of values in the low and intermediate excretory classes appeared reduced and they were approximately half the values obtained with the normal population in Fig. 1.

Discussion

The amount of oxalate excreted in urine is an important risk factor in the development of calcium oxalate nephrolithiasis [19]. As urine normally contains much less oxalate (0.1–0.5 mM) than Ca (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. This has been confirmed experimentally by Robertson and Hughes [19], who added either calcium or oxalate to urine samples and examined calcium oxalate precipitation. It is clear that an understanding of the factors responsible for determining the levels of oxalate excreted in urine is important for designing effective therapies for treating and strategies for preventing calcium oxalate stone disease.

A genetic influence on the amount of oxalate excreted in urine would not be surprising given the impact that urinary oxalate concentration has on calcium oxalate crystal formation and the recognition that idiopathic calcium oxalate nephrolithiasis is a polygenic disease [6, 18]. Three important criteria are fulfilled that support a genetic effect on urinary oxalate excretion: (1) the variability between individuals exceeded the variability within individuals [6, 10], (2) proportions of low, intermediate and high excretors were consistent with the Hardy-Weinberg equilibrium, and (3) segregation of the trait in family studies was compatible with the proposed codominant inheritance. Three lines of evidence support a causal role for the allele producing a high oxalate excretion in the development of calcium oxalate nephrolithiasis: (1) epidemiologic, in the over-representation of high excretors (hyperoxalurics) in the stone-forming population, (2) biochemical, in oxalate being a stone constituent and in its concentration affecting the supersaturation of urine with calcium oxalate, and (3) genetic,

in the susceptibility allele exhibiting a dosage effect among the excretory classes.

Some overlap was evident in the division of the distribution of oxalate excretions of both normal and stone-forming individuals into three excretory classes. This overlap was most evident at the antimodes and is expected given the large variability that occurs in intra-individual oxalate excretion and the lack of dietary control during urine collections [6, 10]. Recent studies in our laboratory using low-oxalate diets have revealed that the absorption of dietary oxalate makes a major contribution to urinary oxalate excretion in most individuals [8, 9], indicating why the control of dietary factors is likely to be important. In support of this dietary effect, when diets of normal individuals were controlled in their contents of oxalate, calcium, magnesium, and fiber – factors that influence oxalate absorption [8] – the variability in oxalate excretion was significantly reduced in five of nine individuals. The failure to reduce the variability in the other four individuals suggests that other factors also contribute to the variability in oxalate excretion. Such factors could include (1) the timing of ingestion of oxalate relative to that of its binding cations, calcium and magnesium, as this was not rigidly controlled, (2) changes in gut flora that may influence uptake in the large intestine, (3) changes in transit time including mouth to cecum transit times, which are known to vary substantially [12], (4) changes in intestinal secretions, or (5) changes in endogenous oxalate synthesis. To classify genotypes more accurately, as will be required before more accurate estimates of gene frequency and relative risks for stone disease are assessed and the gene identified, the factor(s) influencing the variability in oxalate excretion will have to be identified and controlled or an improved test developed to discriminate between genotypes.

The location of the antimode separating low and intermediate excretors among the stone formers appeared to differ from that in the normal population by an increase from 21 to 26 mg/g Cr. This difference could be due to modification of the diet after stone occurrence, with the avoidance of calcium-rich foods, or to the influence of hypercalciuria (45% were hypercalciuric with a calcium excretion >180 mg/g Cr), which may enhance intestinal oxalate absorption and hence oxalate excretion [13]. The greater proportion of high excretors in the stone-forming population is to be expected if hyperoxaluria is a significant risk factor in oxalate stone disease. If the amount of oxalate excreted is related to the risk of stone disease, those with a single dose of the allele for higher oxalate excretion should also be at increased risk for stone disease relative to those with a double dose of the allele for lower oxalate excretion, but at a lesser risk than those homozygous for the higher excretion allele. The calculated relative risks of 3.9 ($P < 0.001$) and 1.6 ($P < 0.2$) for homozygosity and heterozygosity respectively, tend to support such a relationship, although a larger sample size and better discrimination between excretory classes may be required to obtain statistical significance at the 95% confidence level with intermediate excretors. This increased risk for intermediate oxalate excretors occurs primarily because among the low and intermediate oxalate excretory groups, who would with usual classifications be considered ''normo-oxaluric'', the normal population is enriched in individuals with a low oxalate excretion in comparison with the stone-forming group (45% vs 27%). The calculated risk estimates must be considered tentative because the stone formers and non-stone formers compared differ in sex ratio, age distribution and possibly in other factors predisposing to stone disease. Further, as the present methods do not completely separate subjects into discrete classes without overlap, some misclassification has most likely occurred. However, if such errors are random, these preliminary estimates of gene frequency may not be grossly in error.

A genetic trait linking an increase in erythrocyte permeability to oxalate with urolithiasis has been reported in 40–80% of calcium oxalate stone formers [3]. In these studies no definite relationship of the red cell trait with the amount of oxalate excreted was established [3]. The lack of such a relationship could suggest that two different loci involving oxalate may contribute to calcium oxalate stone disease. Alternatively, they may be phenotypic manifestations of the same locus and a relationship may not have been observed because multiple urine collections were not evaluated to reduce the effects of variability in oxalate excretion or because some stone formers had modified their diet subsequent to the stone episode by the avoidance of oxalate-rich foods. A possible association between the red cell anomaly and the amount of oxalate excreted warrants further examination before excluding the possibility that these two different traits result from the activity of the same gene product.

It is possible that a genetic effect influences either dietary oxalate absorption or endogenous synthesis of oxalate. Ascorbate breakdown in the body tissues has been proposed to account for a significant fraction of the urinary oxalate excreted [2, 4]. The validity of these estimates can be questioned, however, because samples were exposed to an alkaline pH during analysis. It is now recognized that exposure of ascorbate to an alkaline pH will result in the breakdown of ascorbate to oxalate [5, 17]. Hepatic synthesis, the other major source of endogenous oxalate, has proved difficult to modulate in our studies, suggesting it is not responsible for the large inter- and intra-individual variabilities observed in oxalate excretion. Large differences in protein intake induce only minor changes in oxalate excretion [10] and an extreme metabolic state (hyperglucagonemia) was required to increase hepatic oxalate synthesis in guinea pigs [11]. Differences in oxalate absorption may contribute to the inter-individual variability, particularly as the contribution of intestinal oxalate absorption to urinary oxalate excretion appears to have been underestimated [8, 9]. It is noteworthy that in their studies Baggio et al. [3] observed a relationship between a high red cell

rate of oxalate exchange and an increased absorption of intestinal oxalate. It is possible that a polymorphism occurs in a gene encoding a protein intimately involved in oxalate absorption and that this polymorphism accounts for the genetic classes we have observed. Such a relationship would suggest a correlation between oxalate absorption and urinary oxalate excretion. Lindsjo et al. [15] did not observe a strong relationship between the absorption of [^{14}C]oxalate and urinary oxalate excretion, but the absorption of an isotopic bolus given with one meal is not a reflection of oxalate absorption during the entire urine collection period. However, five of seven stone formers with a urinary oxalate excretion greater than 40 mg/24 h had a high oxalate absorption (>10%). A single 24-h urine collection from stone patients consuming self-selected diets was used in this study, and these collections were undoubtedly influenced by such variable factors as the amounts of oxalate, calcium, magnesium and fiber ingested. The levels of *Oxalobacter formigines*, the main oxalate-degrading bacteria in the gut, may also vary [1], so fluctuations in the levels of this organism and other oxalate-degrading bacteria have to be considered.

In summary, our results suggest that in spite of considerable intra-individual variability, the pattern of oxalate excretion observed in a large number of individuals is compatible with genetic factors having a significant influence on oxalate excretion. The intra-individual variability undoubtedly contributes to overlap between the three excretory classes detected. However, if the misclassification of individuals occurs equally in both directions there may be less error in the estimated frequency of each excretory class than in the assignment of individuals to a particular excretory class. The values given here reflect the limitations of present techniques for the study of oxalate excretion and should not, of course, be construed as rigorous estimates of the frequency in subclasses of excretors. An accurate assignment of individuals to excretory classes, which is of potential clinical significance, and an assessment of gene frequencies may depend on more rigorous dietary control such as that provided by formula diets.

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